Practical Interventional Cardiology

Second Edition

Edited by

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MARTIN DUNITZ

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Preface

In the spring of 1983, with the dogwood in full bloom, I attended Andreas Gruentzig's coronary angioplasty teaching demonstration course in Emory University in Atlanta, Georgia. I had come at the suggestion of two friends Paul Silverton and David Cumberland (with whom I had shared some preliminary PTCA experience) to learn more about the new technique for the treatment of coronary artery disease. I was immediately impressed and excited not only by Gruentzig's enthusiastic approach but by that of many of the other participants which included Richard Myler, Simon Stertzer, Spencer King III and the young fellow Bernie Meier.

During the meeting, Andreas entertained us in the back garden of his home on a pleasant evening by the pool. He was full of life and fun and pleased to meet the European contingent present. My own enthusiasm for PTCA and its potential was hopefully apparent and I was invited to see cases performed in the Cath Lab after the course was over. Andreas' words to me will be remembered for their simplicity: 'This is only the beginning.' Over the past 12 years, like many of the people at that meeting, my personal experience has developed from simple PTCA with Gruentzig's fixed wire balloon catheter to multilesion, multivessel and complex PTCA, primary PTCA in acute myocardial infarction, directional coronary atherectomy, Rotablator atherectomy, intracoronary stent implantation and intracoronary ultrasound imaging. I have learned much by watching great interventional cardiologists at work like Geoffrey Hartzler in Kansas, Bernie Meier in Geneva, John Simpson and colleagues in California and David Cumberland in Sheffield but the seed had germinated in Emory. This group photograph hangs on my office wall at the Cardiothoracic Centre in Liverpool and is a warm reminder of the friends and colleagues who were fortunate enough to be in Atlanta too that year. Perhaps you can recognise someone?

It is perhaps bold to say that my enthusiasm has contributed in some small way to developing Ever Grech's interest in interventional cardiology and I am proud to have worked with him on this project. Ever and I are grateful to all the contributors to this book and humbled by their knowledge, their generosity and their willingness to participate. We thank our colleagues in industry for their assistance in providing technical details and registry data and for providing some insight into the future technology. We are grateful to Janette Rekatas, Senior radiographer at CTC Liverpool, Jackie Hyland, Tony Hanmer and Ken Maddock for their help in preparing illustrations. We deeply appreciate the personal efforts and technical expertise of all at Martin Dunitz Ltd., and in particular Mr. Alan Burgess, the commissioning editor for his conscientious assistance in coordinating much of the work. Finally, our thanks are owed to our families who have supported us over the past fifteen months.

In 1983, Andreas Gruentzig was of the opinion that 'This is only the beginning!' There have been many great strides and advances in interventional cardiology since then as evident by the contents of this book. Perhaps we can move to say that in 1996, 'This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning' (Winston Churchill, Mansion House Speech, November 1942).

DRR
Liverpool, UK
September 1996

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Preface to second edition

It has been only 4 years since the publication of *Practical Interventional Cardiology*. However, within that short period, developments in the field of interventional cardiology have been so remarkable that the need for a second edition has become increasingly apparent. In preparing this text, we have set out not only to update existing chapters but also to add a number of chapters which introduce new techniques, technologies and modes of treatment—both mechanical and pharmacological. As with the previous edition, the emphasis has been on providing practical advice and illustrated examples wherever possible.

Atherectomy devices such as directional coronary atherectomy (DCA), rotational atherectomy, transluminal extraction coronary atherectomy (TEC) and laser atherectomy have been disappointing in their effects on restenosis and at best have become 'niche-devices' for the treatment of specific lesion subsets by experienced interventionists. Whether their debulking ability will prove useful as an adjunctive device for dealing with intra-stent restenosis remains to be seen and all the devices have been significantly modified over the last few years. More evidence for the usefulness of cutting balloon percutaneous transluminal coronary angioplasty (PTCA) warrants separate discussion of its place in the interventionist's armamentarium.

The balloon and stent have become firmly established as the basic tools of the coronary interventionist. To emphasize the important developments in stenting, two chapters have been devoted to this topic. Stenting in combination with aspirin and clopidogrel has allowed cardiologists to treat a greater number of complex lesions safely without fear of abrupt closure and is having a significant impact on the number and type of cases being referred for coronary artery bypass surgery. Coated, covered, radioactive and drug-eluting stents may all offer major advantages for preventing thrombosis and restenosis and this exciting area should be followed closely over the next year or so. PTCA has also proved its superiority over thrombolytic therapy in acute myocardial infarction and stenting has now been shown to provide additional benefits and can arguably be regarded as the gold standard reperfusion therapy in this condition.

A new class of pharmacological agents has emerged as a useful adjunct to percutaneous coronary intervention (PCI). Low molecular weight heparins, GP IIb/IIIa inhibitors and other antiplatelet agents have been shown to reduce the risk of complications and improve PCI outcomes in patients with acute coronary syndromes. For this reason, a chapter highlighting the value of these agents has been included.

Although stenting has solved some of the shortcomings of PTCA and reduced restenosis rates, the problem of intra-stent restenosis has not yet been overcome. Much time, effort and resources have—and still are—being devoted to finding ways of preventing its occurrence or at least limiting the fibrointimal hyperplastic response that occurs after stent implantation. Research into brachytherapy has shown this to be effective in both prevention and treatment and this is discussed by one of the pioneers in this speciality.

Of course, there are many other aspects of interventional cardiology besides coronary artery intervention. These include mitral balloon valuloplasty, paediatric interventional cardiology and electrophysiological ablative techniques. Even percutaneous closure of post-MI septal defects is now being addressed. Carotid artery intervention is increasingly being performed by interventional cardiologists and surely other peripheral sites such as renal arteries will be included in an ever-expanding area of interest. As interventional cardiology becomes increasingly more complex, so training issues need to be considered. Structured programmes of education and assessment need to be set up and followed before certification to practice is granted. Moreover, effective data collection and analytical techniques, the cornerstone of clinical audit, must become part of routine practice. Accordingly new chapters addressing these issues have been incorporated in the Second Edition.

Since the first PTCA was performed by Andreas Gruentzig in 1977, there have been numerous advances and developments and in recent years the momentum has been breathtaking. It is almost impossible to publish a text quickly enough to avoid being out-of-date even before it is published. What appears 'on the horizon' may already have arrived into a clinical research protocol, clinical practice or have been assessed and shown to be of little worth even before the ink is dry! A glimpse into the future comes most appropriately from Spencer B King III.

It has been a rewarding exercise for us both to put together a second edition with the help of so many colleagues from around the world. It is a tribute to their skill and their dedication to education and teaching which is most impressive. Finally, we wish to express our grateful thanks to Alan Burgess and Clive Lawson at Martin Dunitz, for their invaluable assistance in the production of this book.

Ever D Grech and David R Ramsdale
April 2001

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Epidemiology and pathophysiology of coronary artery disease

Jessica M Mann and Michael J Davies

Epidemiology of coronary artery disease

Coronary artery disease is the leading cause of death in the Western World. In the United Kingdom, coronary artery disease alone is responsible for 26% of all deaths, and this figure is even higher in Scotland and Wales.

Epidemiological studies have demonstrated a relationship between certain 'risk factors' and the presence of symptomatic coronary artery disease. In the last 30 years, their number has increased, and they have been redefined more accurately; worldwide, governments have invested huge sums in an attempt to decrease the prevalence of risk factors and thus reduce morbidity and mortality rates from ischaemic heart disease. Nationwide screening still requires several issues to be resolved, such as the definition of the profile of the patient to be screened and the definition of subpopulations at risk based on risk scores like the lifestyle management score or the Dundee coronary risk-disk. Determining which is the most efficient approach to screening in terms of balancing target groups against available resources, and whether an intervention is successful in reducing clinically expressed disease are also important.

Amongst the risk factors, some can be modified whereas others cannot. Amongst the latter are age (the incidence of ischaemic heart disease increases in direct relation with age), gender (women are protected from ischaemic heart disease until after the menopause, probably by a mechanism involving oestrogen production)[1] and a family history of a parent under the age of 55 with ischaemic heart disease.

Modifiable risk factors for atherosclerosis include dyslipidaemias (high total cholesterol, above 5.2 mmol/l,[2] triglycerides, lipoprotein lp(a) (a glycoprotein with a structural similarity to plasminogen), high levels of low-density lipoprotein (LDL) and low levels of high-density lipoproteins (HDL)), systemic hypertension, obesity, diabetes mellitus, high plasma levels of fibrinogen and cigarette smoking. Other 'possible' risk factors which still remain to be confirmed as such include increasing coffee consumption,[3] personality type A, a high degree of environmental pollution, the degree of hardness of the water, *Helicobacter pylori* infection, *Chlamydia pneumoniae* and many others.

The importance of risk factors in atherosclerosis has been learned from epidemiological studies, which have consistently shown that the higher the number of risk factors or their severity, the larger the surface of the aorta or coronary arteries covered with atherosclerotic plaques, and thus the higher the risk of one of those plaques undergoing fissuring and resulting in clinical symptoms.[4] However, these extensive epidemiological studies also showed that there was a huge interpersonal variability, and that, within the same individual, the severity of the atherosclerotic lesions in one artery could not be used as a predictor of the severity of atherosclerosis in another artery.[5] Most of the epidemiological studies have, for instance, found a positive association between cigarette smoking and aortic atherosclerosis, but the association between cigarette smoking and coronary artery atherosclerosis is less consistent. High plasma levels of HDL have also shown a consistently inverse association with coronary artery lesions. Early atherosclerotic lesions in paediatric populations are related to the plasma lipid profile. In adults, increased total cholesterol has consistently been associated with atherosclerosis.

Reduction of risk factors is assumed to result in a decrease in the size of atherosclerotic plaques, at least in experimental studies in monkeys.[6] Regression of atherosclerotic plaques, mainly in the peripheral circulation, has also been shown in humans undergoing strict dietary and drug interventions.[7] Recent studies have shown that a drastic reduction in risk factors such as cholesterol intake results in a decrease in the frequency of new coronary artery lesions.[8] The SCRIP study

showed that reduction in saturated fat in the diet, together with a reduction of the daily amount of dietary cholesterol and an increase in the amount of ingested carbohydrates, could lead to a decrease in the number of new lesions appearing over a 4-year period.[8] However, the authors admit, that, taking into account the lack of accuracy of the measuring method, i.e. coronary angiography, it is impossible to determine if this radical change in lifestyle is only really modifying the rate of progression of small, non-haemodynamically significant lesions which escaped angiographic detection at the time of inclusion in the trial. Other regression trials have shown minimal angiographic reduction in the degree of coronary artery stenosis (less than 5%), but a significant reduction (up to 70%) in the number of clinical events such as ischaemic death and acute myocardial infarction; the discrepancy between these figures remains puzzling.

Atherosclerosis

Atherosclerosis is a focal, intimal disease which involves large and medium-sized vessels down to 3 mm in diameter. The typical atherosclerotic lesions are called plaques, and can be seen with the naked eye when opening the artery longitudinally.[9]

The atherosclerotic plaque has two main constituents; lipid, which forms the lipid core, generally crescent-shaped, and from which the name atheroma derives (atheros = gruel in Greek), and connective tissue, which surrounds the lipid core, separating it from the lumen of the artery. Both components are present in highly variable ratios within the same individual and even within the same coronary artery; thus, there might be a plaque consisting of 100% connective tissue next to another one which is predominantly lipidic.

Two major cell populations are present in the atherosclerotic plaque: monocyte-derived macrophages and smooth muscle cells. The former play a key role in the formation of the lipid core and in the process of plaque disruption, whereas the latter are responsible for the formation of the fibrous cap surrounding the lipid core and the repair response after plaque disruption. Monocyte-derived macrophages cross the endothelium by means of a sophisticated mechanism involving the production of cellular adhesion molecules (CAMs),[10] which interact with specific endothelial receptors, and thus allow the monocytes to proceed through the rolling, sticking and migrating movements which enable them to cross the endothelial barrier and penetrate the intima. Once within the intima, the monocytes—which are now activated—secrete different substances, including tumour necrosis factor alpha, interleukin-1 and platelet-derived growth factor (PDGF), which will modulate the proliferation of smooth muscle cells and the production of extracellular matrix by these cells. The monocytes are also the cells which ingest lipid and thus become foam cells, the main component of the lipid core. The vast majority of lipid present in the atherosclerotic plaques comes from plasma, and thus the level of plasma LDL is important in determining how much LDL will be available to enter the intimal space. However, it should be remembered that monocytes are unable to ingest LDL unless the latter is oxidized.[11] Oxidation of the LDL molecules seems to take place in the endothelium, although other types of cells have not been completely ruled out, such as macrophages and smooth muscle cells. Once the LDL molecules have been oxidized, they become chemoattractive for monocytes, recruiting more monocytes to the site where oxidation has taken place and at the same time inhibiting the migration of monocytes from the arterial wall;[12] they induce the expression of adhesion molecules by the endothelial cells—so that the monocytes can adhere to them—and they are able to be ingested by the scavenger receptor of the monocytes. Alternative pathways for ingestion of the LDL which involve a putative receptor have also been described.[13] The scavenger receptor does not downregulate, and thus the monocytes do not seem to have any control over the amount of oxidized LDL they ingest. This results in death of the monocytes, and the release of their cytoplasmic contents is what forms the lipid core, together with the skeleton of the dead cells. It has been postulated that oxidized LDL could trigger the mechanism of macrophage death[12] or that it could be a 'programmed death' or apoptosis. Two other significant properties of oxidized LDL are the fact that it could induce the release of tissue factor by macrophages, and thus become an active part of the mechanism involved in the formation of thrombus during the episodes of plaque disruption and the fact that metabolism of oxidized LDL produces substances which impair vasodilatation mediated by nitric oxide by interfering with the enzymatic pathways.

Smooth muscle cells in the media are of the contractile phenotype,[14] with abundant myofilaments and scarcely developed Golgi apparatus and rough endoplasmic reticulum. In the intima, smooth muscle cells have a synthetic phenotype: the number of myofilaments is decreased significantly, and both the Golgi system and the rough endoplasmic reticulum are larger as a result of acquiring the infrastructure to synthesize glycosaminoglycans and other extracellular matrix proteins. The contractile phenotype responds to substances which alter vasomotor tone, whereas the synthetic phenotype expresses genes for growth factors and cytokines. The proliferation of smooth muscle cells and the production of extracellular matrix proteins is the result of a complex balance between those substances which inhibit proliferation (such as nitric oxide) and those which stimulate it (such as PDGF). The interplay between the different substances involved might have therapeutic relevance in modulating and/or controlling the repair process after percutaneous transluminal coronary angioplasty (PTCA) and after plaque disruption, in which smooth muscle cell proliferation is the key event.

Evolution of atherosclerotic lesions

Our knowledge of how coronary artery disease progresses is hampered by the fact that we can only look at coronary arteries and/or aortae once—at necropsy. However, the literature contains several references relating histological findings to a temporal sequence, but even so most of our knowledge of progression of coronary artery disease is inferred from transverse studies as opposed to longitudinal ones. In 1989 Herbert Stary[15] studied a cohort of young people aged from birth to 29 years, who had died suddenly of non-cardiac causes, and he described in great detail the histological findings in different age groups. The earliest atherosclerotic lesion to appear was the 'fatty streak', which appeared as a yellow dot or area in the aorta and coronary arteries of very young children. Histological examination of fatty streaks showed that they consisted of macrophages with their cytoplasm filled with lipid droplets—foam cells—located in the intima. These fatty streaks could, in principle, evolve and turn into intermediate and advanced plaques. On the other hand, epidemiological studies on young subjects coming from populations with a low incidence of coronary artery disease have shown a similar number of fatty streaks to that seen in populations with high incidence of coronary artery disease, but very few advanced plaques.[16] This fact suggests that fatty streaks do not evolve into advanced plaques in low-risk populations. The raised, advanced or fibrolipid plaque, which is the one seen in young adults and thereafter, is the lesion responsible for the appearance of clinical symptoms, namely angina pectoris, acute myocardial infarction and sudden ischaemic death.

Advanced atherosclerotic plaques have a central core of lipid, surrounded by layers of connective tissue matrix. Extensive epidemiological studies have shown a direct relationship between the number and severity of the risk factors present in a certain population and the extent of the intimal surface of the aorta covered with atherosclerotic advanced plaques.[17] It should be remembered, however, that there is always the exception: a single plaque, strategically located, in the very proximal left anterior descending coronary artery, for instance, may prove fatal when it undergoes disruption and occludes the artery.

When the 'advanced' atherosclerotic plaque grows, it encroaches upon the lumen of the artery and results in coronary artery stenosis. It should be remembered, however, that many 'advanced' plaques are not detectable angiographically, and that the adjective is used to qualify a histological appearance rather than a clinical setting.

Coronary angiography is a crude method for looking at coronary artery stenosis, even when we consider the highly sophisticated computer-assisted equipment. The main problem resides in the fact that coronary angiography is performed by injecting contrast dye into the lumen of the artery. Thus, the result is opacification of the lumen, but this does not tell us anything about the atherosclerotic plaque itself. Two main reasons for 'underdiagnosis' of coronary artery disease exist. The first one is that, in clinical practice, the degree of stenosis of a segment of coronary artery is determined by comparing that segment with the adjacent 'normal' one. However, when we look at that 'normal' segment under the microscope, it always shows a certain degree of coronary artery involvement by plaque.[18] Second, when the volume of the atherosclerotic plaque starts to increase, there is a compensatory remodelling mechanism by which the plaque bulges outwards.[19] The result, however, is that the lumen remains unchanged. This remodelling mechanism has been shown to be operative in stenoses under 40%. The problem remains regarding the diagnosis of 'angiographically mild to moderate' stenosis, which will go undetected in a coronary angiogram. It also poses a problem for the 'progression and regression' trials, in that the appearance of 'new' lesions after a certain period of time—between both coronary angiograms—is most probably due to a previous plaque which has grown and now encroaches upon the lumen, rather than to the appearance of true 'de novo' atherosclerotic plaques.

Clinical symptoms

Stable angina pectoris

Autopsy studies of people with stable angina pectoris[20] have shown that they will have at least one area of haemodynamically significant stenosis in the coronary arteries.

The atherosclerotic plaque grows by two main mechanisms. The first is a primary growth mechanism, by which there is an increase in the volume of the plaque due to an increase in both the size of the lipid core and the amount of extracellular matrix present in the plaque. The secondary mechanism is that of thrombosis. Thrombosis can be secondary to a major plaque event, with plaque disruption leading to clinical symptoms, namely acute myocardial infarction, unstable angina and sudden ischaemic death, or it can be an asymptomatic event, with only a minor area of disruption present in the plaque. In both instances, however, the thrombin generated during the process of plaque disruption will stimulate smooth muscle cell proliferation, and might result in an increase in the overall size of the plaque.

Morphological analysis of coronary artery plaques show a very high degree of variability in the ratio between collagen and lipids, both within a defined population and within the same patient's arteries. The relative amount of both lipid and extracellular matrix varies from 0 to nearly 100%. Within the same patient, some of the coronary artery plaques will be nearly 100% extracellular matrix, whereas others will be predominantly lipidic. Recent studies have also shown that

the size of the lipid core is not related to the degree of stenosis, that is, a lipid-rich plaque, where the lipid core occupies 80% of its volume, can result in a 20% diameter stenosis or a 90% diameter stenosis; conversely, plaques which consist exclusively of extracellular matrix can also cause either a 20% diameter stenosis or a 100% diameter stenosis.

Most coronary artery plaques are eccentric in shape, allowing the retention of an arc of normal medial muscle. This area of normal muscle will be responsive to different vasoconstrictive stimuli, and thus a spastic component is superimposed on the fixed atherosclerotic lesion.[21] This is probably the most common mechanism—i.e. that of a small, non-occlusive thrombus together with an increase in vasomotor tone—in patients with unstable angina.

Acute coronary events: unstable angina, acute myocardial infarction and sudden ischaemic death

Acute coronary events are due to thrombus superimposed on an unstable atherosclerotic plaque. In unstable angina, the thrombus will not occlude the lumen of the artery, and there are significant changes in the vasomotor tone, at least in the majority of patients. In acute myocardial infarction, the artery is occluded by thrombus.

Thrombus appears on an unstable atherosclerotic plaque by two different mechanisms. The less frequent mechanism is that of superficial intimal injury, where there is a focal area of endothelial denudation, over which platelets are attracted and form a thrombus. The size of this thrombus varies greatly, from being so small that it can be diagnosed only at ultramicroscopic levels to reach such a size that results in occlusion of the vessel. The main features of this mechanism are that the plaque remains intact; there are no tears, and the lipid core is intact as well. Histological examinations of transverse sections of coronary arteries showing this kind of intimal injury show that the subendothelial space is filled with lipid-laden macrophages. This mechanism can be seen in approximately 25% of patients dying during the acute phase of an acute myocardial infarction.

The second mechanism responsible for acute coronary events is that of deep intimal injury.[22] In this case, a tear appears in the atherosclerotic plaque, putting the lipid core in contact with blood (Fig. 1.1). It should be remembered that the lipid pool is highly thrombogenic, mainly due to the presence of tissue factor. The size of the tear is very variable, going from 100 μm to several millimetres. In any case, if the fissure of the plaque is large enough, blood enters the plaque, and a platelet-rich thrombus starts being formed within the plaque. This results in a typical angiographic appearance, that of a type II lesion,[23] with irregular, ragged edges and a filling defect due to the presence of thrombus. The thrombus can then be reabsorbed into the plaque, with the resulting stenosis being of the same degree as before the episode of plaque disruption, or the thrombus can grow, protrude into the lumen with its intramural component, and even result in occlusion of the vessel. The healing process in any of these instances will result either in a higher degree of stenosis than before the episode of disruption (Fig. 1.2), in total occlusion of the vessel, or in recanalization with formation of multiple channels (Fig. 1.3). This mechanism is responsible for approximately 75% of all acute coronary events, and has lately been called 'plaque disruption'.

Autopsy studies have defined the profile of the atherosclerotic plaque at high risk of rupture;[24] these are plaques with a large lipid core, generally occupying more than 40% of the volume of the plaque (Fig. 1.4), with an increase in the

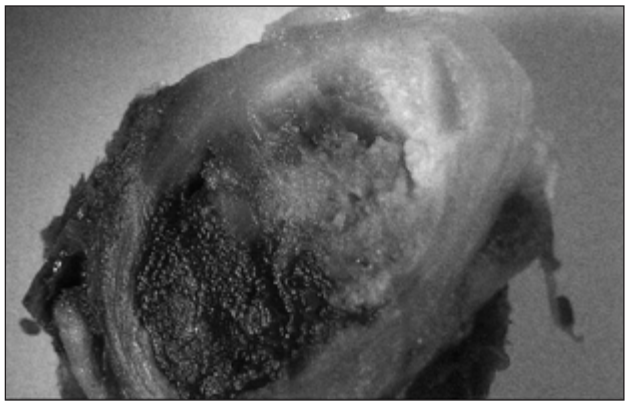

Figure 1.1
Transverse view of a human coronary artery showing plaque disruption. The atherosclerotic plaque is torn, and blood has entered the plaque, forming a thrombus which, in this case, is not occluding the lumen. (Courtesy of Dr Mary Sheppard.)

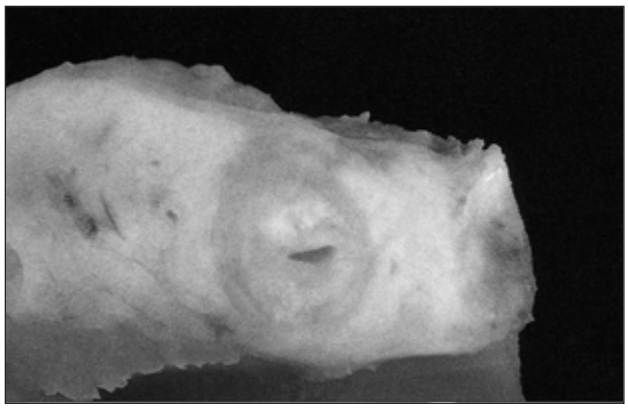

Figure 1.2
Transverse section of a concentric atherosclerotic plaque. The lumen is central, and the integrity of the media is preserved. The lumen of the artery is filled with contrast medium. (Courtesy of Dr Mary Sheppard.)

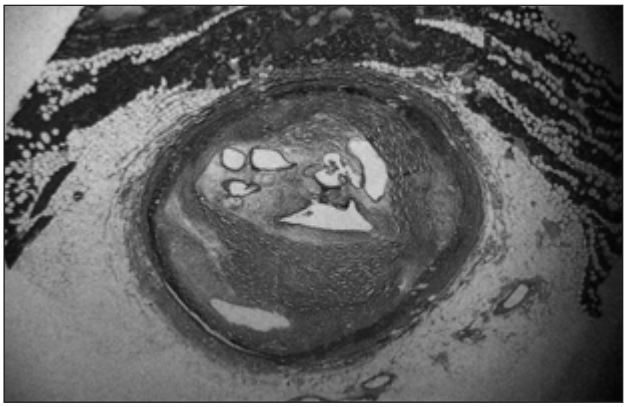

Figure 1.3
Histological section of a recanalized coronary artery. The atherosclerotic plaque has undergone plaque disruption in the past. The healing process has resulted in this multichannelled image. (Courtesy of Dr Mary Sheppard.)

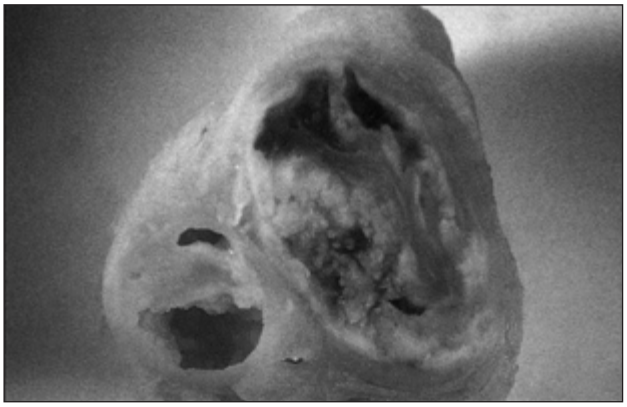

Figure 1.4
Transverse section of an atherosclerotic plaque undergoing plaque disruption. The fibrous cap has been torn, and blood has entered the lipid core. Thrombus is present both within and without the plaque, resulting in near-occlusion of the artery. (Courtesy of Dr Mary Sheppard.)

number of monocyte-derived macrophages, and a decrease in the number of smooth muscle cells and the amount of glycosaminoglycans. The size of the lipid core has been shown[25] to change the distribution of the forces within the plaque, increasing the stress at the angle where the lipid pool comes in contact with the fibrous cap. This is mostly due to the fact that the lipid core lacks collagen support underneath, so that the lipid is in an 'empty space', and the forces going through it need to be redistributed throughout the remaining volumes of the atherosclerotic plaque. It has also been shown that the thinner the cap, the higher the stress the plaque has to bear, and thus the higher its vulnerability. In summary, plaques at high risk of disruption are those plaques which have a large lipid pool, a thin fibrous cap, an increased number of monocyte-derived macrophages and a reduced number of smooth muscle cells. Unfortunately, coronary angiography is not yet able to detect these 'high-risk' plaques. Intravascular ultrasound seems promising as a tool, but is still too far away from producing reliable results.[26] An example of a low risk plaque is shown in Fig. 1.5.

Restenosis

PTCA has been successfully used since 1977 for the treatment of coronary artery stenosis.[27] In the 24 years since its creation, technical improvements to the guiding catheters (increased stability, torque control) and the dilatation catheters (lower spatial profile, reduced thickness, increased resistance to higher pressures up to 20 atmospheres) have significantly changed the procedure from the one Gruentzig and colleagues performed in the 1970s. Clinical indications have also changed, from a proximal lesion in single-vessel disease in a patient with stable angina, to multivessel disease with bad left ventricular function, long lesions and calcified ones.[28] However, one phenomenon has remained unchanged since the introduction of PTCA in clinical practice, and that is restenosis. Multicentre trials still report an angiographic incidence of restenosis ranging from 30% to 50%[29] at 6 months. Assessment of restenosis was exclusively angiographic in the 1980s, since the number of patients undergoing PTCA was statistically not big enough to provide reliable significant differences in clinical variables. However, in the last few years, since the number of patients undergoing PTCA has increased dramatically, several trials have identified important clinical variables in the development of restenosis. Diabetes mellitus and the presence of unstable angina have been consistently related to the development of restenosis. The mechanism by which

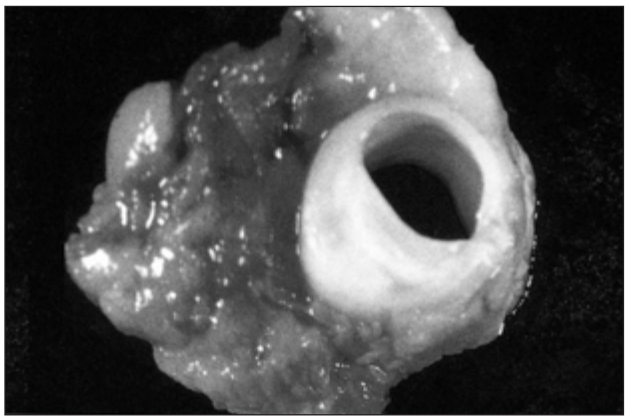

Figure 1.5
Transverse section of an eccentric atherosclerotic lesion. The lipid core is sizeable, but the fibrous tissue cap is homogeneously thick, thus putting this plaque in the 'low-risk' category for disruption. The media behind the atherosclerotic plaque is atrophied, whereas the area away from the plaque is intact and can still react to substances which alter the vasomotor tone. (Courtesy of Dr Mary Sheppard.)

diabetes is a risk factor for restenosis could be related to the stimulating effect of insulin on the proliferation of smooth muscle cells. Those patients undergoing angioplasty at the time they become unstable are assumed to have a greater risk of restenosis due to the double injury: spontaneous plaque rupture and superimposed angioplasty. Others[30] have shown angina class and severity of anginal pain to be clinical predictors of restenosis, together with the anatomical length of the stenotic segment, the presence of coronary artery calcification and the residual percentage diameter stenosis.

Clinical trials have tested over 20 different substances in an attempt to reduce the incidence of restenosis, including ciprostene, inhibitors of thromboxane A_2 and aspirin.[31,32] Most have shown a decrease in the frequency of ischaemic events, but no decrease in the angiographic frequency of restenosis. Other studies, such as CAVEAT, have shown diametrically opposite results, with the angiographic restenosis rate falling but the frequency of clinical events increasing.

Recent experimental approaches to the problem of restenosis include local drug delivery, antibodies to specific growth factors and gene therapy.[33,34]

Although the intrinsic mechanisms by which restenosis develops are not well known, it is a 'healing' response to injury involving smooth muscle cell proliferation. Vascular recoil[35] and the presence of thrombus at the site of PTCA are both concomitant factors, but the relative importance of each of them remains to be determined.

Examination of the coronary arteries of patients who died shortly after PTCA[36] shows the presence of a tear or split involving the intima and the media of the artery (Fig. 1.6); this tear is generally circumferential or spiral, and results in the presence of a flap, easily recognizable on angiography. However, more recent studies[37] have shown that angiographic identification of tears involving the media is quite difficult, and have suggested that the angiographic criteria for medial involvement (haziness and smooth-walled dilatation of the coronary artery segment which was angioplastied) should be revised. These authors also pointed out the fact that most, if not all (13/14, 94%), of the atherosclerotic lesions where the media was involved were eccentric plaques.

Smooth muscle cells, once they have entered the intima and changed phenotype, become able to secrete different molecules which act as transducers for other substances secreted by other cellular populations such as the endothelium and platelets. Smooth muscle cell proliferation (Fig. 1.7) and subsequent connective tissue production seem to be the result of a very finely tuned and delicate balance between

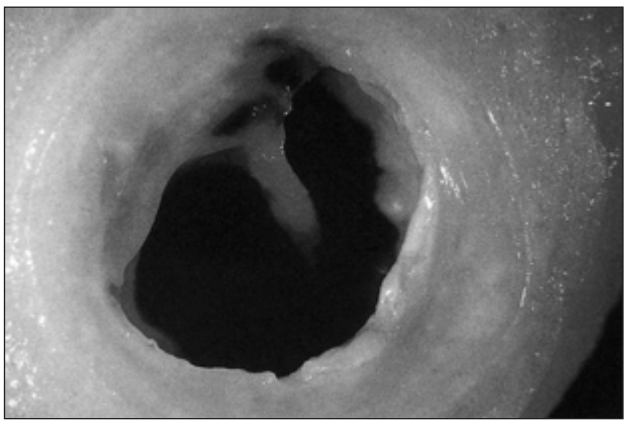

Figure 1.6
Macroscopic section of a coronary artery after PTCA. A small thrombus is present in the atherosclerotic plaque, and a flap is protruding into the lumen.

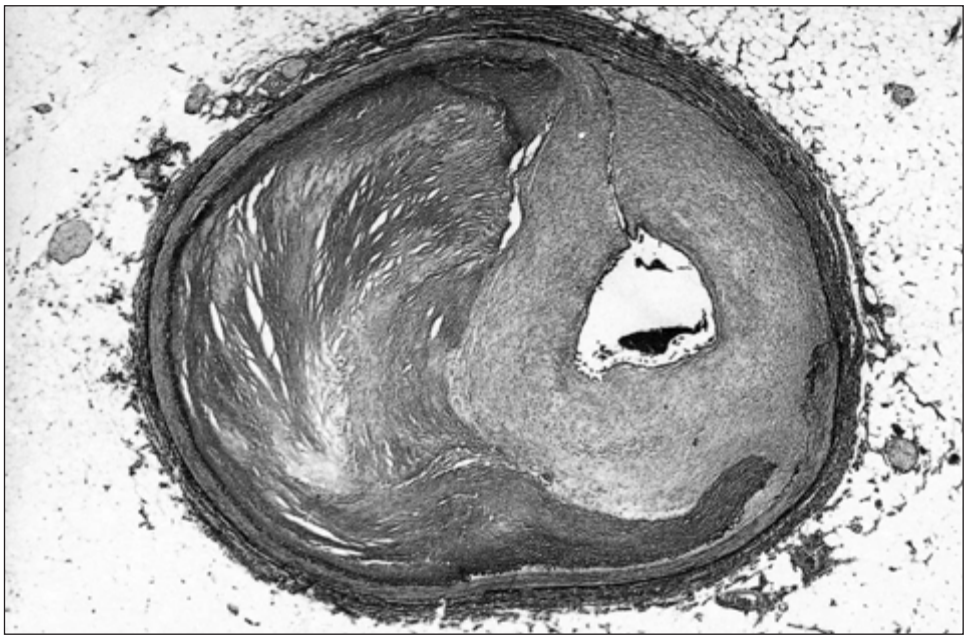

Figure 1.7
Histological section of a coronary artery showing concentric smooth muscle cell proliferation resulting in restenosis post-PTCA. (Courtesy of Professor A.E. Becker.)

stimulating factors and inhibiting factors. Amongst these are PDGF, which seems to have a predominant role in attracting more smooth muscle cells into the intima,[38] interleukins 1 and 6, and tumour growth factor beta, all of them produced by macrophages or platelets, except for the interleukins, which are exclusively of macrophage origin. Inhibiting factors include nitric oxide produced by the endothelial cells. Basic fibroblast growth factor has been shown to be produced by damaged smooth muscle cells during PTCA, and to stimulate smooth muscle cell proliferation in the vicinity of the tear.

In patients who died early after PTCA,[39,40] thrombus has been consistently found in the early cases (24 hours to 30 days). Smooth muscle cell proliferation with connective tissue matrix production appears after the first week post-PTCA and seems to be more significant when the split of the atherosclerotic plaque involves the media of the artery, as demonstrated by image analysis.[40]

It is a widely accepted fact that the smooth muscle cells present in restenosis are those with a synthetic phenotype,[41] and it has been postulated that these synthetic smooth muscle cells express an isoform of myosin heavy chain which is not present in normal smooth muscle cells in normal vessels.[42] Recent studies have shown that restenosis is more frequent in those patients whose native atherosclerotic plaque smooth muscle cells express the B isoform of myosin heavy chain.

It is also well known that thrombus stimulates smooth muscle cell proliferation[43] by several different mechanisms, including production of cytokines and growth factors.[44] The thrombin produced during the generation of the thrombus is a potent smooth muscle cell stimulator,[45] as well as a platelet activator. Thrombin might stimulate endothelial cells to produce PDGF and thus indirectly stimulate smooth muscle cell proliferation.

In conclusion, restenosis is still the main problem after interventional techniques such as PTCA directional coronary atherectomy and even stenting. A deeper knowledge of the intrinsic mechanisms involved in smooth muscle cell proliferation should result in an anti-restenosis strategy, hopefully in the near future.

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2

Coronary angiography for the interventional cardiologist

Michael S Norell

Introduction

The advent of percutaneous coronary intervention has altered the requirements of diagnostic angiography. Whereas the cardiac surgeon needs to appreciate the significance of an obstructive lesion and the quality of the distal vessel, the interventional cardiologist now requires much more information. The exact site of the lesion in relation to the vessel ostium and side branches, as well as lesion characteristics (which themselves have generated a new system of classification) form only part of the data vital to the success of coronary angioplasty. With percutaneous intervention in mind, 'routine' coronary angiography is no longer sufficient. The angiographer must be constantly aware of particular techniques, different catheter types and variable radiographic projections, in order to acquire the maximum information of the highest quality. This chapter describes such techniques in order to aid the coronary angiographer obtain optimal images which can assist the cardiac interventionalist in the planning stages of the procedure.

Basic angiographic technique

In addition to the anatomical findings, other aspects of coronary angiography are also relevant to the interventionist. How well did the patient tolerate the angiographic procedure? Did the patient require premedication and was there evidence of a hypersensitive contrast reaction? The French size and shape of the diagnostic catheter used may also give important clues in terms of subsequent intervention. Thus a dilated aortic root requiring a left 5 Judkins diagnostic catheter is likely to require a sizeable guiding catheter during subsequent percutaneous intervention.

There is a tendency to use small calibre catheters for diagnostic angiography with some centres using 4 French catheters routinely. Although these catheters have advantages in terms of femoral arterial haemostasis and subsequent patient ambulation, they may have drawbacks in terms of the quality of diagnostic images obtained. Unless engaged well in the coronary ostium, hand injection of contrast through 4 French catheters can often produce significant recoil resulting in poor vessel opacification.

Significantly it is also possible for small calibre catheters to engage the coronary artery beyond a significant aorta-ostial stenosis. Both right and left main ostial lesions may be overlooked with this approach. The distal anatomy may appear suitable for percutaneous intervention but it is only when a larger (6 French or more) guiding catheter is introduced that ostial disease is then apparent, perhaps making this approach inappropriate.

Localized coronary arterial spasm, particularly at the tip of the diagnostic catheter, is not uncommon and is often seen during right coronary artery contrast injection. It is important to establish whether such appearances indicate genuine fixed obstructive disease or simply changes in vasomotor tone. Selective intra-coronary nitrate administration usually resolves this question as illustrated in Fig. 2.1.

Collateral filling

The degree, if any, of either late anterograde or retrograde filling of the distal vessel is of significant value in diagnostic angiography. It is usually associated with high-grade proximal obstruction, but is particularly important in what would appear to be a total coronary occlusion.

The ability to percutaneously recanalize chronic total occlusions depends heavily on the characteristics of the occluded segment and whether or not there is any (even faint) anterograde flow through the lesion. The extent of retrograde filling

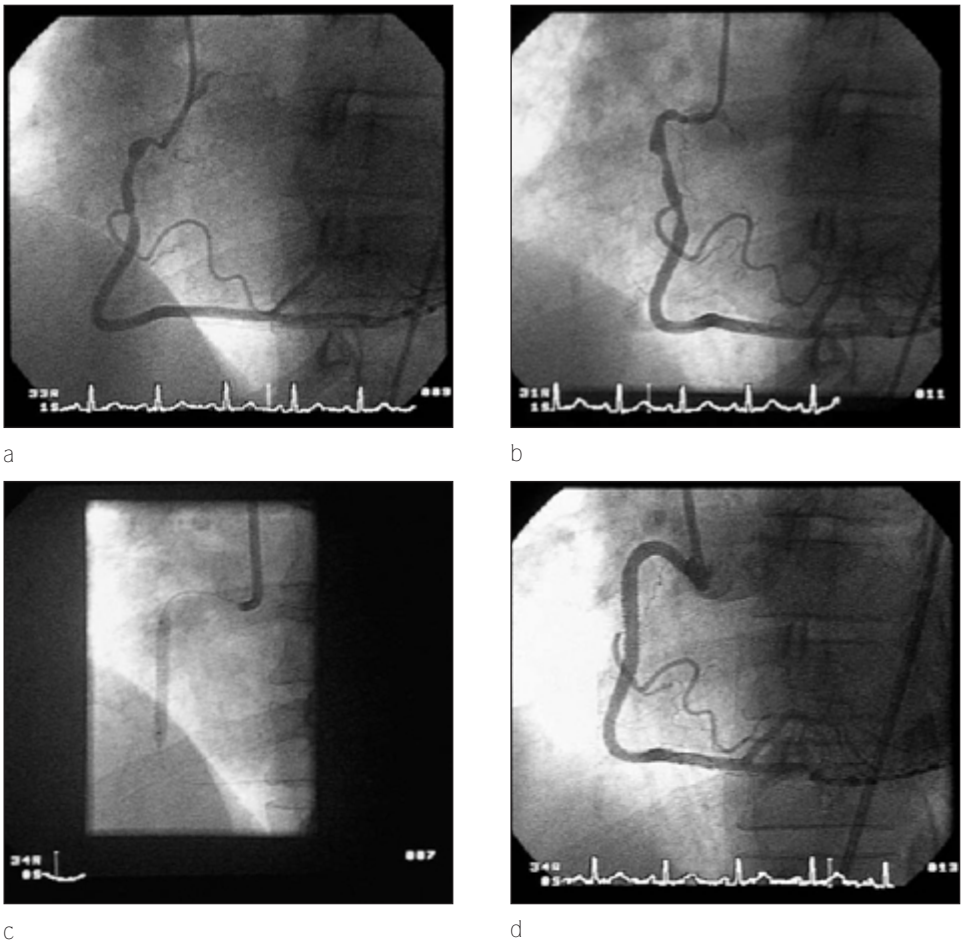


Figure 2.1
LAO projection of spasm seen in the proximal RCA in a patient with disease suitable for PCI in the mid-segment (a). Following intracoronary nitrate injection (b) the calibre of the entire artery increases and the proximal obstruction is shown to be reversible. A good result is obtained following PTCA and stenting to the mid-RCA segment (c and d). (Acknowledgement: Dr ED Grech).

beyond a chronic occlusion is also of value and if sufficiently extensive, filling back to the point of occlusion, can give guidance to the operator in terms of the direction that his recanalizing guidewire needs to take in order to traverse the occlusion.

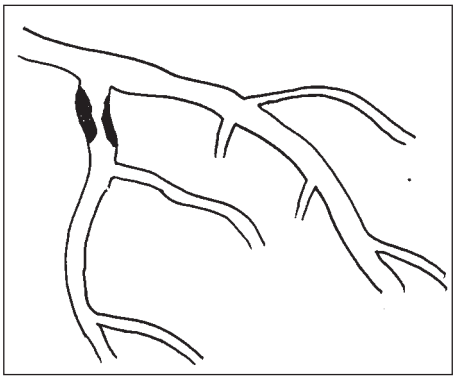
Late opacification of distal vessels, if bidirectional, gives an indication of some degree of anterograde flow through obstructive lesions. Following angioplasty, absence of collateralization has been considered a good indicator of successful lesion dilatation. For these reasons, during diagnostic image acquisition, it is important to continue runs long enough to allow late anterograde, or retrograde, filling of vessels to occur.

Vessel calibre

Most operators tend to eyeball a diagnostic angiogram and thereby estimate the reference diameter related to obstructive lesions. This is done almost subconsciously by relating the opacified vessels to the diagnostic catheter which is of known dimension. It is useful therefore to indicate the French size of diagnostic catheter used and whether any intracoronary nitrate was given. Most angiographic centres now have online QCA, which enables the vessel diameter to be accurately determined at the time of diagnostic angiography. Frequently, however, this technology is not employed until the time of coronary intervention.

Vessel calcification

With the availability of increasingly sophisticated X-ray equipment, fluoroscopic evidence of vessel calcification is now more obvious than with previous systems. The significance of vessel calcification should not be underestimated and, if associated with tortuous anatomy, can frequently present significant obstruction in terms of the passage of a balloon or stent. Evidence of calcification in association with coronary obstruction should always cause the operator to pause before considering percutaneous intervention. Intravascular ultrasound would undoubtedly provide more information about vessel calcification, but even in centres that have such technology available it is rarely used routinely. Similarly, although rotational atherectomy might be valuable in such calcified disease, most centres do not use this device either. Thus consideration should be given before approaching a significantly calcified stenosis with a balloon and stent alone, as the results of lesion expansion in this setting can be unpredictable.



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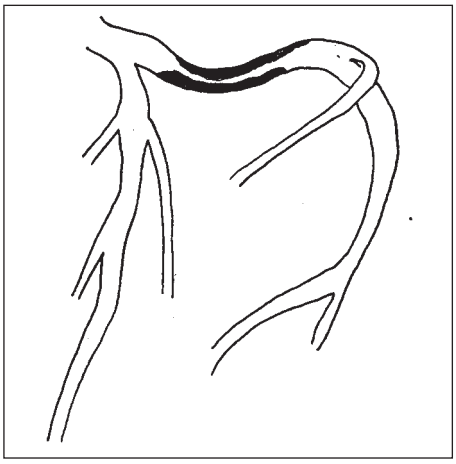
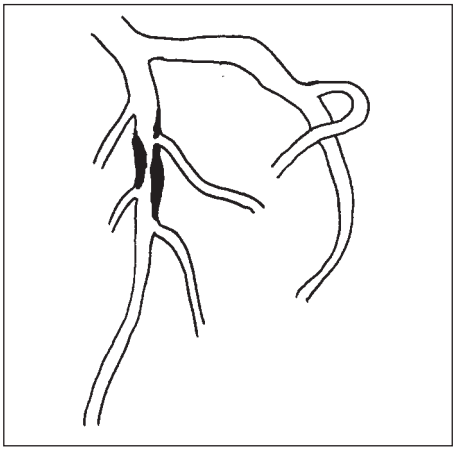


b

Figure 2.2
Illustration of proximal disease in the circumflex artery seen from an RAO projection (a). When viewed from an LAO projection with cranial angulation (b), it becomes apparent that the proximal vessel may be more tortuous, and the diseased segment is longer than it appeared initially.



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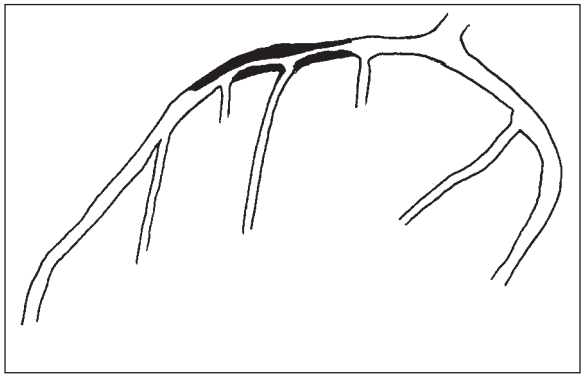


b

Figure 2.3
Disease in the mid-LAD seen from an LAO/cranial projection (a). This view foreshortens the vessel and the true length of disease is easier to appreciate using the left lateral projection (b).

Lesion length

It is important to be aware of the foreshortening effects associated with certain vessel segments viewed from specific projections. These problems are well recognized in, for instance, the proximal circumflex in the RAO view (Fig. 2.2a–b), and the proximal and mid-LAD seen in the LAO/cranial projection (Fig. 2.3a–b). Analysis of these and other areas from orthogonal projections is the only sure way to assess true lesion length and therefore its suitability for percutaneous intervention.

Lesion eccentricity

Multiple radiographic projections are carried out in order to identify the presence of lesion eccentricity. In the prestent era, such a finding would significantly influence the outcome of angioplasty, and even now the approach to an eccentric lesion (perhaps with direct stenting) may differ from that with a concentric obstruction. Although eccentric disease may be suspected by the appearance of reduced contrast density in the affected segment, it is only by close examination of this site from different projections that this lesion characteristic can be defined.

Left ventricular angiography

This aspect of diagnostic angiography does not convey much information for the coronary interventionist. However it can be useful, particularly in terms of regional wall motion abnormalities. Thus it might be anticipated that percutaneous recanalization of a chronically occluded artery supplying a well-contracting segment of myocardium would be more likely to produce symptomatic relief than if left ventriculography suggested extensive akinesis. This does not detract from the merits of revascularization to improve myocardial 'hibernation', but nevertheless does give some practical guidance.

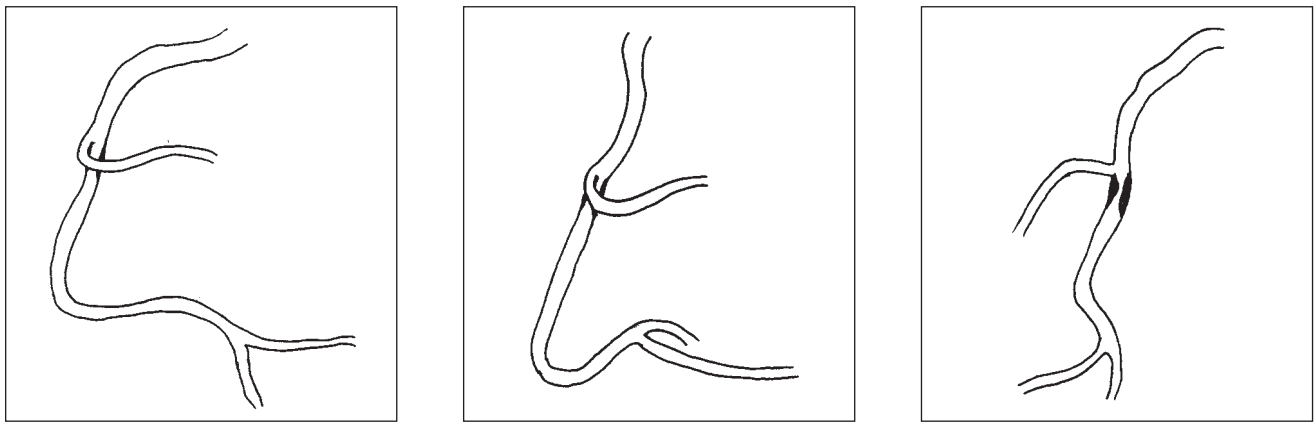
Similarly, the extent to which an operator feels that complete percutaneous revascularization is required may also depend on whether or not there is regional wall motion abnormality. In the setting of multivessel intervention, an operator may feel it unnecessary to attempt to re-open a chronically occluded vessel, if it appears to supply an akinetic territory.

The right coronary artery

As mentioned above, small calibre diagnostic catheters can miss ostial disease. This should be suspected if there is pressure damping in which case extubation of the guiding catheter to allow a sinus contrast injection can often demonstrate the obstruction. Left and right anterior oblique projections are usually sufficient to delineate the right coronary anatomy, but additional views are often helpful in some circumstances. The left lateral projection may uncover obstruction hidden by a right ventricular branch (Fig. 2.4a–c). Disease at the right heart border may be obscured by the patient's diaphragm and thus deep inspiration may be necessary to visualize this segment adequately.

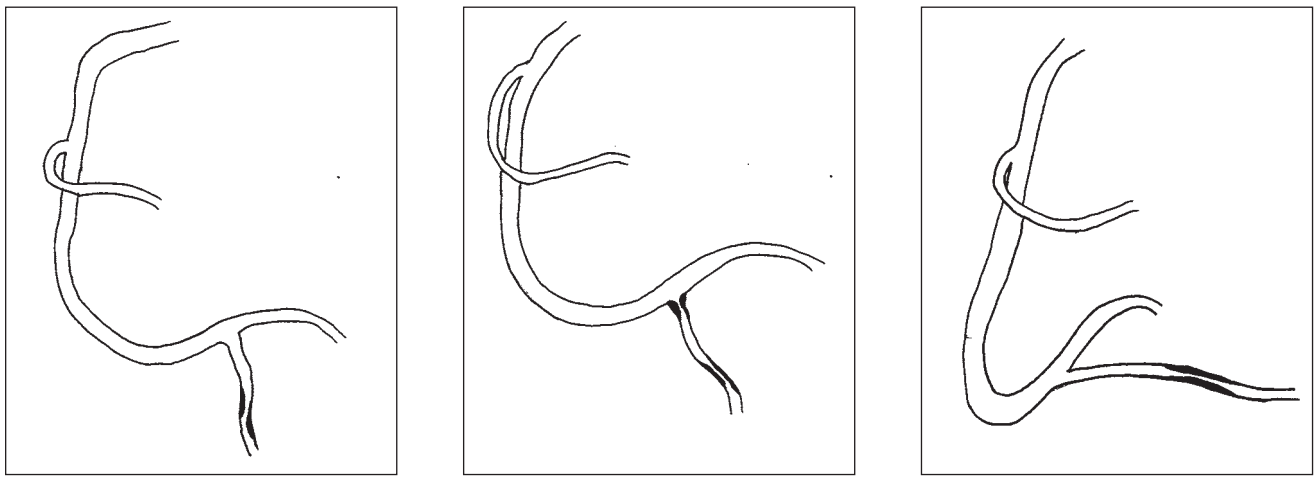
A particular site that is frequently overlooked is the origin of the posterior descending branch which may not be well seen unless images are taken with left caudo-cranial angulation (Fig. 2.5a and Fig. 2.5b). Disease in this branch itself is better appreciated either in this view or in the RAO view (Fig. 2.5c).

In large or very dominant right coronary arteries the vascular territory beyond the posterior descending origin may be



a b c

Figure 2.4
Localized disease in the mid-segment of the RCA. This is not seen well from either LAO (a) or RAO (b) views. It is best visualized from a left lateral projection (c).



a b c

Figure 2.5
Disease at the ostium of the PDA may be obscured in the LAO view (a) due to foreshortening, which may also underestimate the extent of obstruction within the PDA itself. An LAO view with cranial angulation exposes the PDA ostium (b), while the RAO projection accurately assesses mid-PDA disease (c).

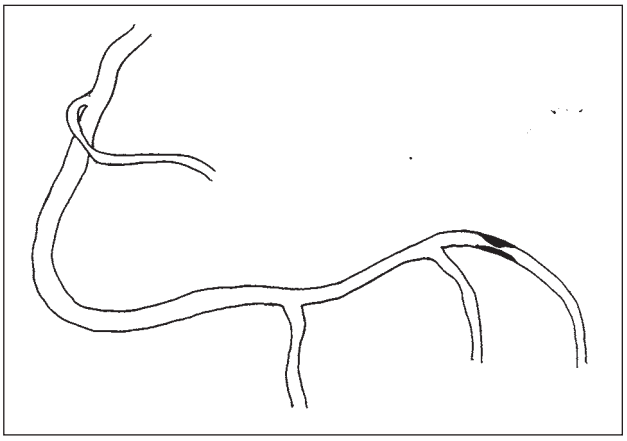


Figure 2.6
It is important not to miss treatable disease in the distal portion of a very dominant RCA seen here from the LAO projection.

extensive and may also contain significant obstruction jeopardizing inferior left ventricular branches. Although this disease is distal it may still be of sufficient calibre to justify percutaneous intervention (Fig. 2.6).

The angle of the diagnostic catheter to the right coronary ostium should be noted, as frequently this may be up to 90° or so. If this is the case, then during an interventional procedure the catheter may need to be rotated clockwise in order to allow more coaxial engagement and therefore offer better guide catheter support. As is often the case with coronary angiography, what may appear to be a relatively smooth curve on one projection may actually turn out to be a markedly tortuous course on another (Fig. 2.7a–b).

The left coronary artery

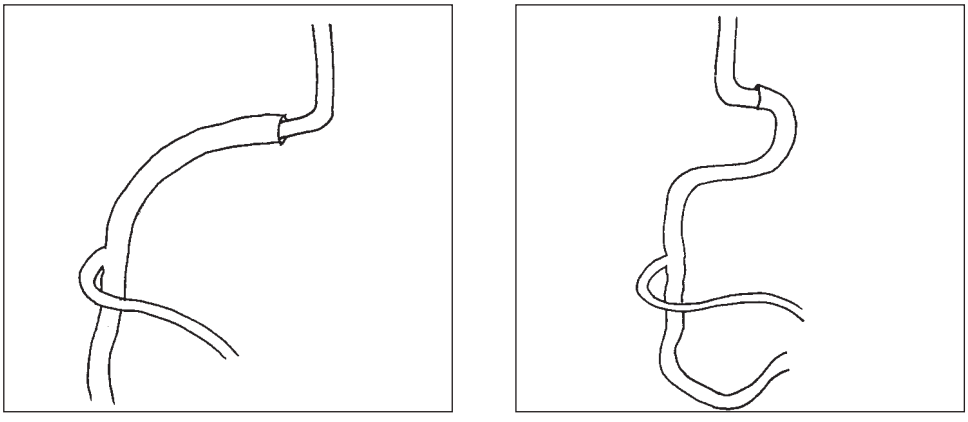
As with the right coronary artery, ostial left main stem disease should be suspected if there is damping of catheter tip pressure, in which case a sinus injection is valuable. Obstructive disease confined to the mid segment of the left main stem is not usual, but when present is usually easily appreciated. Distal left main stem disease, however, may be missed unless care is taken to view that site from a number of projections to avoid either the proximal LAD or circumflex overlying the area of interest. It may be necessary to 'experiment' with multiple views, perhaps with only slight changes in angulation, with or without deep inspiration, in order to be sure of the anatomy in the distal left main stem. The so-called 'spider view' (left anterior-oblique with caudal angulation) and a straight postero-anterior view can sometimes show the left main bifurcation best (see Fig. 2.9 later).

The circumflex coronary artery

Disease in the circumflex ostium may be difficult to identify and as mentioned above, the spider view can demonstrate this. Obstruction within the main circumflex trunk may not be appreciated on right anterior oblique views, and a more orthogonal projection is achieved with a left anterior oblique view, particularly with cranial angulation. Not only can this reveal obstructive disease, but it may also unmask significant tortuosity in the proximal circumflex system that may not otherwise be apparent (Fig. 2.2a–b).

The obtuse marginal circumflex branches are well seen in the right anterior oblique projection particularly with caudal angulation, but their origins may be difficult to visualize using 'standard' left coronary views. Right anterior oblique with cranial angulation may uncover ostial disease in an obtuse marginal circumflex branch. However, as is often the case, it may simply be a question of trial and error in terms of experimenting with variable degrees of angulation (Fig. 2.8a–b).

In a dominant circumflex system, inferior left ventricular branches or a posterior descending branch may not be visualized without using an LAO projection with cranial angulation (as with the right coronary artery previously described (Fig. 2.5a–c)).



a b

Figure 2.7
Viewing the proximal RCA from the LAO projection (a) can frequently fail to demonstrate the true tortuosity of this segment, or the angle of engagement with the Judkins catheter (b).

a b

Figure 2.8
The ostium of marginal circumflex branches may not be apparent from routine RAO views (a). The employment of steep cranial angulation can sometimes demonstrate localized disease here (b).

The left anterior descending coronary artery

Ostial LAD disease is important to identify and yet can be difficult to document. Multiple X-ray projections may be required and, as with ostial circumflex disease, a left anterior oblique projection with caudal angulation can frequently provide the necessary evidence.

Obstructive disease in the proximal LAD may also only be apparent on selected views. Its distance from the ostium and its relationship to any septal or diagonal branches can be of major importance. A left lateral projection may be helpful, but in this situation as in others involving most of the LAD, a left-anterior oblique view with cranial angulation is of great value. It is important to have sufficient leftward angulation to avoid the LAD overlying the vertebral column, as well as enough cranial angle to 'look down' onto the LAD and minimize the inevitable degree of foreshortening that is associated with this view (Fig. 2.3a–b).

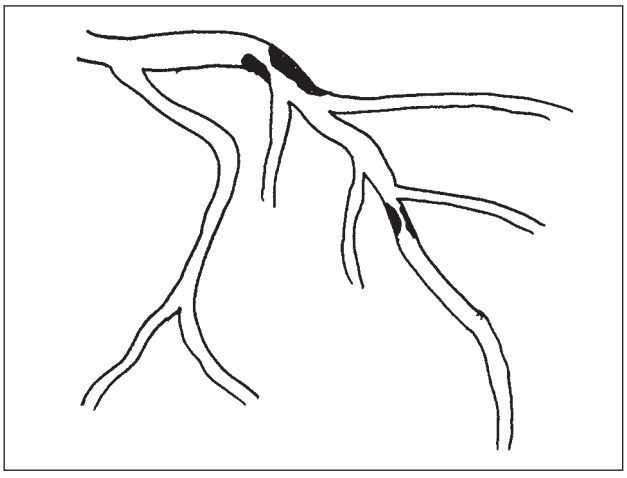


Figure 2.9
Disease in the proximal and mid-LAD is sometimes best appreciated from a shallow RAO projection with steep cranial angulation.

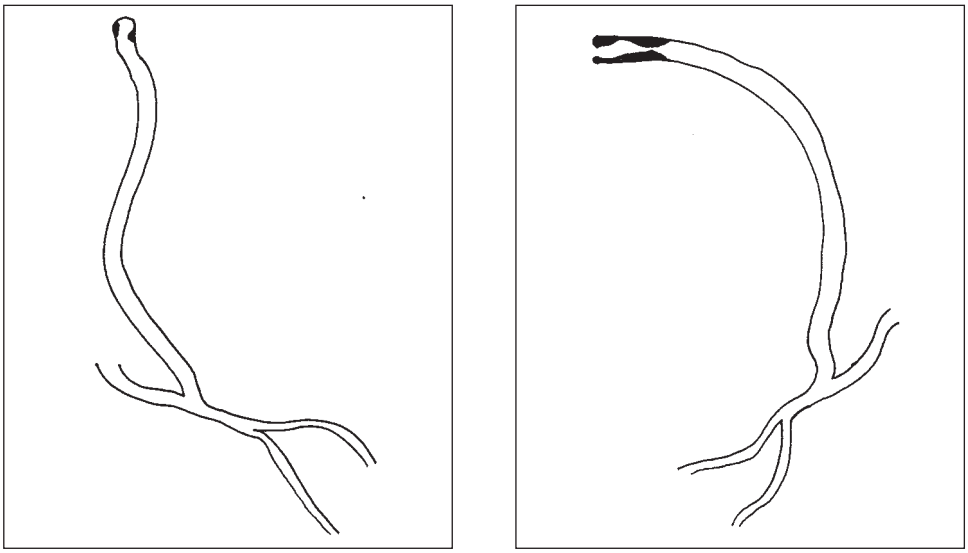
It can sometimes be surprisingly difficult to discriminate between septal and diagonal branches, yet it is clearly important in the planning of any future intervention. Usually a combination of left lateral, LAO with cranial angulation and RAO with caudal angulation resolves any problem. In addition, however, a shallow RAO projection with steep cranial angulation is often very useful in detailing the mid LAD and particularly the position of lesions here with respect to diagonal or septal origins (Fig. 2.9).

Coronary bypass grafts

An increasing proportion of patients undergoing diagnostic angiography are those who have undergone previous CABG and may be candidates for percutaneous intervention. It is insufficient simply to ascertain the patency (or otherwise) of these grafts, and their run-off; attention must be paid to proximal and distal anastomoses as well as to the body of the graft in question.

Proximal disease in the left internal mammary artery (LIMA) is unusual, but may be present as a manifestation of aorta-subclavian disease. The main body of a LIMA graft may be excessively tortuous, which itself may provide a challenge to the interventional cardiologist. Rarely, if ever, is the course of the LIMA obstructed along its length, but this can occur as a result of injudicious positioning of a sternal wire during closure of the chest at the time of surgery. Selective opacification of a LIMA graft is essential as non-selective contrast injection into the left subclavian artery rarely provides sufficient contrast flow to give adequate information about its distal anastomosis and the LAD beyond. The distal anastomosis is the commonest site at which significant obstruction occurs and this needs to be viewed from a number of projections in order to be certain of the anatomy.

Selective opacification of saphenous vein grafts is similarly important. Unlike the LIMA, their proximal (aortic) anastomosis may be diseased such that guide catheter engagement



a b

Figure 2.10
The proximal anastomosis of a circumflex vein graft is not well seen from the RAO view (a). The LAO projection can clearly identify obstruction here (b).

may be problematical. It is important to find a radiographic projection that adequately profiles this segment in order to be certain that any lesion here is just proximal or truly ostial in location (Fig. 2.10a–b).

Obstruction can develop at any point throughout the body of a vein graft and thus these conduits need to be imaged down their entire course, from multiple views, ensuring that any sternal wires do not overlie particular segments of interest. The distal anastomosis and run-off from these grafts must also be visualized. Stenting disease in the body of a vein graft may only be appropriate if the distal circulation is sufficient to maintain brisk, antegrade flow down the graft and thus increase the chance of long-term stent patency.

Summary

Diagnostic coronary angiography is a dynamic process that requires thinking on one's feet. The procedure must take into account the needs of the interventionist in terms of the lesion characteristics, its position in the target vessel and its relationship to side branches. Failure to provide these data may result in a more complicated angioplasty procedure than was initially anticipated, or a patient being referred for bypass surgery when a percutaneous procedure could have been feasible. There are no strict rules to indicate which radiographic projections should be used for specific vessels; a good angiographer should know when to adjust projection angles, or experiment with other views in order to get the maximum amount of anatomical information.

3

Radiation protection, image archiving and communication systems

Anthony A Nicholson

Radiation protection

The health risks associated with prolonged fluoroscopic imaging during interventional cardiology procedures are very real and should not be ignored. Both the patient, the operator and his assistants are at risk. Monitoring bodies in Europe and the USA have received numerous reports of serious radiation-induced skin injuries resulting from prolonged fluoroscopic imaging during interventional therapeutic procedures[1] (Fig. 3.1). These procedures mainly involve (although are not exclusive to) coronary angioplasty and radiofrequency cardiac catheter ablation. In many of the reports, the physicians performing the procedures have been unaware that radiation doses exceeded the expected threshold for injury, or were unaware of the intensity of the fluoroscopic beam.[2] It is very important to note that the onset of these injuries is usually delayed up to 2 weeks, so that the physician cannot discern the damage by observing the patient immediately after treatment. The radiation dose required to cause skin injury depends on a number of factors, including the type of injury, the area of skin exposed, the age of the patient (and other patient-specific characteristics) as well as the circumstances of the exposure. In addition to these acute effects, very large doses can lead to an increased risk of delayed effects such as malignancy.

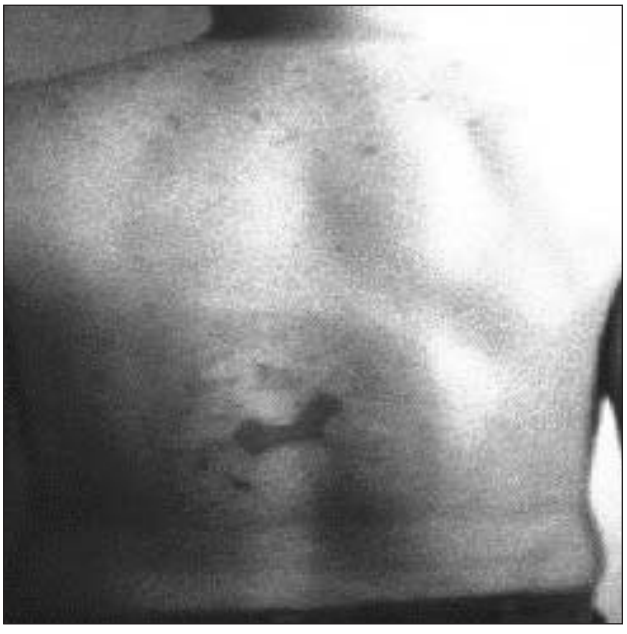


Figure 3.1
Radiation burns on a patient's back 6 weeks after PTCA.

Although there is no hard evidence at the present time that staff performing X-ray guided therapeutic procedures are more prone to developing cancers than the ordinary population, individual cases of radiation-induced osteonecrosis, cataracts and aplastic anaemia are well recorded. Knowledge of the principles of radiation protection and of the doses received by patients undergoing interventional cardiological procedures is therefore very important.[1] Indeed, it is now a legal requirement in Europe.

Radiation units

The Grey (Gy) is the SI system for the measurement of radiation dose. It is defined as the quantity of radiation which results in an energy deposition of 1 joule per kilogram ($1\ J\ kg^{-1}$).

Ionizing radiation can be caused by alpha, gamma and X-rays. All of these cause different rates of energy deposition within the cell, and the Sievert (Sv) is the unit of dose equivalent which takes this into account. For medical radiation protection purposes, units of radiation are usually very small and measured in mGy, mSv, μGy or μSv.

Risk estimates

The level of radiation required to produce acute effects is largely related to the dose and is thus deterministic or non-stochastic. It can therefore be accurately measured and typically threshold doses of 3 Gy produce temporary epilation, 6 Gy will produce erythema and 15–20 Gy desquamative dermal necrosis and ulceration.[2] The absorbed dose rate in the skin from a direct beam of a fluoroscopic X-ray system is typically between 0.02 Gy and 0.05 Gy per minute, but may be higher depending on the mode in which the equipment is operated and the size of the patient. Typical dose rates can result in skin injury in less than one hour of fluoroscopy.

The evaluation of chronic effects is more difficult because the effects are of a random statistical nature and the severity is unrelated to the dose. Such effects are therefore non-deterministic or stochastic. Much of the data on induced cancers come from atom bomb casualties,[3] and for radiation protection purposes these data have to be extrapolated to the lower dose levels used in fluoroscopy. These levels have to be compared with annual doses received from natural background radiation, which in Europe is approximately 2.5 mSv per year. The estimated incidence of cancers and genetic defects for this dose of radiation per 10,000 patients is shown in Table 3.1.[4]

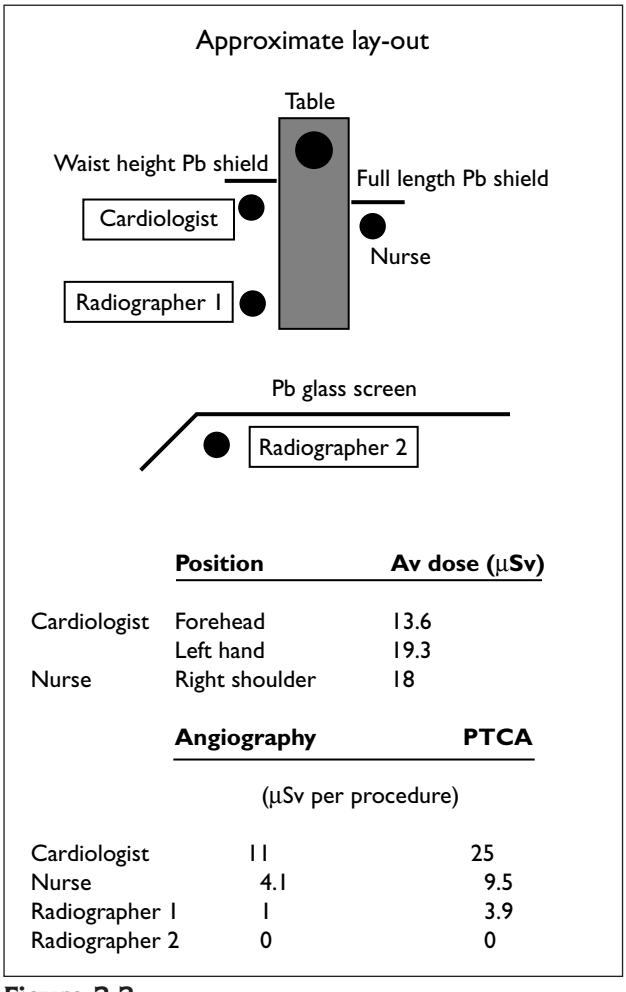
Fundamentals of radiation protection

New regulations on the medical use of ionizing radiation were adopted by the European Union Council on 30 June 1997. They passed into law in the United Kingdom in 1999 (Ionizing Radiation Medical Exposures Regulations 1999). They define certain responsibilities of all those involved where a patient receives a radiation dose, including advice about keeping exposures as low as practicable, equipment quality, maintenance and quality assurance. It also states that all exposures should 'show a significant net benefit when the total potential diagnostic or therapeutic benefits it produces, including the direct health benefits to an individual and the benefits to society, are set against the individual determent that the exposure might cause, taking into account the efficacy, benefits and risks of available alternative techniques having the same objective but involving no or less exposure to ionizing radiation'. Put simply, it is a criminal offence to expose a patient unjustifiably to ionizing radiation. This applies not only to doctors but also to all allied health workers who are involved with ionizing radiation.

In order to decrease the absorbed dose to the patient and the staff the radiation protection principles of time, distance and shielding have to be adhered to. Dose is directly related to time, so half the time leads to half the dose. Only essential staff should be in the catheter lab. Figure 3.2 illustrates typical

Table 3.1 Stochastic and non-stochastic effects of radiation dose and their incidence.

Stochastic effects	*Incidence × 10^{-4}*
Breast cancer	100
Leukaemia	20
Lung cancer	20
Thyroid cancer	100
Osteosarcoma	5
Skin cancer	100
Other	50
Total cancers	395
Genetic (non-stochastic effects)	
Intra-uterine exposure	200
Fetal malformations, weeks 8–15	4000
Fetal childhood tumours	230



	Position	Av dose (μSv)
Cardiologist	Forehead	13.6
	Left hand	19.3
Nurse	Right shoulder	18

	Angiography	PTCA
	(μSv per procedure)	
Cardiologist	11	25
Nurse	4.1	9.5
Radiographer 1	1	3.9
Radiographer 2	0	0

Figure 3.2
Average radiation dose received by a laboratory team during coronary angiography and PTCA.

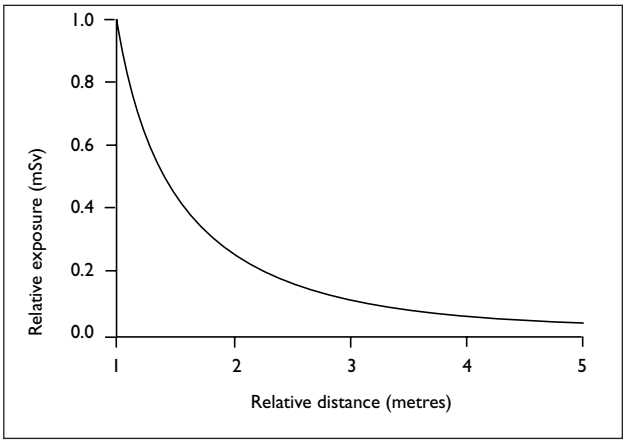


Figure 3.3
Reduction of radiation intensity according to the inverse square law.

doses received during diagnostic and therapeutic cardiac procedures. It also illustrates the inverse square law in which the intensity of radiation dose decreases as the square of the distance between the source and the operator. In other words, for each step back from the source there is a 4-fold decrease in radiation dose (Fig. 3.3).

Even with protective lead shielding placed close to the primary beam the dose to the operator is not inconsiderable and varies at different body sites. The aim of lead coats is to protect sensitive parts of the body, the bone marrow being most sensitive. The dose received by the operators is generally not from the direct beam but scattered radiation from the patient. The attenuation or loss of intensity of the X-ray beam as it passes through matter is exponential (Fig. 3.4). Therefore small amounts of shielding of appropriate density can greatly reduce the intensity of the X-ray beam. 0.5 mm of lead, which is the standard thickness of lead in a lead coat, can reduce the intensity of the beam by 90%.

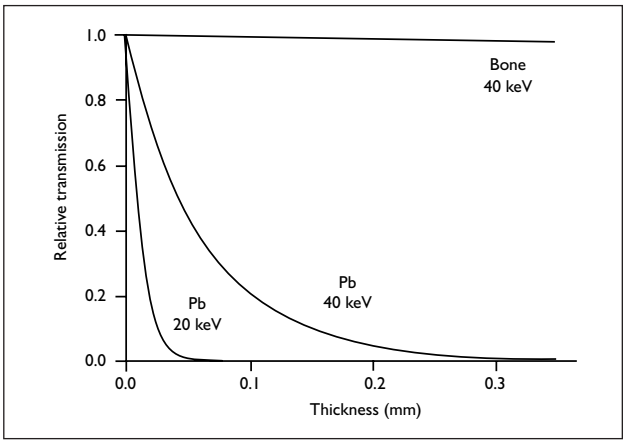


Figure 3.4
Absorption/transmission of X-rays by different thicknesses of lead and bone at different energies (keV: kilo electron volts).

Patient and staff protection

Both patient and staff protection depend on three further principles.

(1) **Justification.** The clinician requesting or clinically directing a particular examination requiring X-rays must carefully consider the need for the examination and treatment in terms of the relative risk and benefit of the procedure. The operator should be in no doubt that angiography is necessary. A negative stress test requires a reappraisal of diagnosis rather than a coronary angiogram. At the time of writing, coronary angiography is the only imaging modality that provides accurate images of the coronary arteries. However, in the very near future, magnetic resonance imaging will almost certainly provide these data and will become a non-invasive, non-ionizing investigation of choice. Angiographic data should be of sufficiently high quality to give adequate diagnostic information. However, this need not necessarily be the best possible imaging quality if the patient is not to be unnecessarily irradiated. For example, pulsed fluoroscopy should be set to the lowest radiation dose that provides accurate information.

(2) **ALARP (As Low as Readily Practicable).** The type of examination and imaging modality should be selected so as to minimize the dose to the patient. Radiographic equipment should be selected and maintained to be as dose efficient as possible. There should be a system of quality assurance and planned replacement of outdated equipment. Screening time should be limited and views restricted.

(3) **Dose limits.** Operators should be fully aware of the dose limits for ionizing radiation and should limit examinations and treatment accordingly. Strict dose limits apply to staff. There is, however, a requirement to record sufficient information so that an estimate of dose can subsequently be made. This can then be checked against the reference dose levels based on the upper quartile of national patient dose surveys.

Staff protection

Figure 3.5 shows the results of a survey carried out in the USA in 1992 on personal protection practice amongst a group of angiographers. It is clear that while the use of thyroid shields, lead glasses, screens and gloves can reduce dose considerably to sensitive areas, they are rejected by the majority of operators. Factors which may contribute to this include discomfort and impracticality. However, the concern about the absorbed dose to the fluoroscopist's eye, which can cause cataracts, is reflected in equal concern about the thyroid and hands. About 6 Gy of diagnostic irradiation over several weeks will produce a cataract in the human eye.

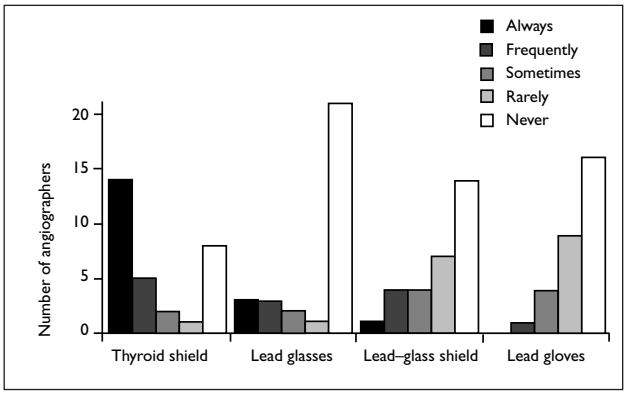


Figure 3.5
Survey of personal radiation protection practice in a group of angiographers.

Improvements in design and materials make it imperative that such protection should be persisted with by all interventional cardiologists.

Patient protection

Table 3.2 illustrates the radiation dose that patients receive with different imaging modalities and field size. Note that modern digital imaging can cause higher doses than cine imaging. However, the other advantages of digital imaging outweigh this potential disadvantage. Digital screening provides a relatively small dose compared to digital acquisition. It is therefore wise to acquire images only when it is necessary to obtain a record or when post acquisition viewing of the recorded image can reduce fluoroscopy times by factors of 10 or 20. Increasing field size from 14 inch to 6 inch more than trebles the entrance dose.

Table 3.2 Typical entrance surface doses (ESD).

Examination/projection	*ESD (mGy)*
Chest X-ray	4.5
Coronary angiography	
cine 25 fps	75 @ 14
	150 @ 10
	300 @ 6
digital 12.5 fps	225 @ 14
	525 @ 10
	750 @ 6
Fluoroscopy / minute	11.1 @ 14
	19.5 @ 10
	33.9 @ 6

Cine or digital cardiac angiography?

Patient exposure during conventional cine angiography is relatively high (Table 3.2). Good image quality in each cine frame requires an input exposure at the image intensifier of about 0.2 μGy at 6 inch field size. With the sensitivity of modern image intensifiers, it would be possible to use a lower exposure but the quantum noise would be unacceptably high.

The exposure level of the beam at the entrance field on the patient's body is much higher as most of the radiation energy is absorbed in the body and only a very small portion of the beam exits the body and reaches the image intensifier. A typical attenuation factor would be around ×600. At that attenuation the typical entrance exposure for a patient would be 600 × 0.2 μGy = 120 μGy per cine frame.

The same arguments and values apply to filmless digital acquisition. This would suggest that there is no dose advantage in digital acquisition. However, because digital imaging allows the frame rate to be drastically reduced without compromising the study quality, there is in fact a huge advantage. The standard cine film rate was 50–60 frames per second. With techniques like digital gap filling and sequential scanning, the frame rate can be reduced to 12.5–15 frames per second with a consequent ×4 reduction in dose to the patient.

Pulsed fluoroscopy

Fluoroscopic imaging is a dynamic process. Single images are not perceived individually. Instead the eye takes the average of the dynamic ranges presented during the eye integration period of about 0.2 seconds. Thus we do not have to worry about the X-ray noise in each image, only the noise presented to the eye during the integration period. Acceptable fluoro image quality can be obtained with a typical input exposure rate at the image intensifier of 0.7 μGy/s for a 6 inch field. Reducing the fluoro frame rate has virtually no influence on the required fluoro dose rate. However, such savings can only really be obtained with slow moving objects. The heart is not one of these. For cardiac imaging the mA has to increase in order to maintain the same 0.7 μGy/s and keep the image sharp. In practice, the kV is also generally higher, giving a harder X-ray beam which is less attenuated by the patient. Instead of the ×600 attenuation seen in cine studies, this is only ×400 for fluoroscopy. Thus the entrance dose would be 400 × 0.7 = 280 μGy/s. Further copper filtration increases beam hardness even more with still further reduction in attenuation.

Thus, there is a trade-off. If the patient entrance dose is kept the same the image is more noise-free. If the dose rate at the image intensifier is kept the same the patient dose can be reduced. Modern cardiovascular equipment allows the dose to the patient to be monitored and recorded as the dose area product (DAP), which is related to the risk of future carcinogenic effects.

Summary

Interventional cardiology demands an increased awareness of the principles of time, distance and shielding as well as clinical judgement. Staff exposures can be reduced by the proper configuration of radiographic equipment and the use of shielding.

Image archiving and communication systems

Digital cardiac imaging (DCI) has only been accepted as a standard since the mid-1990s. For 40 years cine film was the universal standard. This was mainly because the image quality of cine film is excellent. It was also possible to view cine film anywhere, no matter which vendor the film came from or what type of equipment was being used. In addition, a single cardiac angiographic study consists of 2000–3000 images. If this data were stored as a 512 matrix, it would require 500–750 Mbytes of storage. Even when compressed in a loss-less fashion, over 200 Mbytes are required. Ten years ago this was an insurmountable problem. The major disadvantages of cine film as an archiving and storage medium include high cost (£70 per patient), high duplication costs (so that each film is a unique and far too valuable record of the examination), fragility (fogging and damage occur frequently) and because of its bulk, high storage costs.

By the mid-1980s analogue optical disks combined with super VHS tapes began to appear. Images from catheter laboratories were transferred to a recording station where they were recorded on analogue optical disks for permanent archiving and review. For exchange, studies were copied onto super VHS tapes. This innovation led to a 95% reduction in storage space requirements and a considerable saving in employee hours per week.[6] However, the quality of super VHS video tape was suboptimal and, although studies could be reopened from optical disk and digitized, this was time-consuming and the images could not be used for quantitative analysis (Table 3.3). This innovation made it even more obvious that images obtained digitally should remain in the digital format. Thus analogue images were rendered obsolete by digital ones. However, the best technical solution to this was far from clear. Different manufacturers developed different solutions. It was clear that unless all systems could communicate, hospitals would be handicapped by the inability to share data. To sort out this problem the cardiology community turned to their radiological colleagues.

DICOM

The American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA) developed standard protocols for transferring medical images between devices produced by different manufacturers. In 1994, after several earlier attempts, ACR-NEMA produced a document called *Digital Imaging and Communications in Medicine (DICOM)*.[7] This new standard provided network support via transmission support protocol/internet protocol (TCP/IP) and the International Standards Organization Open Systems Interconnection (ISO-OSI) stack. In simple terms, this meant that manufacturers no longer had to support general purpose computer networks but could utilize commercially available, off the shelf networking hardware and software. The way was open for hundreds of devices with different

Table 3.3 Comparison of digital storage media.

	Type	*Price (£/Gbyte)*	*Capacity (Gbytes)*	*Transfer rate (Mbytes/s)*	*Access time (s)*	*Erasability*	*Consumer acceptance*
Compact cassette	Magnetic tape	1	10	15	12	Yes	Low
IBM3490	Magnetic tape	10	0.4	7	28	Yes	Low
12" WORM	Optical disk	45	6	<1	<1	No	Low
$3\frac{1}{2}$" MOD	Optical disk	170	0.23	<1	<1	Yes	Medium
CD-R	Optical disk	1	0.7	<1	<1	No	High

capabilities to be connected to a network and build a common ground to complete the task set by the user. DICOM defines 'service object pairs' (SOP) which describe both the information object to be transferred and the command to be performed. An example would be a command to store a medical image.

Picture archiving and communication systems

Picture archiving and communication systems were given the acronym PACS in the early 1980s.[8] The basic principles were stated at that time but were ahead of the technology, which is only now being developed. PACS hold out the promise of replacing the current manual systems of film, video and paper by an automatic system offering convenience, reliability, speed and space. Recent developments in electronic imaging, optical disk 'jukeboxes', fibre optic computer networks, compact disk technology and computer software have allowed the specifications for PACS to catch up with the long held user requirements. The purpose of PACS is to replace X-ray films, cine and videotape and in so doing provide the following:

- Image acquisition. For cardiology this means angiography, but PACS would also be capable of acquiring chest X-rays and echo images as well as holding the electronic patient record.
- Image display including multidisplay at several sites simultaneously.
- Image transport. This is likely to be via compact discs which will be played either on computers or CD readers through conventional monitors.
- Image archiving, negating the problem of storage and lost/misplaced film.
- Image management including image manipulation. e.g. QCA.

Image archiving

The archiving requirements of PACS are potentially vast. A single catheter lab performing 20 examinations per day will generate 2 Gbytes of new data each day. Given the minimum legal requirement to store conventional examinations for 5 years, even with compression, a PACS system is going to be required to store hundreds of terabytes in its useful lifetime. Keeping such data instantly available is not economic so PACS systems are organized hierarchically. Small amounts of important data that can be accessed quickly are backed up by larger amounts of less important data. The management of such a system is complex, but has to be efficient if PACS is to work.

Types of storage media

Random access memory (RAM)
RAM is the fastest but most expensive storage medium. Accessing a 10 Mbyte image from RAM takes about 0.1 seconds, but sufficient RAM to store that costs £300. It is therefore not suitable for long term storage, but most work stations contain enough RAM for 5–6 images.

Redundant arrays of independent disks (RAID)
RAID utilize several conventional hard magnetic disks working in parallel. They are highly reliable with fast access time. They are relatively cheap at £20 per 10 Mbytes and will recover this amount of information in about 1 second. They are therefore good for short term storage over 5–6 days. Images can be rapidly transferred to workstation RAM for rapid display.

Magneto optical disks (MOD)
These are erasable and therefore rewritable. They are insecure and can be tampered with.

Write once read many (WORM)
WORM disks are optical disks that cannot be erased. They are therefore secure. They are very cheap as a 10 Gbyte disk costs £300 and the cost per Mbyte is therefore 30p. They are, however, slow, taking 30 seconds to read 10 Mbyte images. They are arranged in 'jukeboxes' of 100 disks. Once all the disks are full they are removed and replaced. However, the information stored is a permanent accessible record. These disks are usually at the bottom of the storage hierarchy since they provide large amounts of storage at low cost.

Other storage media
Digital audio tape (DAT) has high storage capacity and high reliability. However, it deteriorates with time. Optical tape has potentially the highest storage capacity and fastest access, but as yet the costs are high. CD-writable, is discussed at length later in this chapter. It is very cheap but has low capacity and is therefore only useful for transporting images for review purposes.

Digital coronary angiography

Modern fluoroscopic images are acquired by allowing X-rays to impinge on a caesium iodide input screen coupled to an image intensifier. This amplifies the light produced on the input screen by accelerating photoelectrons through a potential difference of 20–30 kV. As the input screen is generally

35 cm and the output screen 2.5 cm there is considerable increase in signal but also loss of spatial resolution. It is the gain of a bright image that makes it possible to study moving structures like the heart. The images produced are picked up by a TV camera and the consequent video signal passed through an analogue-digital converter (ADC). The image matrix produced can vary in size but 1024 × 1024 × 8 bits is usually adequate. A frame rate required to monitor the passage of contrast media through the coronary arteries varies but is around 30 frames per second. Such units, producing vast amounts of data, present special problems for PACS. Ten seconds' worth of real time cardiac imaging at 30 frames per second generates 300 Mbytes of image data. To put this in context, this much data is equivalent to abdominal CT scans on 12 patients.

CD-Recordable is a good solution to this problem. It is a spin off of both the DICOM standard and the establishment of the CD-Recordable as a standard exchange medium. CD technology is already a consumer standard in CD digital audio, CD interactive (CDI) and CD ROM. CDs offer several advantages over film:

- They can store raw material permanently, and original data are always available for post processing and analysis.
- They are compact, and require less storage space than film.
- They do not require chemical processing.
- They do not deteriorate with age.
- They facilitate random access.
- They are cheap, costing as little as £1 each.

In addition, like film, CD has become a consumer standard, reducing the risk that it will become obsolete. CD thus meets the basic principles of a digital imaging management system without compromising image quality, diagnostic capability or departmental efficiency, in that:

- it is cost effective;
- it has the ability to perform the basic clinical information functions of review, exchange and archiving;
- it is a standardized format.

CD images are similar to film in that a single patient record can be hand carried to a viewing station for review. Therefore the same work flow pattern can be maintained. DICOM allows the transfer of image data to other areas of the hospital for multiconferencing (Fig. 3.6). The optimal archiving solution performs like the file servers in the PC environment. Thus images from previous studies can be called up and viewed on screen rather than requiring retrieval of disks for each study.

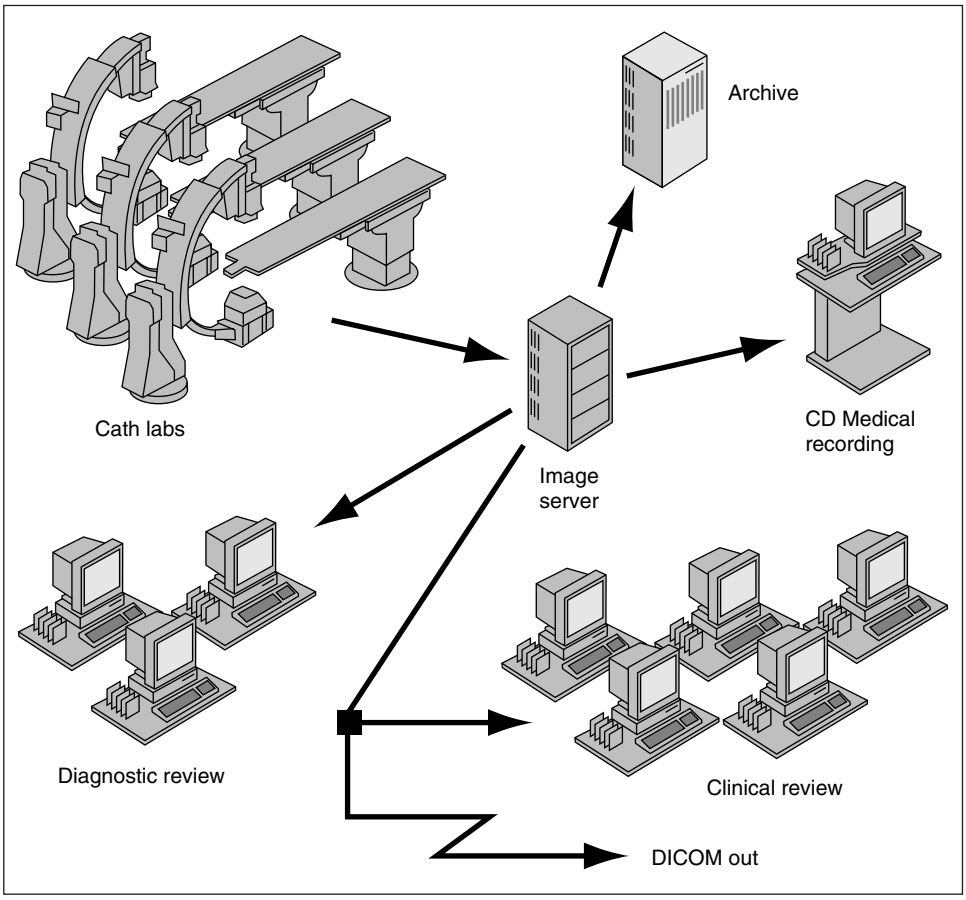


Figure 3.6
CDs can be used in the same way as film, but in addition they can be used for transport or viewing images at several different workstations at the same time. Multiple examinations on one patient or the integration of whole departments is also possible.

Conclusion

PACS has the potential to increase the efficiency of cardiology as a whole and therefore bring benefits to the delivery of patient care and the hospital. Its value lies in convenience, reliability, speed of image retrieval and display and the flexibility of image data use. PACS cannot work in any one department. It has to be installed in the whole hospital. It is no use having digital data stored on optical disks for workstation retrieval and downloading to CD-writable if no one else has the technology to read the images. PACS will not change the outcome for patients, the treatments will be the same. Hopefully, however, it will be delivered more efficiently. It will also decrease the radiation dose to the patient, because:

- digital imaging provides higher detection efficiency;
- there will be fewer retakes, as there is less scope for poor technique;
- there will be fewer repeat examinations as images will not be lost or unavailable.

In the future PACS will allow the real development of telecardiology, when diagnostic medicine will be taken to the patient and the GP so that they can avoid travel. Cardiologists at major centres will be called upon to offer advice about patients in remote facilities. The demand for multimedia presentations involving teleconferencing, telemetry, live presentations, DICOM-encoded medical images, text, graphics and digitized vital signs will shape the future of PACS.

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4

Percutaneous transluminal coronary angioplasty: history, techniques, indications and complications

Brian O'Murchu and Richard K Myler

History

When Andreas Gruentzig[1] performed the first human percutaneous transluminal coronary angioplasty (PTCA) in September 1977, a milestone in the treatment of cardiovascular disease was established. The pioneering and courageous work of Forssmann in 1929 ushered in the era of percutaneous cardiac catheterization when he inserted a catheter into his own right atrium via the left basilic vein in seeking 'a safer approach for intracardiac drug injection'.[2] Cardiac catheters were first used for diagnostic purposes in 1941 by Cournand[3,4] and Richards[5] and were later developed for selective coronary angiography by Sones[6,7] and Judkins.[8] In1964, catheters were used by Dotter for mechanical 'dilation' of stenoses in peripheral arteries.[9–12] While a combination of complications and scepticism continued to roughen the diamond, other workers, notably Zeitler and Schoop in Europe, continued to probe the possibilities contained within the therapeutic envelope.[13–15]

By the mid-1970s, Gruentzig, a pupil of Zeitler, developed a prototype catheter with a dual lumen, which allowed inflation of a distal tip balloon which was made of low-compliance polyvinyl chloride (PVC).[16] Encouraging preliminary results in peripheral arteries spurred Gruentzig to miniaturize this balloon catheter for use in coronary arteries.[17,18] In 1976, coronary angioplasty was successfully performed in canine and post-mortem human coronary arteries.[17,18] In May 1977, the first human coronary angioplasties were performed. During elective multivessel coronary artery bypass grafting, Gruentzig and Myler with Hanna and Turina in San Francisco and Zurich advanced a balloon catheter in a retrograde fashion through the coronary arteriotomy (which would be used for graft insertion) into a proximal stenosis.[19] The balloon addressed the lesion; postoperative angiography showed reduction in the angioplasty-treated stenosis. In September of 1977, Gruentzig, working in Zurich, performed the first non-operative PTCA,[1] soon followed by reports from Gruentzig and his colleagues.[20–22] The era of coronary angioplasty had arrived

In the 18 years following these seminal reports, the utilization of PTCA witnessed a dramatic increase in the number and complexity of lesions for which PTCA was attempted.[23] There were an estimated 350 000 cases in 1995 in the USA, and about 450 000–500 000 patients worldwide. While percutaneous revascularization continues to evolve, numerous randomized and non-randomized trials of PTCA have established its effectiveness in a wide array of acute and chronic ischaemic coronary syndromes.[24–32]

A variety of new interventional devices has been introduced in the past several years. New devices have filled niches in the interventional armamentarium directed at specific lesions in which balloon angioplasty has been wanting. A superb review of the history of invasive and interventional cardiology was published in 1995.[33] (Fig. 4.1).

Technique and technology

Coronary angioplasty is performed either percutaneously through the femoral artery or by a cut-down method (or percutaneously) via the brachial artery. In the first era (1977–80), coronary angioplasty equipment was cumbersome. Guiding catheters had high profiles, with poor memory and torque control. Dilatation catheters also had high profiles and low balloon burst points (5 atm). There were no guidewires. This primitive equipment resulted in a high percentage (25–30%) of unsuccessful though uncomplicated procedures. Technical advances occurred rapidly in the early 1980s with the development of introducer sheaths[34,35] and bonded multilayered guiding catheters with an inner surface of Teflon (to decrease friction), a middle layer of

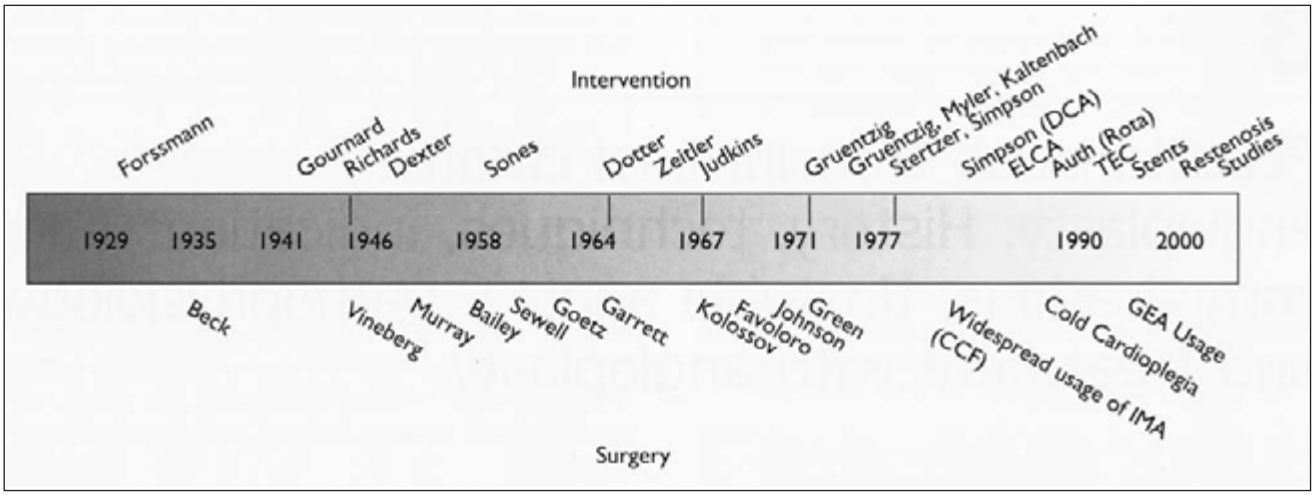

Figure 4.1
History of coronary and peripheral interventional techniques (1929–present) and surgery (1935–present) for coronary artery disease. Abbreviations: CCF, Cleveland Clinic Foundation; DCA, directional coronary atherectomy; ELCA, excimer laser coronary angioplasty; GEA, gastroepiploic artery (graft); IMA, internal mammary artery (graft); Rota, Rotablator™; TEC, thrombus extraction catheter.

woven mesh (for torque control) and an outer layer of polyurethane (to maintain form).[36] Various catheter configurations with softer tips are now widely available for vessels with atypical proximal segments.[37,38] In addition to standard Judkins and Amplatz configurations, many other shapes were developed and are now in wide usage. Recently, newer iterations of guiding catheters have been developed with very thin walls (i.e. large lumens) to accommodate newer devices (e.g. rotational atherectomy burrs, directional atherectomy catheters). The brachial technique was described many years ago[39] and is utilized when the femoral approach is not possible or in certain special circumstances.[40]

The prototype balloon angioplasty catheter, developed by Gruentzig in 1976, had a central lumen to allow perfusion and pressure transduction. In 1979, in an attempt to improve steerability, a short wire was fixed onto the distal tip.[36,37] In 1982, Simpson[41,42] developed a movable long guidewire, which could be advanced through the central lumen. This was a major breakthrough and allowed better directional control and access to distal arterial sites. Contemporary guidewire configurations vary in diameter from 0.009 to 0.018 inch. Guidewires in various configurations and lengths were developed with silicone coating (to decrease friction and improve trackability) and tip deflection.[43]

Balloon catheters also underwent a rapid evolution to the current ultrasophisticated models. Contemporary catheters are of lower profile, have greater trackability and lower cost than earlier versions. Fixed-wire, over-the-wire and monorail systems have come and gone.[44–47] Longer balloons (up to 40 mm), and tapered and perfusion balloons all increased the interventionalist's armamentarium. The advent of balloon manufacture using polyethylene terephthalate (PET) afforded enhanced profile and conformability, and permitted the higher inflation pressures (18–20 atm) necessary for calcified lesions. PET is a material of very low compliance which allows both expansion to nominal size at low pressure and more accurate sizing[48,49] by minimizing 'dog-boning'. This material also allows maximum conformability in angulated lesions.

A discussion of developments in cardiac imaging is beyond the scope of this chapter. However, the importance of special radiographic projections cannot be overemphasized and reflects the demands of the interventional rather than the diagnostic cardiologist.[50] Digital and high-resolution imaging allowing immediate playback and on-line quantitative analysis add to the improvement in success rates. In addition, quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) have enhanced the assessment of lesion severity and composition.

Indications

In the infancy of PTCA, criteria for patient selection were very rigorous: refractory angina and single-vessel atherosclerotic coronary disease with normal or well-preserved left ventricular function in patients who were, otherwise, good candidates for coronary artery bypass grafting (CABG).[23] Ideal PTCA lesions were proximal, discrete, concentric, noncalcific stenoses which did not involve major branches or angulations. However, this initial application of PTCA to low-risk clinical situations steadily widened to include those with more complex clinical and morphologic characteristics.[23]

Currently, PTCA/PCI can be safely and successfully performed in the elderly,[51–54] in post-CABG patients[55,56] (see Chapter 17) and in those with left ventricular dysfunction.[57,58] Mechanical circulatory support[59–64] permits percutaneous revascularization in very high-risk subgroups,

with good success. Many of these patients would otherwise have required high-risk CABG.

While initial patient selection emphasized those with stable clinical syndromes, the procedure gained acceptance in patients with acute ischaemic syndromes including acute myocardial infarction and unstable angina.[65–69] In acute myocardial infarction, PCI now has a therapeutic role which rivals, and in certain patients surpasses that of thrombolytic therapy.[27–29] The role of PCI in unstable angina is discussed in Chapter 13.

The extension of PTCA to lesions with complex morphologies emphasized that lesion characteristics were important predictors of success and complications. This was reflected in a 1988 combined American College of Cardiology/American Heart Association (ACC/AHA) lesion classification,[70] which was revised in 1993.[71] This scheme, and its modification by Ellis,[72] estimated both success and risk for type A, B and C lesions.

However, further evaluation of lesion-specific characteristics has stressed the importance of the type of individual lesion characteristics in predicting the success and complication rates for specific lesions treated with PTCA.[73–76]

In a recent comprehensive study from our centre,[75] coronary angioplasty in 1000 consecutive lesions decorating 764 target vessels in 533 consecutive patients was associated with a procedural (hospital) success of 92.3% and untoward major adverse cardiac events (MACE) in 3% (0.8% myocardial infarction, 1.3% emergency coronary bypass surgery, or both in 0.9%, and no hospital deaths) (Fig. 4.2). The only statistically significant predictor of complications was the presence of intravascular thrombus. Unsuccessful uncomplicated outcome occurred in 4.7%, most commonly associated with old (>3 months) occlusions.

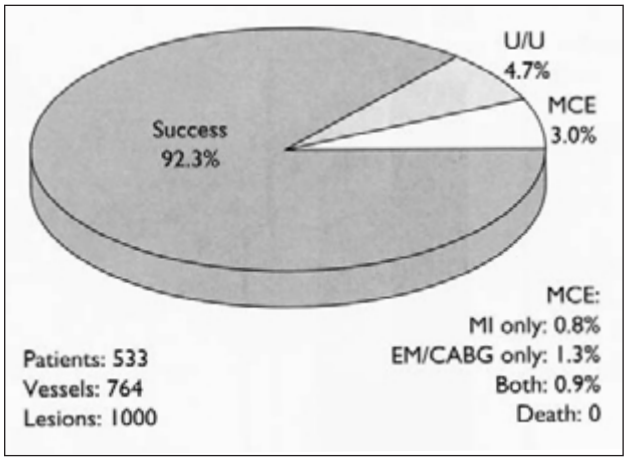

Figure 4.2
Coronary angioplasty procedural results in 533 consecutive patients at SFHI in 1990–1991. Abbreviations: EM/CABG, emergency coronary bypass surgery; MCE, untoward major cardiac events; MI, myocardial infarction; U/U, unsuccessful uncomplicated outcome. Reprint with permission from Myler et al.[75]

In this study and other analyses, high procedural success rates with low complication rates were seen with angulated,[75,77] eccentric, ostial[75] bifurcation,[75,78–81] diffuse[75,82–85] and calcified[75,86,87] lesions.

Our study[75] (Fig. 4.3) and a recent report from the UK[76] showed that success and complication rates in patients undergoing coronary angioplasty were not congruent with the predictions of the ABC lesion-type classification scheme of the 1988 AHA/ACC task force.[70] We concluded that it was

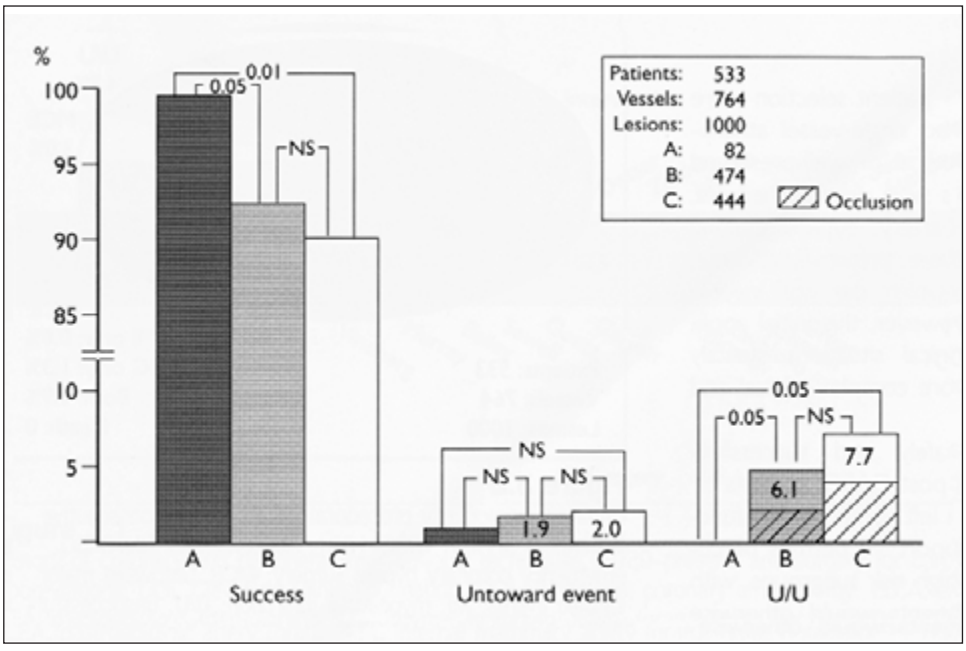

Figure 4.3
Coronary angioplasty outcome versus lesion type in 533 patients. 1990–91 at SFHI. Abbreviation as in Fig. 4.2. Reprinted with permission from Myler et al.[75,123]

far more accurate to specify lesion types vis-à-vis coronary angioplasty outcomes (Figs. 4.4 and 4.5) than to address the lesions in a 'classification' system which groups together a motley array of lesions with heterogeneous morphologic patterns and very dissimilar angioplasty results.

In addition to lesion morphology, coronary angioplasty has been utilized in a variety of clinical presentations discussed above (Table 4.1). Patients with single-vessel disease and stable angina refractory to medical therapy have improved exercise tolerance after PTCA compared to patients treated

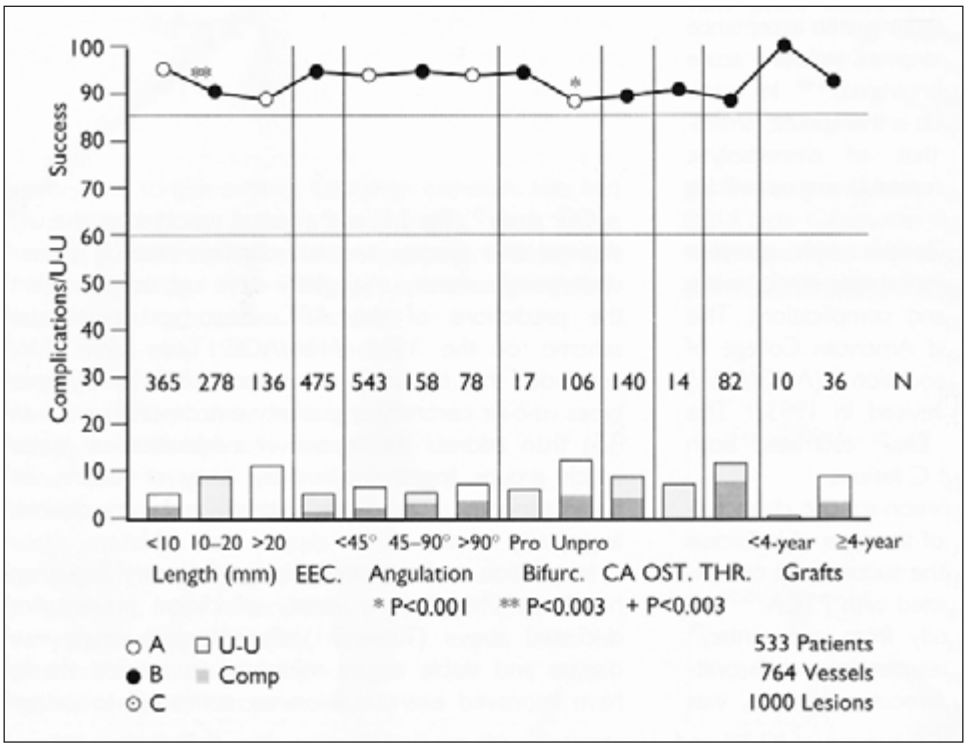

Figure 4.4
Comparison of successes and complications in 533 patients. 1990–91 at SFHI. Lesion-specific analysis versus 1988 ACC/AHA Task Force ABC lesion classification.[70] Abbreviations: BIFURC, bifurcation; CA, calcified; Comp, complication; ECC, eccentric; OST, ostial; PRO, protected; THR, thrombus; UNPRO, unprotected; U-U, unsuccessful uncomplicated. Reprinted with permission from Myler et al.[122]

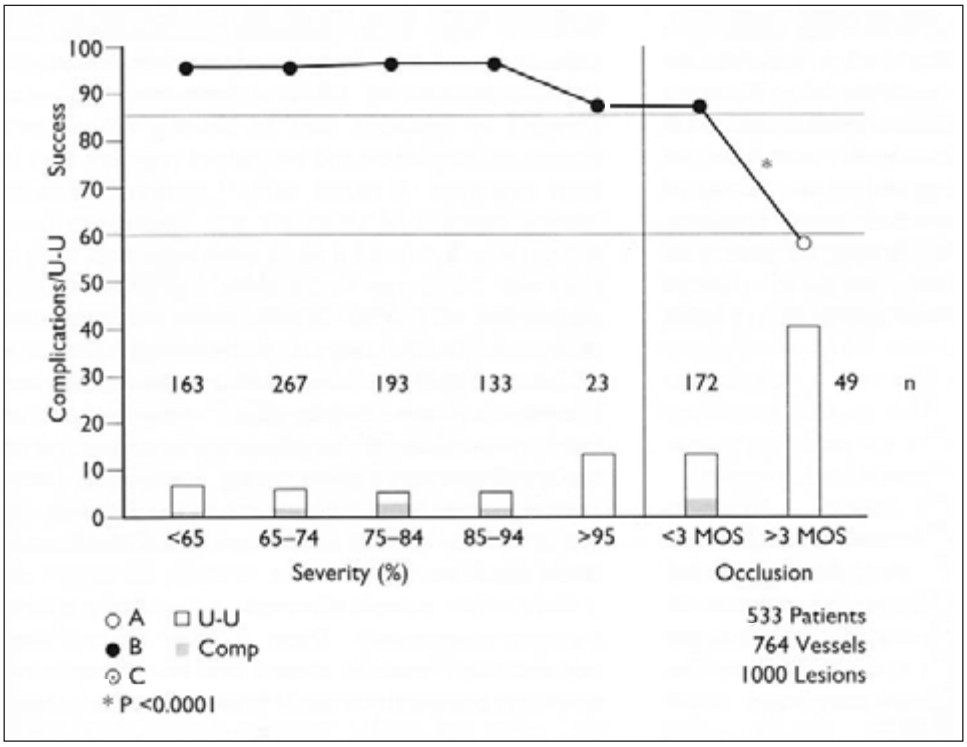

Figure 4.5
Same as in Fig. 4.4. Lesion severity versus angioplasty outcome. Reprinted with permission from Myler et al.[122]

Table 4.1 Coronary angioplasty indications.

Clinical
- Stable and unstable angina
- Acute myocardial infarction
- Depressed left ventricular function
  - (low output, congestive heart failure)
- Elderly
- Post-coronary bypass surgery

Morphologic
- Arteries
  - Single- and multivessel
  - Protected left main
- Grafts
  - Saphenous vein
  - Internal mammary artery
- Lesions
  - Discrete, tandem, long[a]
  - Concentric, eccentric[a]
  - Angulated
  - Bifurcation
  - Subtotal and total occlusions
  - Proximal (including ostial[a])
  - Mid and distal
  - Calcified[a]

[a]Results improved with new device and adjunctive balloon angioplasty.
Reprinted with permission from Myler et al.[122]

Table 4.2 Coronary angioplasty: contraindications, limitations and problems.

Contraindications
- Unprotected left main
- Old degenerated saphenous vein grafts with diffuse friable lesions[a]
- Markedly ectatic arteries

Limitations
- Occlusions
  - Old, long, calcified

Problems
- Flow-limiting disruptions/dissections[a]
- Restenosis[a]

[a]Stents appear to have made inroads in 'solving' these problems.
Reprinted with permission from Myler et al.[122]

with medical therapy alone.[26] Patients with multi-vessel coronary disease, treated with angioplasty or CABG, showed similar early and late survival, incidence of non-fatal myocardial infarction and angina-free status in prospective multicentre randomized trials.[30,31] However, the need for repeat revascularization was substantially higher in the PTCA cohort because of restenosis. In a retrospective 'interrogation' study from our centre[88] in patients with triple-vessel revascularization, PTCA or CABG patients, with nearly identical clinical and morphologic profiles, had similar early and late (5-year) outcomes (survival, non-fatal infarction, angina-free status). The initial cost advantage of PTCA over CABG cohorts was lost at 5 years because of restenosis in the former group. However, because of both shorter hospitalization and out-of-work time, about half the working days, and therefore half the wages, were lost in the PTCA compared to the CABG cohort.

During acute myocardial infarction in selected patients, angioplasty provides clinical benefit equivalent to thrombolytic therapy[27–29] and confers advantage over thrombolytic therapy in certain subgroups, including the elderly, patients with anterior infarcts or those with persistent sinus tachycardia.[27] During acute myocardial infarction complicated by cardiogenic shock, PTCA, with intra-aortic balloon pump haemodynamic support, especially when performed early, has improved survival.[24,25] Clinical outcome and left ventricular ejection fraction with exercise are improved by immediate PTCA compared to medical therapy in patients with acute myocardial infarction who have failed reperfusion with thrombolytic therapy.[32]

Yet, with widening indications, there are still notable contraindications, limitations and problems with PTCA at present (Table 4.2). Contraindications include unprotected left main stenoses and old degenerated saphenous vein grafts with diffuse friable lesions, although endovascular prostheses (stents) may have a role in the latter. Markedly ectatic coronary arteries with stenoses probably should be avoided with interventional techniques. Limitations of PTCA at present include old, long and/or calcified occlusions in which guidewire passage is thwarted. Problems with PTCA currently include flow-limiting disruptions or dissections following the procedure. The use of stents has significantly improved outcome with this complication.

Complications

In light of the available data,[70–72,75,76] there are many clinical and angiographic variables that are useful in predicting the occurrence of the major ischaemic complication of coronary angioplasty, namely acute occlusion of the target vessel during or shortly after (<24 h) the procedure. The frequency with which acute occlusion complicates PTCA has varied among reports.[72,73,75,76,89–95] The second National Heart, Lung and Blood Institute (NHLBI) PTCA Registry (1985–1986) indicated a complication rate of less than 5%.[95] Our own experience in 1990–1991[75] showed a 3.0% complication rate.

Aspirin has an important prophylactic role in prevention of acute thrombotic occlusion[96] and non-Q-wave myocardial infarction[97] complicating PTCA. Recent data support a role for the antiplatelet agents, ticlopidine and clopidogrel, in reducing acute closure rates in patients who cannot take aspirin.[98] Systemic anticoagulation with heparin during balloon angioplasty is uniformly performed and seems prudent. In uncomplicated PTCA, post-procedural heparinization is not routinely employed. Studies have failed to show a favourable effect upon rates of acute occlusion,[99–101] and have shown a slightly increased incidence of bleeding. Prolonged (24 h) post-procedural heparin infusion is widely used when the PTCA results in intimal dissection or luminal thrombus, and occasionally for a suboptimal result. While thrombolytic therapy prior to angioplasty in unstable angina does not decrease the incidence of acute occlusion,[102] recent studies with a platelet glycoprotein IIb/IIIa receptor blocker have demonstrated its clinical usefulness for the prevention of ischaemic complications following angioplasty.[103]

Mechanical approaches for dealing with abrupt closure include prolonged repeat conventional balloon angioplasty, and the use of autoperfusion balloon technology.[104–106] The latter may be very effective in retrieving angiographic success.[107,108] However, since the landmark study of Sigwart et al,[109] and the later confirmatory studies of Roubin et al[110] and George et al,[111] emergency intracoronary stenting has emerged as the gold standard for treatment of acute occlusion due to intimal dissection. Initially stenting was accompanied by a substantial rate of subacute thrombosis[110–112] and significant rates of bleeding related to the intense anticoagulation and antiplatelet regimens that were employed. A comparison of post-stent medical regimens of ticlopidine and aspirin with heparin and Coumadin showed a significantly lower rate of thrombosis with the former,[113] although clopidogrel has now largely replaced ticlopidine. The use of weight-adjusted and shorter duration heparin regimens has also helped to reduce complications. Furthermore, high pressure balloon deployment of (Palmaz–Schatz) stents with intravascular ultrasound (IVUS) guidance was associated with a low incidence of stent thrombosis and, because prolonged postprocedural anticoagulation could be omitted, a shorter hospital stay.[114] Hence high-pressure stent deployment together with antiplatelet agents have resulted in almost abolition of abrupt closure due to thrombosis and less frequent puncture-site bleeding events. When haemodynamic instability or ischaemia complicate acute closure, percutaneous circulatory support using intra-aortic balloon counterpulsation[59,115] and percutaneous cardiopulmonary bypass[116,117] can provide support and allow stabilization in critical situations.

Many minor complications can occur during coronary angiography/angioplasty. These include contrast allergy, nephropathy,[118] embolic stroke, side branch occlusion,[119] tachy- or brady-arrhythmia[119,120] and, very rarely, cardiac tamponade (associated with placement of a right ventricular pacing catheter).[121] Access site bleeding and late structural abnormalities, including pseudoaneurysm and arteriovenous fistula formation, also may occur,[119] as can post-procedural anaemia, due to access site bleeding, especially during complex and prolonged procedures.

Summary and conclusions

In the 24 years since the introduction of percutaneous transluminal coronary angioplasty many thousands of patients have been treated. In recent years, especially with the addition of new balloon technology and new devices, very high success rates (>95%) and low complication rates (<3%) have been noted.

Studies from our centres[75] and the UK[76] have shown that certain lesions are not as amenable to balloon angioplasty as others because of mechanical limitations, chronic occlusions, diffuse disease, eccentric, ostial and heavily calcified lesions. Flow-limiting dissections, which occur in about 3–5% of cases, were responsible for (almost) all of the untoward initial results of angioplasty, including acute myocardial infarction, emergency coronary artery bypass, surgery and death. However, these outcomes have been greatly improved by stenting.

In the past 15 years, several new devices have been introduced directed at specific lesions in which balloon angioplasty was wanting[122,123] though balloon angioplasty is usually used adjunctively with these devices.[124] Directional coronary atherectomy (DCA), now in occasional use, appears to be useful for discrete non-calcified eccentric lesions in non-angulated large (≥ 3 mm) vessels. Fast rotational ablation with the Rotablator has been quite effective in longer or diffuse lesions with or without calcification and in eccentric stable stenoses in vessels which may or may not be angulated. Laser angioplasty (ELCA) has been effective in longer or diffuse non-calcific disease and, with the directional iteration, in eccentric lesions. In saphenous vein grafts (SVG) or large native arteries associated with a significant thrombus burden, extraction atherectomy with the TEC® device has shown promising results. Endovascular stents have been very effective in scaffolding flow-limiting dissections. Moreover, with discrete de novo stenosis in large (≥ 3 mm) vessels, lower restenosis rates after stenting in two randomized trials[125,126] and excellent long term results of stents in SVGs[127,128] and ostial lesions support their increased use.[128,129]

Restenosis (see Chapter 19) remains the Achilles' heel of all interventional techniques, although its pathophysiology is better understood.[130,131] Stents offer the first 'mechanical' breakthrough, reducing stenosis in certain lesions. By scaffolding the artery, the hoop (radial) strength of the stent may oppose the potential constrictive force of the adventitial hyperplasia (associated with restenosis). Yet, it appears that appropriate and locally delivered pharmacotherapy, to modify the vascular response to the 'necessary' device-induced injury, may be the next major step forward in the angioplasty experience.

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5

Percutaneous transluminal coronary angioplasty of single or multivessel disease and chronic total occlusions

Beat J Meyer and Bernhard Meier

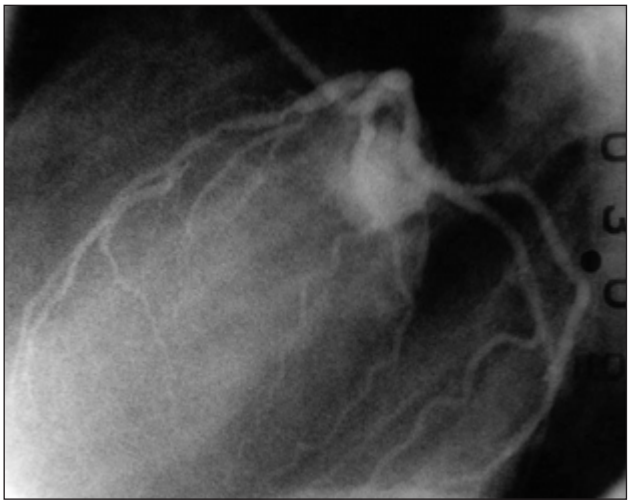
After percutaneous transluminal coronary angioplasty (PTCA) had been first introduced by Andreas Gruentzig in 1977[1] as an alternative form of myocardial revascularization for patients with coronary artery disease, it appeared that it should be limited to patients with single, proximal vessel coronary artery disease, well-preserved left ventricular function and stable angina refractory to medical treatment. However, subsequent improvements in equipment and technique have led to its use in patients with stenoses that are more complex, located in distal arterial segments or located in more than one coronary artery.[2]

General considerations

Coronary artery disease remains the most frequent cause of morbidity and mortality in the industrialized countries despite a decline in recent years.[3] Coronary artery bypass graft (CABG) surgery and PTCA are the principal revascularization modalities in the management of patients with symptomatic coronary artery disease. Although the number of coronary angioplasties has long surpassed the number of coronary bypass procedures both in Europe and in the United States,[4,5] there is great interest in defining the most appropriate use of this procedure. The leading indication for surgery continues to be relief of angina, an approach supported by findings of randomized trials. These trials have shown that surgical revascularization significantly reduces symptoms and improves quality of life compared with medical therapy.[6] At the same time there has been an expansion of patients for whom it is recognized that bypass surgery improves survival. This improvement in survival[7–14] has been established in patients with left main coronary disease,[7] certain patients with three-vessel disease,[8–10] some patients with two vessel disease and involvement of the proximal left anterior descending coronary artery,[9,11] as well as in subsets of patients with severe symptoms[12] or with a positive stress test.[15] Although PTCA has been effective in alleviating angina in many classes of patients, there have been few trials comparing angioplasty with medical therapy or surgery in the subsets shown to have improved survival with surgical revascularization.

Single-vessel disease: practical considerations

Single-vessel disease with a single stenosis remains the favourite indication for coronary angioplasty for several reasons. There is usually a close correlation between symptomatology and the angiographic findings before and after the intervention. In other words, good angiographic results renders the patient asymptomatic and vice versa. Persistence or recurrence of symptoms reliably indicates a significant residual or recurrent stenosis, respectively (Fig. 5.1). The procedure is generally short, complications are limited to a single myocardial area, and collaterals from healthy arteries are frequently present or recruitable if needed. Most of these advantages also hold true for tandem or multiple stenoses in single vessel disease (Fig. 5.2), although the interventions tend to be longer with higher rates of complications and recurrence in more complex lesions (Fig. 5.3, Table 5.1).[13]



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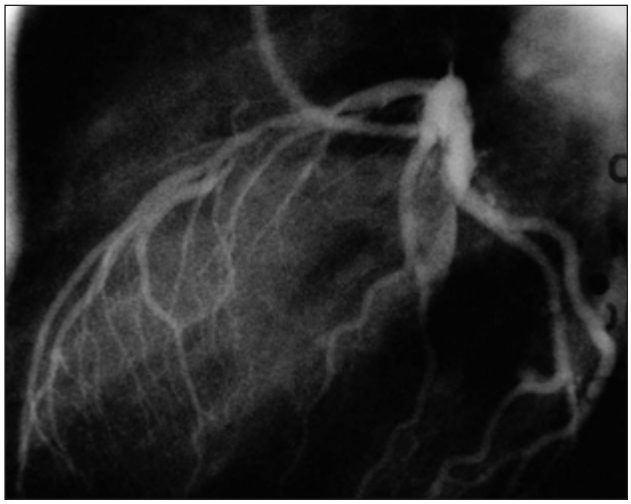

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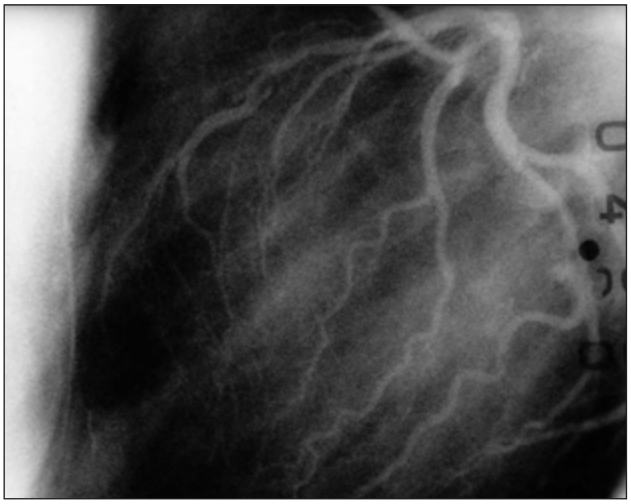

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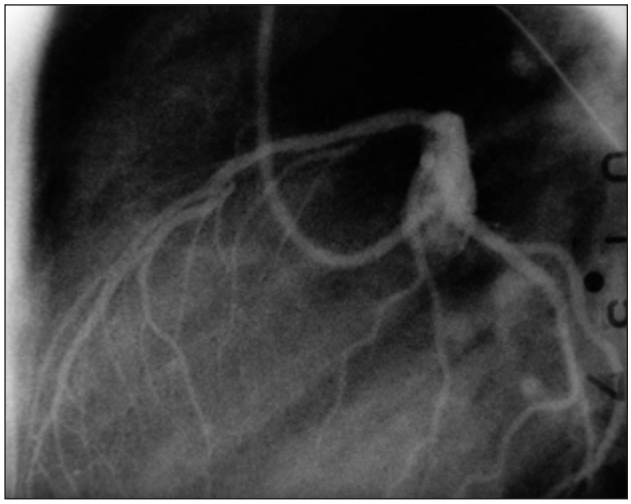

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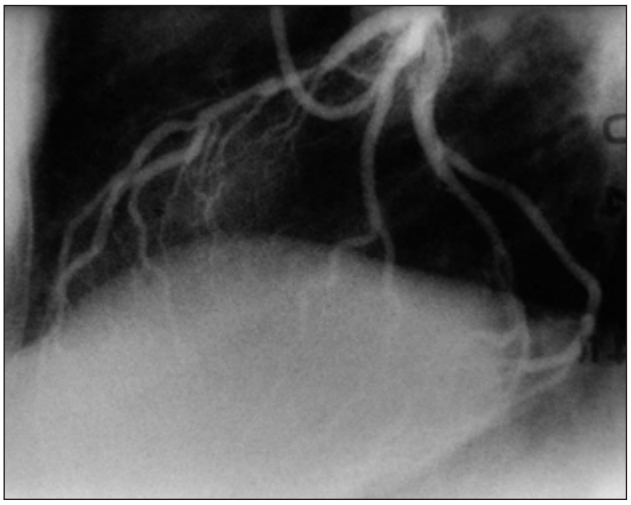

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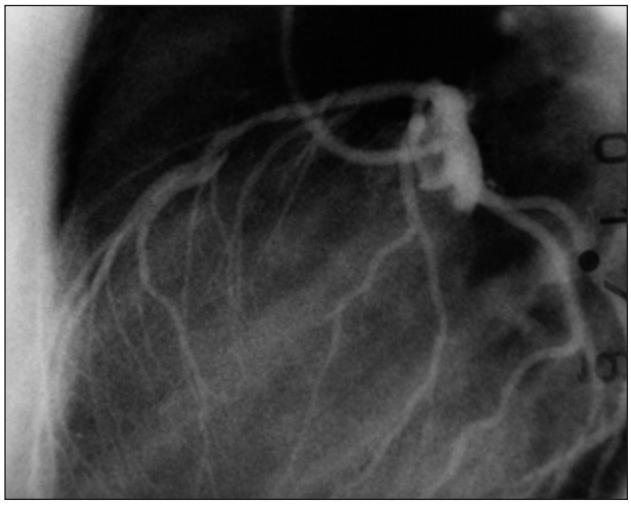

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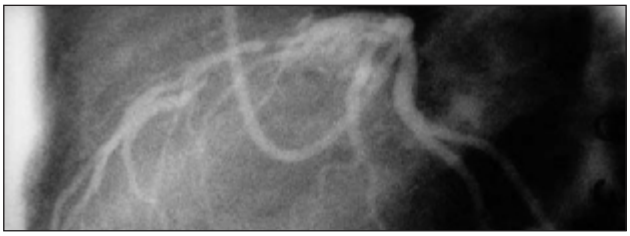

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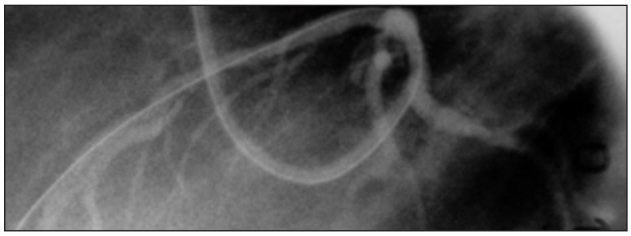

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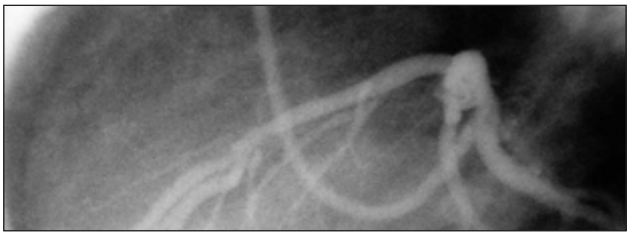

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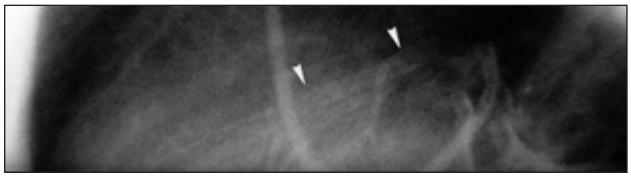

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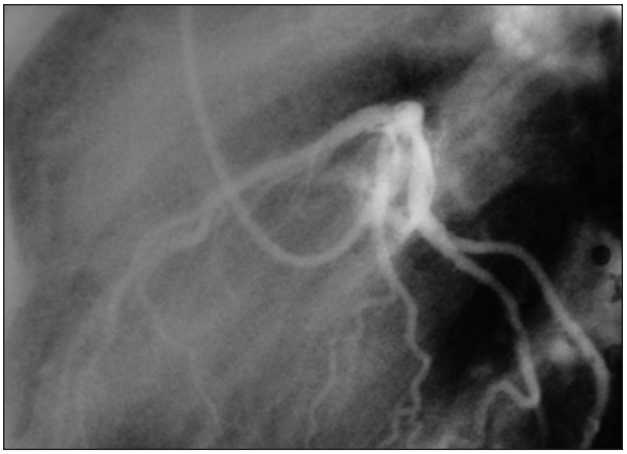
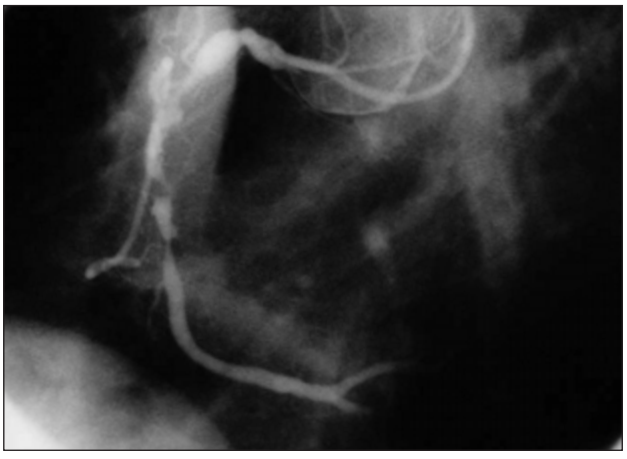


k

Figure 5.1
Single vessel PTCA for proximal LAD stenosis. Angioplasty in a 46-year-old woman with a proximal LAD stenosis (a) with a good immediate result (b). Two months later there is recurrent chest pain and restenosis (c) and successful re-PTCA (d). There are recurrent symptoms 3 months later with angiographically documented restenosis (e), and a third successful angioplasty (f). There is a third clinical and angiographic restenosis 3 months later (g). Elective implantation of a 3.5 mm Wallstent is performed despite a perfect immediate result of the initial balloon dilatation (h). Final angiographic result (i) with the stent in place (j, arrows). There were no further symptoms and absence of restenosis on follow-up angiogram 6 months later (k). Although the prevention of restenosis in this case cannot be attributed unequivocally to the stent, it is reasonable to electively stent a restenotic lesion, especially if it has recurred several times.



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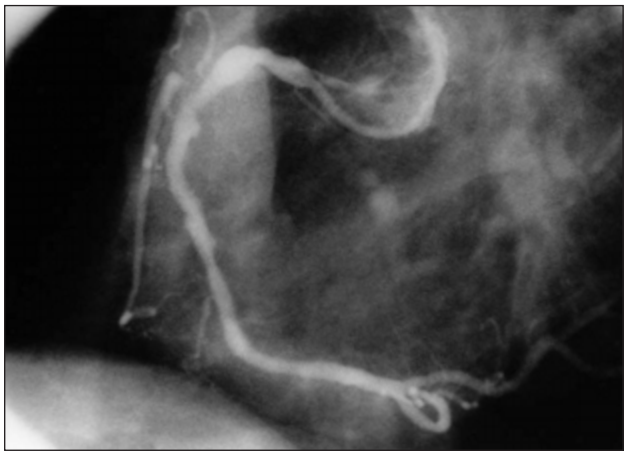
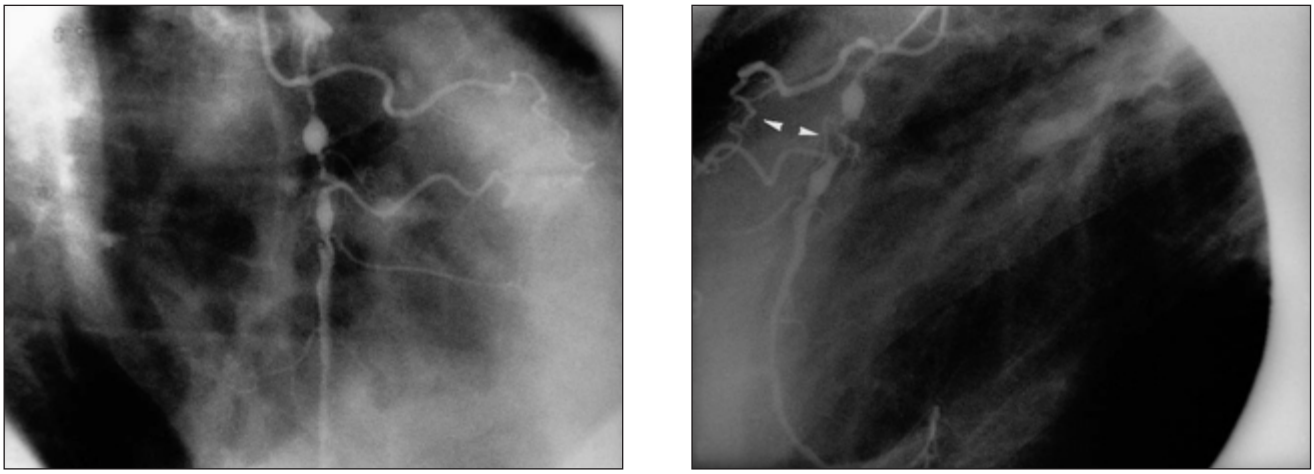


b

Figure 5.2
Single vessel PTCA for serial stenosis. Angioplasty for serial stenosis of the RCA of a 67-year-old man (a). The procedural result in this case was excellent (b) but, in general, serial lesions yield less satisfactory procedural success rates and higher recurrence rates.



a b

Figure 5.3
Serial stenoses unsuitable for PTCA. Severe and diffuse proximal RCA lesion of a 65-year old man seemingly amenable for PTCA in the RAO projection (a). However in the LAO projection a total chronic occlusion with ipsilateral and bridging collaterals (arrows, b) renders this lesion unsuitable for PTCA.

Table 5.1 Lesion specific characteristics of type A, B, and C lesions.

Type A lesions (minimally complex; high success, > 85%; low risk)	*Type B lesions (moderately complex; moderate success, 60-85%; moderate risk)*	*Type C lesion (severely complex; low success, < 60%; high risk)*
• Discrete (<10 mm)	• Tubular (10–20 mm)	• Diffuse (>20 mm in length)
• Concentric	• Eccentric	• Excessive tortuosity of proximal segment
• Readily accessible	• Moderate tortuosity of proximal segment	• Extremely angulated segments, >90°
• Nonangulated segment, <45°	• Moderately angulated segment, >45°, <90°	• Total occlusion >3 months old, bridging collaterals
• Smooth contour	• Irregular contour	• Inability to protect major side branches
• Little or no calcium	• Moderate to heavy calcification	• Degenerated vein grafts with friable lesions
• Less than totally occlusive	• Total occlusion <3 months old	
• Not ostial in location	• Ostial in location	
• No major side branch involvement	• Bifurcation lesions requiring double guidewire	
• Absence of thrombus	• Some thrombus present	

Adapted with permission from ACC/AHA Task Force: Guidelines for percutaneous transluminal coronary angioplasty.[13]

Single-vessel disease: clinical trials

During the early 1980s, PTCA emerged as a third method to treat patients with coronary artery disease, but the great majority of procedures were still performed in patients who had moderate-to-severe angina despite medical therapy.[16] More recently, there has been a tendency to use PTCA for patients with milder angina of a type that had previously been managed medically. By 1988, data from Emory University[17] showed that 30% of consecutive patients undergoing their first cardiac catheterization for the evaluation of coronary artery disease had PTCA performed within the next month, 29% had bypass surgery and 41% continued to receive medical therapy. Among patients with single-vessel disease—nearly 50% of those who underwent cardiac catheterization—PTCA was performed in 46%, whereas only 4% had bypass surgery and 50% continued to receive medical therapy. Similar figures were reported from our institution 10 years later.[18] The Coronary Artery Surgery Study (CASS) demonstrated, that CABG surgery reduced neither mortality nor subsequent myocardial infarction in patients with stable single vessel-disease.[19] Therefore, a non-surgical approach appears more appropriate for patients with single-vessel disease and a low risk profile, as also shown in a recent meta analysis.[20] If the risk of restenosis and reintervention is acceptable to patient and physician, PTCA of single-vessel coronary artery disease even involving the proximal left anterior descending coronary artery remains a suitable option and a simpler alternative to CABG, as demonstrated by a recent randomized trial.[21]

The growth of the use of PTCA has been based on its perceived benefits as compared with medical or surgical treatment, yet these benefits have been demonstrated by a few randomized clinical trials only.[22,23] Specifically, the question of whether PTCA offers any advantage over drug therapy in patients with single-vessel coronary artery disease and mild-to-moderate stable angina has been addressed in only a few randomized comparative trials (Table 5.2). In the ACME (Angioplasty Compared to Medicine) trial nearly 10,000 patients at eight participating US Veterans Affairs medical centres were screened over a 3-year period; 371 patients with mild single-vessel coronary artery disease suitable for PTCA were identified. A total of 212 of these patients (2%) were then randomly assigned to receive either conventional medical therapy or PTCA; all patients received aspirin.[24] Both the PTCA group and the medical group showed an improvement in exercise tolerance at 6 months.

Table 5.2 Randomized comparison of medical therapy or CABG with single vessel angioplasty in patients with stable CAD.

				Endpoints							
Trial	*Follow-up (months)*	*N*	*Treatment*	*Death*	*MI*	*Death or MI*	*Angina Free*	*Angina improved*	*CABG*	*PTCA*	*Repeat Hospitalization*
ACME[24,25]	6	107	Medical	0.9	2.8	3.7	36.5	—	0	9	—
		105	PTCA	0	4.8	4.8	53.9[c]	—	7[f]	16	—
	60	162	Medical				55.0	—			
		166	PTCA				67.0	—			
RITA-2[27]	36	514	Medical	1.4	1.9	3.3	47	30	—	17.1	—
		504	PTCA	2.2	4.1	6.3[b]	64	38[d]	—	11.1	—
AVERT[28]	18	164	Medical[a]	0.6	2.4	3.0	—	41	1.2	11.0	6.7
		177	PTCA/stent	0.6	2.8	3.4	—	54[e]	5.1	11.9	14.1
MASS[29]	60	72	Medical	2.9	4.2	—	25.8	—	11.1	5.6	—
		72	PTCA	5.7	6.9	—	72.7[f]	—	0	0	—
		70	LIMA	2.9	11.1	—	64.7[f]	—	11.1	30.3	—
Lausanne[21]	60	68	PTCA	9.0	15.0	—	74.0	—	5.0	19.0[g]	—
		68	LIMA	3.0	2.9	—	71.0	—	0	9.0	—

[a]Plus atorvastatin. [b]$P = 0.02$. [c]$P < 0.01$. [d]17% excess of grade 2+ angina in the medical group 3 months after randomization ($P < 0.001$). [e]$P < 0.05$. [f]$P < 0.01$. [g]An additional 15% of patients had combined PTCA + CABG.

The increase in the duration of exercise, however, was significantly greater (2.1 versus 0.5 minutes) for the patients treated with PTCA (who performed the exercise test after antianginal medication had been temporarily withheld) than for those in the medically treated group (who were studied while receiving their optimal antianginal regimen). In the PTCA group exercise testing also demonstrated an increase in the product of peak heart rate and the systolic blood pressure, suggesting improvement in coronary blood flow. This finding was confirmed by the demonstration of a persistent reduction in the severity of the index coronary stenoses in the PTCA group at 6 months. Patients who underwent PTCA also reported better general health and vitality, less frequent use of antianginal drugs and more frequent freedom from angina (54% versus 36%) at 6 months—although these patients had been hospitalized more often than the medically treated patients. At 5 years, 67% of PTCA-treated patients were free of angina compared with 55% of medically treated patients.[25] Moreover, at 5 years almost one-third of PTCA-treated patients were free of antianginal drugs compared with 17% of medically treated patients. Although there was a beneficial effect on quality of life results in both patient groups, it was significantly higher in the PTCA-treated group. The better relief of ischaemic symptoms occurred at a considerable cost for the initial and restenosis treatment. However, after 5 years of follow-up a US$1500 incremental cost per year yielded clear gains in functional status of patients. These costs may even be reduced with current device technology and contemporary risk reduction strategies which are associated with a lower rate of restenosis and better clinical outcomes in patients with single vessel disease.[26]

These results are similar to those reported from the larger RITA-2 trial which included 60% of patients with single vessel disease.[27] Angioplasty was associated with greater symptomatic improvement compared with medical therapy at the cost of a small excess hazard due to procedure-related complications (Table 5.2). However, both studies tend to show somewhat less complete relief of angina at long-term follow-up with either treatment than the value of 95% reported after bypass surgery.[14] In the recent AVERT trial,[28] a strategy of aggressive lipid-lowering therapy with atorvastatin was compared with angioplasty in minimally symptomatic (CCS class I-II), mostly single-vessel coronary disease patients. There was a non-significant trend towards a reduction in the composite endpoint of death, MI, revascularization and worsening angina in patients allocated to atorvastatin (13% versus 21% in the angioplasty group, P = ns), but the differences in favour of atorvastatin therapy were exclusively limited to a decreased revascularization and rehospitalization rate. As in previous trials, patients undergoing angioplasty had significantly improved symptoms compared with medically managed patients, and one wonders why the interventionally treated patients were withheld adequate cholesterol control despite established evidence of its beneficial effect in secondary prevention.

Angioplasty has been compared with LIMA grafting in patients with isolated proximal LAD stenosis in two randomized trials (Table 5.2).[21,29] At 5 years of follow-up, there were no significant differences between groups with respect to death and Q-wave myocardial infarction. However, patients allocated to angioplasty had more frequent non-Q-wave infarction related to abrupt closure or unstable angina related to restenosis. They required additional revascularization procedures more often than surgically revascularized patients. CABG for isolated proximal LAD stenosis seemed to be associated with better survival in the recent New York State registry experience.[30]

In summary, PTCA is superior to medical therapy for the management of symptoms in patients with stable angina. Since patients with single-vessel disease have excellent longevity and therefore are unsuited for a survival endpoint study, the value of angioplasty in terms of improvement of quality of life must be weighted against the inherent risks and greater initial costs of the procedure. Decision analysis[31] suggests that PTCA is preferable to both medical and surgical therapy in patients with severe angina and single vessel lesion amenable to treatment with PTCA. However, selected patients with isolated proximal left anterior descending coronary artery stenosis may have greater freedom from subsequent events following left internal mammary grafting compared to angioplasty.[21,29,30] Even though PTCA may actually be less cost effective than medical therapy in patients with mild angina, it remains an appropriate choice for the large number of patients with single vessel disease and suitable coronary anatomy.

Multivessel disease: dilatation strategy

Multivessel disease does not necessarily require multivessel revascularization. There may be significant stenoses in branches too small for consideration or in completely infarcted territories. However, in most cases, more than one of the involved vessels need revascularization and true multivessel angioplasty is necessary. With improvements in equipment and techniques the indications for multivessel angioplasty have broadened in some centres. Multivessel dilatations accounted for more than 20% of interventions of some large series.[32] In our own experience[33] and according to annual European surveys[4,5] true multivessel angioplasty (angioplasty in two or more major vessels during the same intervention) has never accounted for more than 20% of the interventions.

In selecting patients with multivessel disease for coronary angioplasty, several factors need to be considered including completeness of revascularization, amount of myocardium subtended by the target artery, lesion morphology and collaterals (Table 5.1, Fig. 5.4).

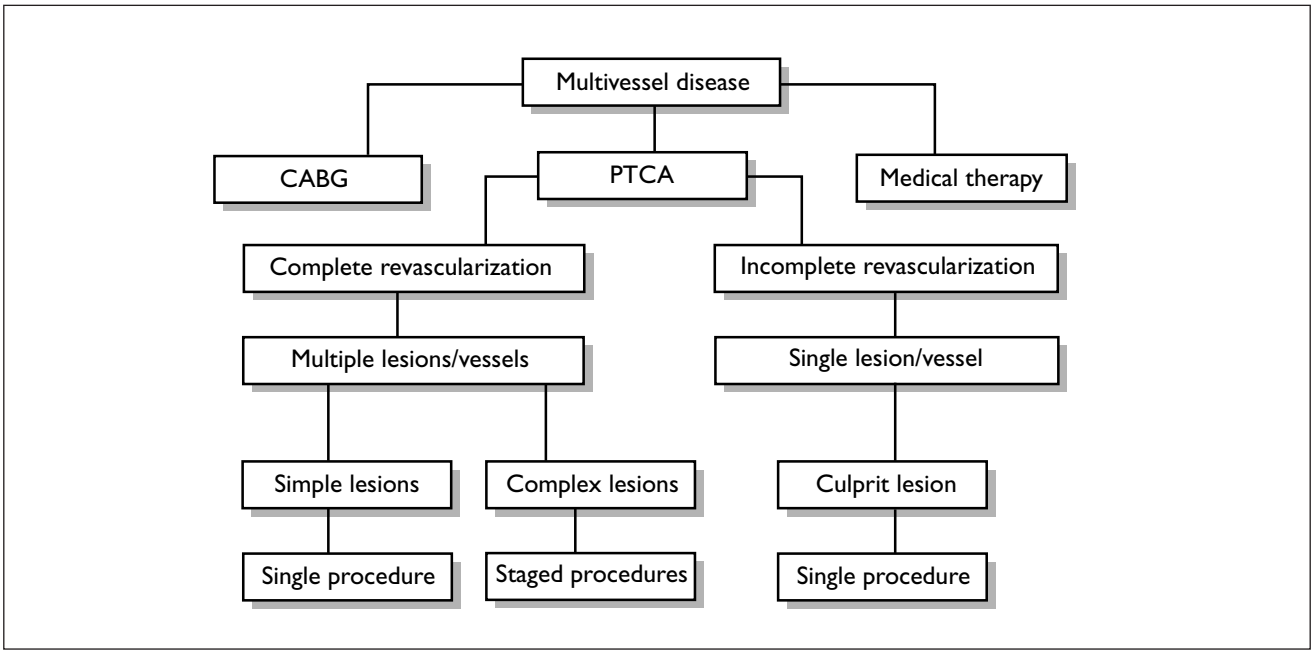
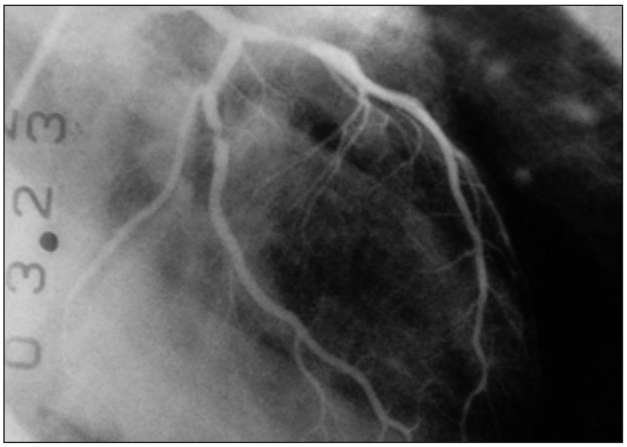


Figure 5.4
Algorithm for treatment of multivessel coronary artery disease with percutaneous transluminal coronary angioplasty (PTCA).

(1) An important concept is that of completeness of revascularization achievable by angioplasty (Fig. 5.5). This is based on cardiac surgical experience, which has documented that if revascularization is complete, the clinical outcome will be improved.[34] Although complete revascularization is ideal, it cannot be achieved in a substantial number of patients with multivessel disease because of the presence of chronic total occlusions that cannot be dilated, diffuse and distal disease or stenosis of small side branches.[35] However, many patients with successful dilatation but incomplete revascularization do well.[36,37] In these patients, attempts are made to identify and dilate a 'culprit' lesion. Coronary angioplasty of these physiologically most important stenoses often results in an excellent outcome.[38–40]
(2) Should all attempted lesions occlude simultaneously, there still has to be enough perfused and viable myocardium to ensure a sufficient cardiac output until revascularization by repeat angioplasty or bypass surgery can be achieved (Fig. 5.6). The risk of multiple acute occlusions exists only during and immediately after the procedure and can be reliably circumvented by staged interventions, even if they are done on two consecutive days (Fig. 5.7).
(3) Angioplasty of more than three stenoses in more than two vessels in a single intervention is too consuming in terms of time, contrast agent, and irradiation. It is risky, and rarely successful in all attempted lesions. A two-stage procedure may be an alternative approach. Considering the control studies and repeat procedures to be expected, some patients might be better off with a single elective bypass operation, particularly if both internal mammary arteries are used as conduits.
(4) A stenosed left main coronary artery as a special case of multivessel disease generally represents a contraindication to coronary angioplasty unless the circumflex coronary artery is extremely small or at least one of the principal arteries is protected by a functioning bypass graft or by generous collaterals.
(5) If two stenosed arteries are linked by collaterals, angioplasty of the recipient vessel is attempted first. Angioplasty of the supplying vessel is only followed if the result in the recipient vessel is good, i.e. collaterals are no longer visible or have reversed their direction.
(6) Other subsets have emerged as possible indications for multivessel coronary angioplasty. For example, patients with refractory angina and severe left ventricular dysfunction and at least one 'suitable' coronary artery stenosis may have angioplasty with favourable early and late results.[41] In addition, coronary angioplasty in elderly patients may result in similar long-term survival rates when compared with patients treated with CABG and matched for left ventricular function.[42–44]

However, some of the contraindications to PTCA may be overruled for an occasional patient with relative or absolute contraindications to bypass surgery (age, other consuming disease, absence of graft material, etc.) and severely limiting angina despite medical therapy.[45,46]



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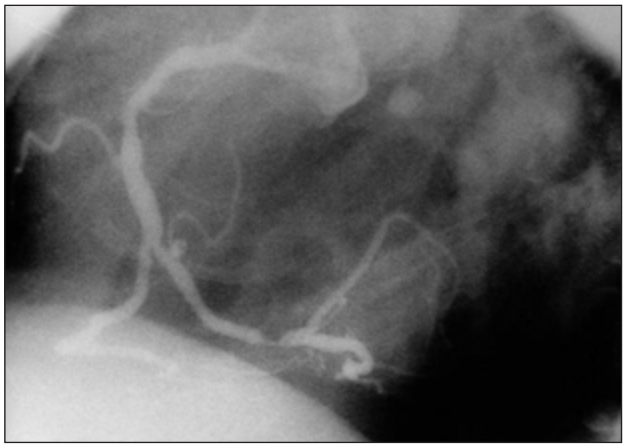

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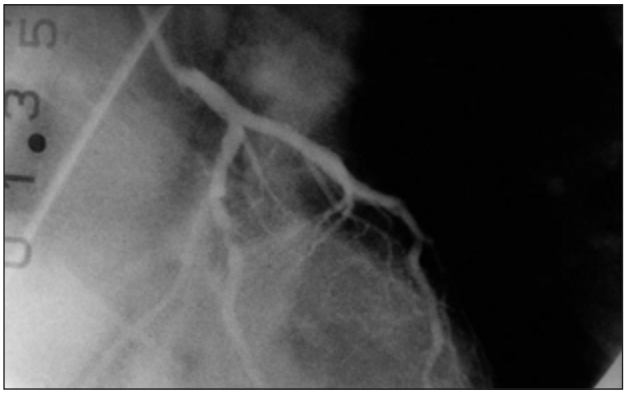

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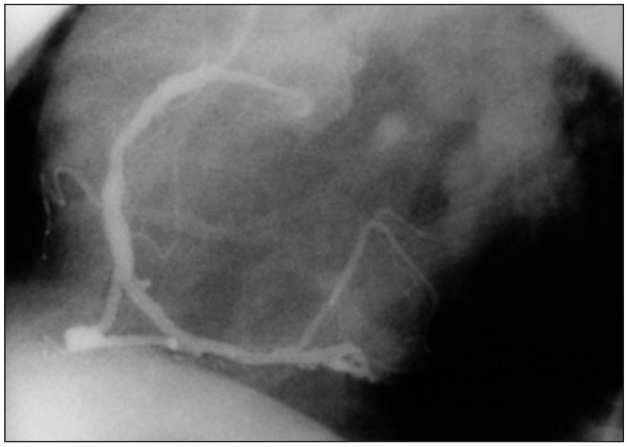

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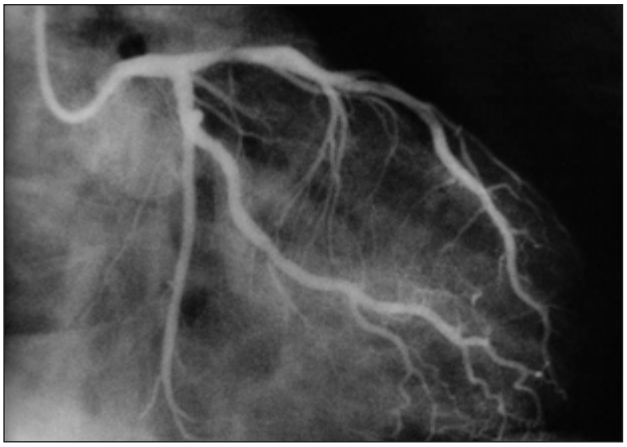

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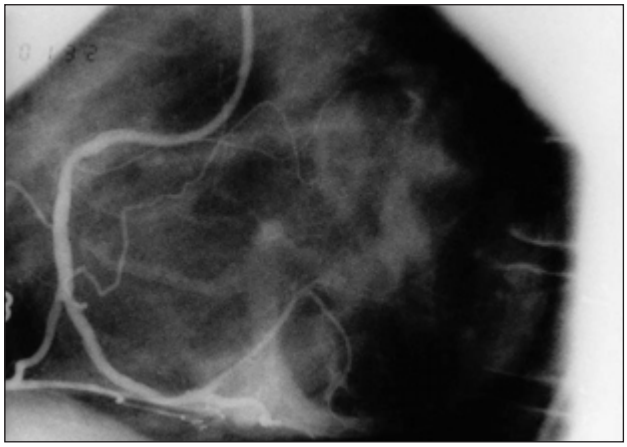

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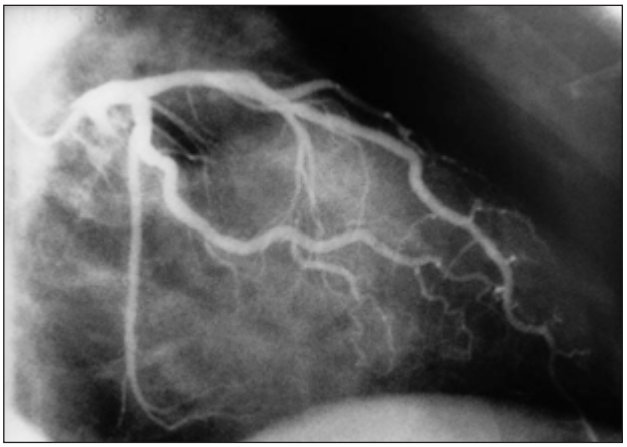

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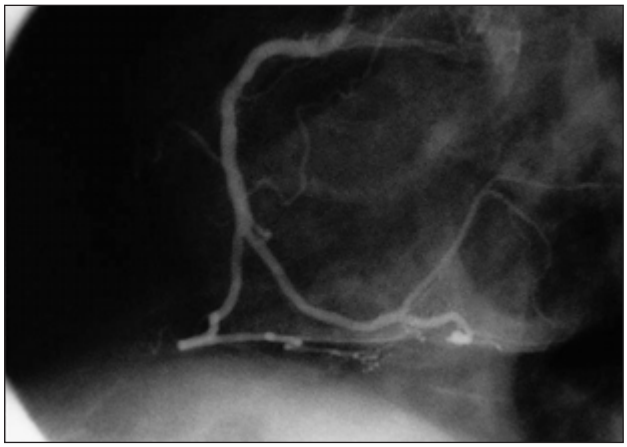

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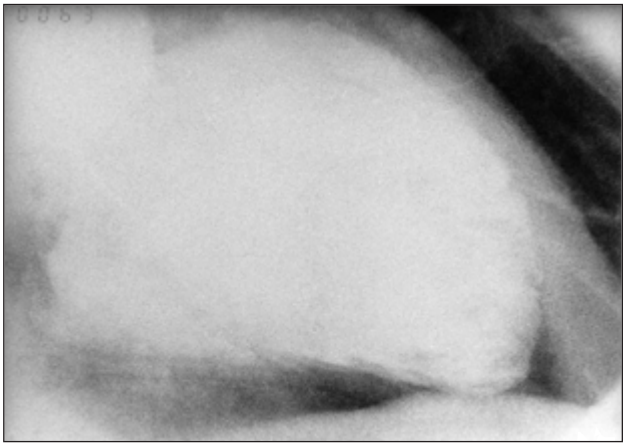

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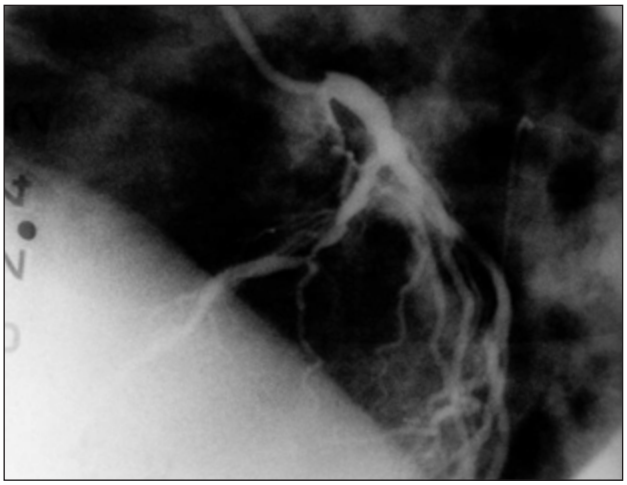
j

Figure 5.5
Staged multivessel PTCA for triple-vessel disease. Stenoses of the proximal LAD, LCx (a), and distal RCA (b) in a 57-year old man. Firstly, the LAD stenosis (major myocardial mass) was dilated. Based on a good immediate result (c) the RCA lesion was dilated at the same sitting (d). The following day reassessment of the lesions through the sheath left in place, revealed a stable result and allowed for angioplasty of the LCx (e, f). The patient made an uneventful recovery. A routine angiogram performed 2 years later revealed an excellent long-term result (g, h) with normal left ventricular function (i, j).



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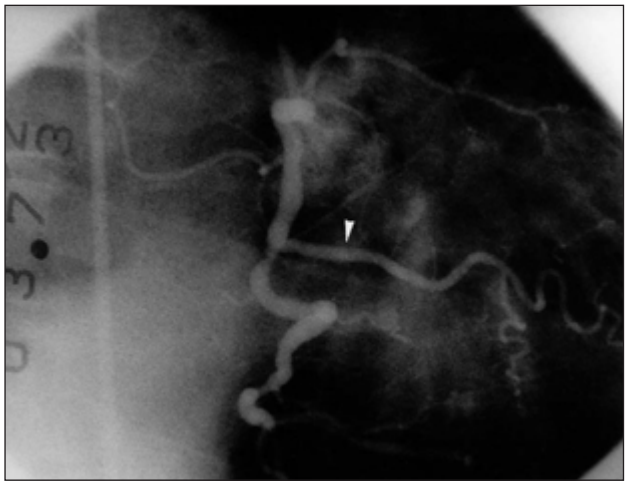

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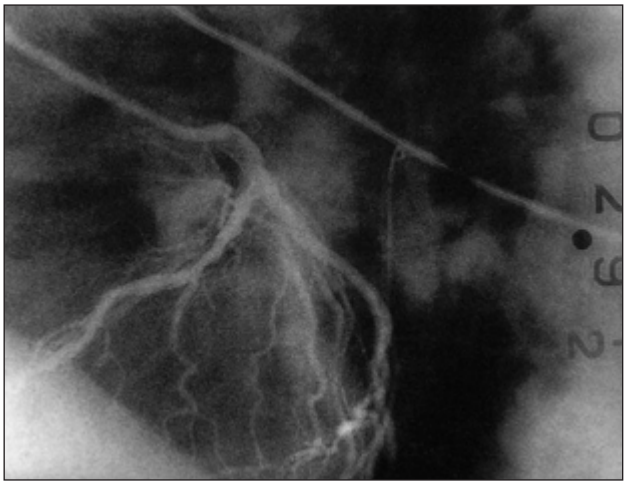

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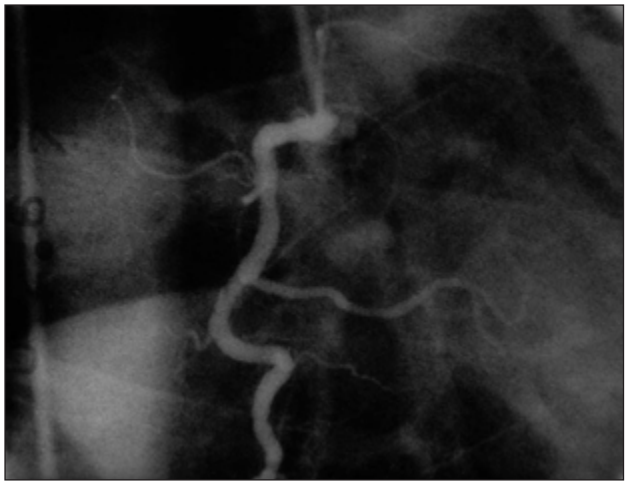

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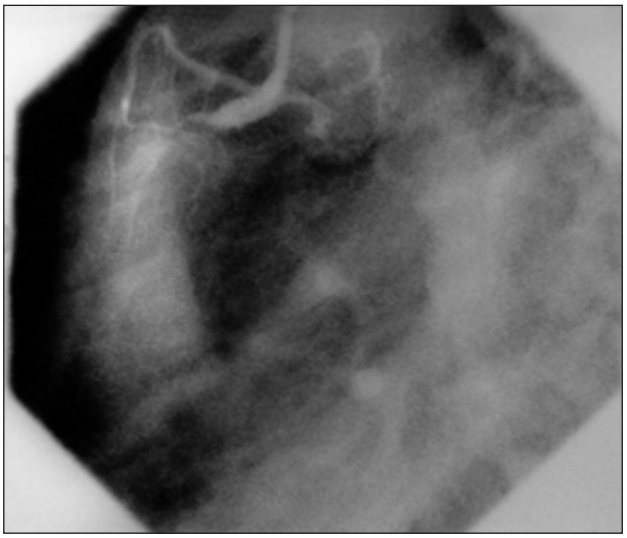
Figure 5.6
Multivessel PTCA at the same sitting. Double-vessel disease with stenoses of the LAD (a) and RCA (b) in a 62-year-old man. Collaterals from the RCA to the LAD via a branch that originated proximal to the RCA stenosis are present (arrow). Following an adequate result of the LAD angioplasty (c), dilatation of the RCA stenosis at the same sitting was performed (d). Although the total myocardium at risk is considerable in this situation, such an approach is relatively safe since the LAD was collateralized by an RCA branch which originated proximal to the RCA stenosis. Even in the worst case scenario of acute closure of both dilated lesions, the LAD would still be protected by collaterals. A 4-month follow-up angiogram for angina showed a good long-term result of the RCA and an LAD restenosis which was successfully redilated.



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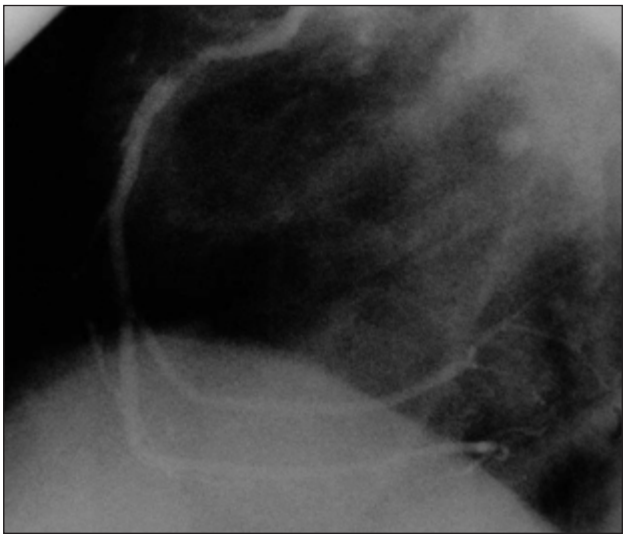

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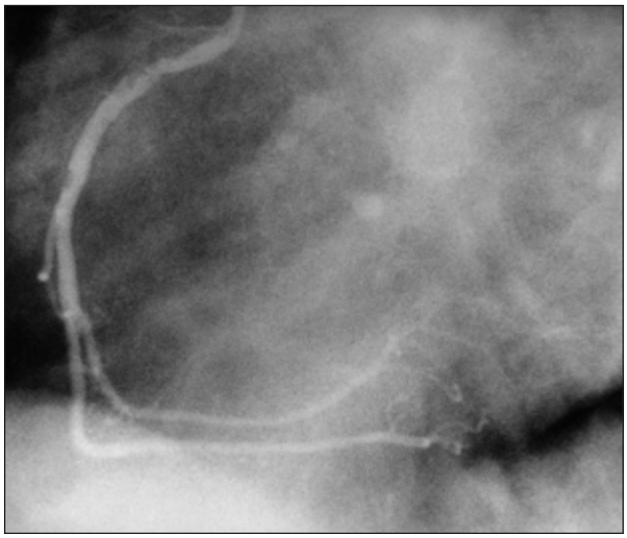

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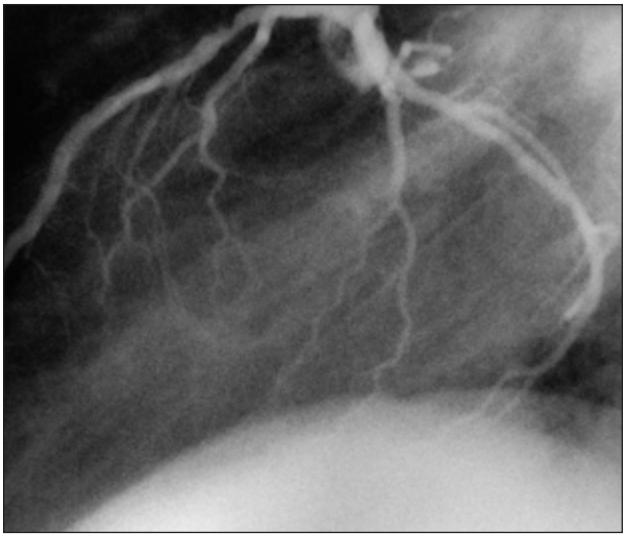

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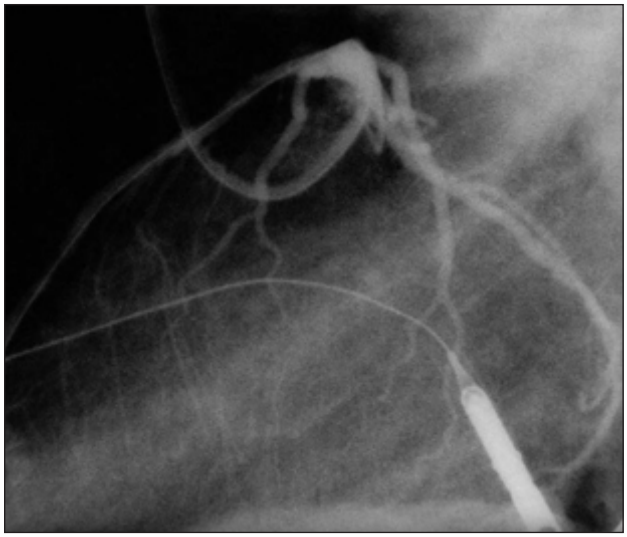


e

Figure 5.7
Staged multivessel PTCA for double-vessel disease. Occluded RCA (a) of a 40-year old man, with collateralization from the LAD which is also significantly stenosed. Recanalization of the RCA on the first day, with an acceptable result (b). The next day, a control angiogram revealed a stable RCA angioplasty result (c) and dilatation of the LAD lesion (d) produced a good result (e). In such a situation the presence of collaterals is advantageous for both interventions.

Multivessel disease: results of randomized trials

The role of PTCA compared with CABG in selected patients with multivessel disease has been established with several randomized trials[47–52] (Table 5.3); three prospective trials (ARTS, SOS, ERACI-II) comparing stent-supported angioplasty and bypass grafting are still in progress, but preliminary results of the ARTS trial have been reported.[53]

The patients included in these trials were highly selected, and only approximately 5% of screened patients with multivessel disease were randomized into the trials (Table 5.3). The trials excluded patients in whom survival had already been shown to be longer with CABG than with medical therapy. More than half of the patients were excluded for appropriate angiographic reasons, including left main coronary artery disease, chronic total occlusion, diffuse disease or inability to achieve complete revascularization. However, among a large group of patients with multivessel disease suitable for inclusion, only half were actually randomized. It appeared that physicians elected not to include many patients with three vessel disease in the trials but rather refer them for bypass surgery, whereas patients with two vessel disease tended to be referred for angioplasty rather than be enrolled in the trials. In addition, most of the patients had well-preserved left ventricular systolic function (Table 5.3). Due to the number and the relatively low-risk groups of patients included in the trials, none of the trials was sufficiently powered to detect differences in mortality between the two revascularization techniques.

Overall, the results of these trials were remarkably consistent, with low acute complications for both procedures which tended to be higher with CABG (Table 5.4). The initial cost and length of stay in hospital were lower for angioplasty than for CABG. Patients having angioplasty returned to work sooner and were able to exercise more at 1 month. The extent of revascularization achieved by CABG was generally higher than with angioplasty.[54] An initial strategy of angioplasty or CABG resulted in (1) similar survival and freedom of myocardial infarction 1 to 7 years after the procedure, (2) better relief of angina in CABG patients at least during the first year following the procedure, (3) an increased need for further coronary revascularization procedures in patients allocated to angioplasty mostly during the first year after the initial intervention (Fig. 5.8) and (4) similar long-term costs during a follow-up period of 5 to 8 years. Although the results

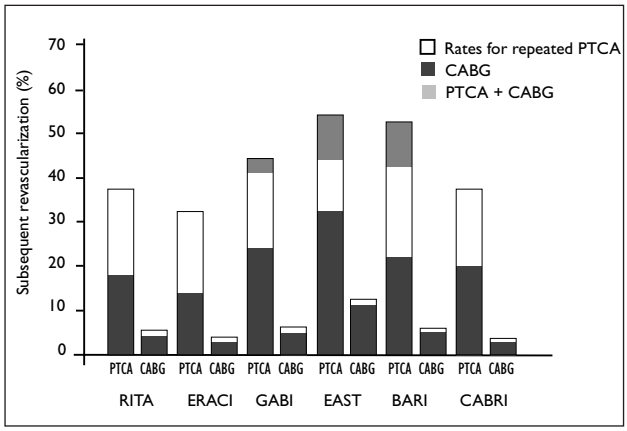


Figure 5.8
Rates of subsequent revascularizations (PTCA, CABG or both) in six randomized trials comparing angioplasty with coronary artery bypass surgery.

Table 5.3 Clinical trials in multivessel coronary angioplasty versus CABG.

	Randomization			*Patient characteristics*			*Follow-up (years)*	
TRIAL	*Year*	*N*	*Rate (%)*	*Mean age (y)*	*Men (%)*	*Mean LVEF*	*Early*	*Late*
RITA-1	1993	1011	4.8	57	81	—	2.5	5
ERACI	1993	127	16.9	58	85	61	1	3 and 5
GABI	1994	359	4.0	59	89	—	1	—
EAST	1994	392	7.7	62	74	61	0.5 and 1	3
BARI	1995	1829	7.3	62	73	57	—	5
CABRI	1995	1054	2.5	60	78	63	1	3 and 5

RITA-1: Randomised Intervention Treatment of Angina.[47,87]
ERACI: Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease.[48,88]
GABI: German Angioplasty Bypass Surgery Investigation.[49]
EAST: Emory Angioplasty versus Surgery Trial.[50]
BARI: Bypass Angioplasty Revascularization Investigation.[51,55]
CABRI: European Coronary Angioplasty versus Bypass Revascularization Investigation.[52,89]

Table 5.4 CABG versus PTCA: Early and late outcomes of six randomized controlled trials.

Trial	Treatment	Acute outcome %		Late outcome %			Follow-up (years)
		Death	MI	Death	MI	Prevalence of angina	
RITA-1	CABG	1.2	2.4	9.0	7.4	16.6	5
	PTCA	0.8	3.5	7.6	10.8	25.6*	
ERACI	CABG	4.6	6.2	4.7	7.8	3.2	3
	PTCA	1.5	6.3	9.5	7.8	4.8	
GABI	CABG	2.5	8.0	6.5	9.4	26	1
	PTCA	1.1	2.3[a]	2.6	4.5	29	
EAST	CABG	1.0	10.3	6.2	19.6	12	3
	PTCA	1.0	3.0[a]	7.1	16.6	20	
BARI	CABG	1.3	4.6	10.7	19.6	—	5
	PTCA	1.1	2.1	13.7	21.3	—	
CABRI	CABG	1.3	—	2.7	3.5	10.1	1
	PTCA	1.3	—	3.9	4.9	13.9[a]	

Abbreviations and references as in Table 5.3.
[a] $P < 0.05$ comparing CABG and PTCA cohorts.

of the BARI trial were consistent with those of previous studies, secondary analysis of 353 patients with diabetes mellitus treated with insulin or an oral hypoglycemic agent provided new and controversial information.[51,55] In this subgroup of the BARI trial, the 5-year survival rate was significantly better with CABG than with angioplasty (81% versus 66%, $P = 0.003$).

Although newer techniques such as atherectomy, laser and stents have been introduced in recent years and used in 10 to 30% of all treated lesions, there is no evidence that they result in better outcomes in patients with multivessel disease.[56] However, the advent of coronary stents has significantly reduced the need for target vessel revascularization and trials have been initiated to compare stent-supported angioplasty with CABG (ARTS, SOS, ERACI-II). The 1-year follow-up results of the ARTS trial including 1205 patients have recently been reported[53] and revealed (1) a similar incidence of death, myocardial infarction and stroke, (2) an increased need for additional revascularization procedures in patients initially treated by coronary angioplasty and (3) a cost saving of 4278 Euros during the initial hospitalization and 2965 Euros at 1-year follow-up in favour of coronary stenting. An important finding of ARTS is the reduction by more than half in the need for additional revascularization procedures in patients undergoing coronary stenting (17%) as compared with previous trials featuring repeat revascularization rates of 30 to 40%. A further improvement of angioplasty might be predicted by the addition of platelet glycoprotein IIb/IIIa receptor inhibitors to coronary stenting as indicated by the additional benefit of abciximab in the EPISTENT trial.[57]

Future improvements in balloon angioplasty techniques or a solution to the problem of restenosis may have a greater influence on the decision regarding PTCA versus CABG. Furthermore, because of the progressive decline in graft patency over time, definitive conclusions regarding the relative benefits of PTCA and bypass surgery must await longer follow-

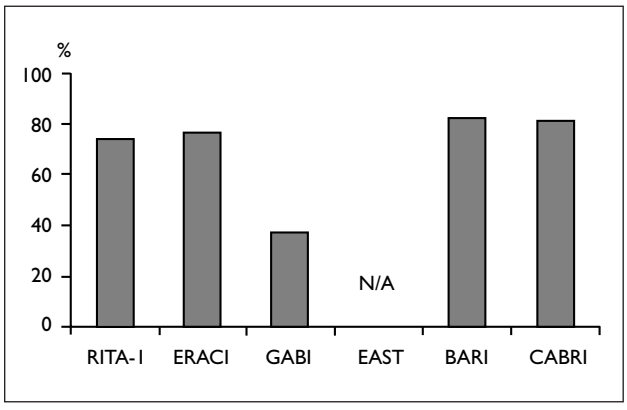


Figure 5.9
Percentage of patients in the CABG group with at least one internal mammary artery graft in six randomized trials comparing angioplasty with coronary artery bypass surgery.

up of patients enrolled in these trials. However, higher use of internal mammary arteries (Fig. 5.9) or complete arterial revascularization may yield a more satisfactory long-term clinical outcome[58] and future comparative trials will have to address this issue. In addition, the fact that more vessels were grafted by surgeons than dilated by cardiologists reflects the conceptual difference between the two treatment strategies. The attempt to treat the culprit lesion may be a potential advantage of balloon angioplasty in multivessel disease for patients in whom symptomatic relief but not complete revascularization is targeted.

Although many patients with multivessel coronary disease are excellent candidates for angioplasty or bypass surgery, the low inclusion rates of approximately 5% reported in all the trials (Table 5.3) do not allow general recommendations on therapeutic decision making. Many patients were excluded because of factors that would make angioplasty unsafe or unlikely to be successful, including left main coronary artery disease, one or more occluded coronary arteries, complex coronary stenoses or previous myocardial revascularization. A recent 3-year survival analysis of 60 000 patients of the New York State registry who had CABG and PTCA in the early 1990s indicated a better survival in surgically-treated patients with severe proximal LAD stenosis.[30] In these patients with multivessel disease, bypass grafting will continue to be the preferred revascularization procedure.

Treatment of chronic total occlusion

Chronic total coronary artery occlusions are tackled in about 10 to 20% of angioplasty procedures[59,60] and constitute one of the main criteria when selecting between angioplasty and bypass surgery. Chronic occlusion angioplasty carries a reduced risk for complications but it is technically more intricate and plagued by a reduced success rate when compared with angioplasty of non-total lesions.

A number of dedicated techniques and materials for chronic occlusion angioplasty have been described and evaluated. They include specific mechanical guidewires such as the ball-tipped Magnum wire,[61] the laser wire,[62] hydrophilic guidewires,[63,64] or particularly robust wires.[65] Randomized comparisons between these methods are scarce and published results depend heavily on indications and patient selection.

The indication for a recanalization attempt balances the anticipated benefit of the patient in terms of symptom reduction, improvement of prognosis and obviation of need for bypass surgery against the technical difficulties and procedural risks.

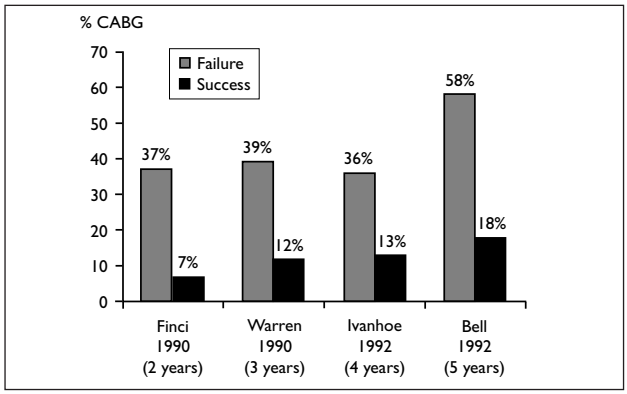


Figure 5.10
Subsequent need for coronary artery bypass surgery in patients with successful or failed recanalization of chronic total coronary occlusions.[66,68–70]

Benefit in case of success

It is noteworthy that successful recanalization of a chronic total occlusion was the first indication of coronary angioplasty yielding the promise of improved longevity in a carefully analysed study.[66] Nonetheless, improved survival is not the foremost goal of recanalization attempts. The natural course of patients with a chronically occluded coronary artery is rather benign (3% mortality during the first year), with the exception of patients with a recent occlusion of the left anterior descending coronary artery whose 1-year mortality is 10%.[67]

A marked reduction of subsequent coronary artery bypass operations is the most conspicuous benefit of the procedure.[66,68–70] On average, a reduction of bypass surgery by two thirds can be expected (Fig. 5.10).

Improvement in myocardial function after recanalization of a chronic total occlusion has been the focus of numerous studies. While no acute effect has been observed, gradual improvement in regional and global ejection fraction has been conclusively demonstrated, provided long-term patency could be achieved.[71,72]

Clinical improvement is certainly the driving force for the patient to undergo an attempt to recanalize a chronically occluded coronary artery. As clinical improvement is difficult to quantify, exercise test data serve as a surrogate. They corroborate the impression that patients with successful recanalization have significantly less ischaemia during follow-up than those with a failed attempt and medical treatment alone.[68]

Practical considerations

Prediction of success

Success or failure can be predicted to a certain degree based on a variety of factors.[73] Duration of occlusion emerges from

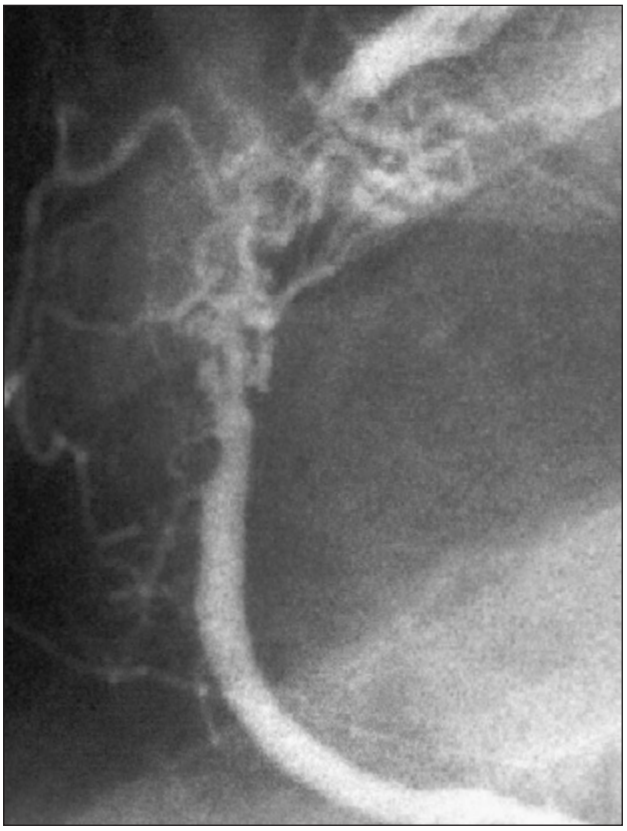


Figure 5.11
Bridging collaterals in an old occlusion of the right coronary artery. Tortuous but well developed 'bridging' collaterals provide complete and prompt contrast filling of the distal artery.

most studies as the key variable with a rapid decline of success during the first 4 weeks.[74,75] The presumed length of the occluded segment is the next important variable.[76] The presence of a stump or a tapered segment leading into the occlusion is a favourable attribute,[66,77] while bridging collaterals exert a strongly negative influence (Fig. 5.11).[77] Only particularly dedicated operators achieve acceptable success rates in the presence of bridging collaterals.[78] Chronically occluded bypass grafts are a target to be left alone according to several authors.[79,80]

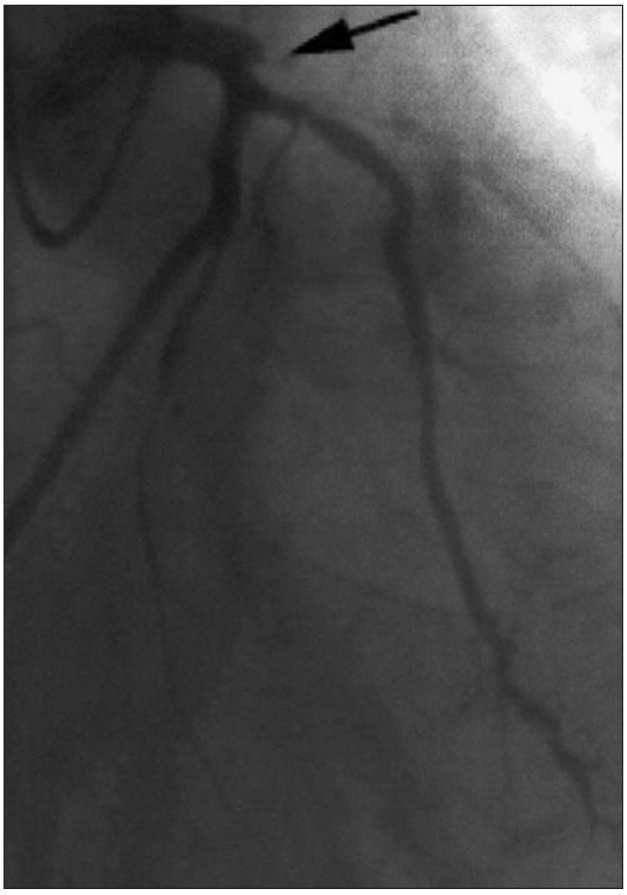
Selection of material

The major drawback of Monorail dilatation systems[81] is the inability to reshape or exchange coronary guidewires while securing the attained position in front of the occlusion with the balloon catheter. This may be more important in the setting of chronic total coronary occlusions than in other settings. Hence, some operators retain this indication as their only remaining non-Monorail (over-the-wire) approach. This makes sense for operators starting with a soft wire since a wire exchange will invariably become necessary unless the initial diagnosis of a chronic occlusion was erroneous. Starting with a robust wire with a pre-shaped tip usually succeeds without wire exchange or allows a conclusive enough attempt in case of failure to obviate the need or temptation for immediate further tackling with other wires. A typical time to abandon the procedure is when a long subintimal path has been created that cannot be avoided in spite of repeated attempts starting well proximal of the entry.

Hydrophilic guidewires[64] of the stiff variety offer the best potential to cross a chronic occlusion of any type. Their drawback is that they also harbour the highest risk for subintimal pathways or perforations.[82] A wire perforation within the occluded segment typically is clinically irrelevant. It will close again immediately after the recanalization attempt is finished or if the true passage is found and the dilatation with or without subsequent stenting is carried out. An unrecognized wire perforation, however, that is enlarged by advancement or even inflation of the balloon catheter, engenders a vessel tear or rupture and may have grave consequences. It is likely to require pericardiocentesis, implantation of a (covered) stent, emergency surgery or a combination thereof. The same holds true for the perforation of a healthy, thin-walled peripheral coronary artery with the tip of a hydrophilic guidewire that had correctly negotiated the occluded segment but was poorly controlled during subsequent balloon manipulations, catheter exchanges or stent implantations. Such holes may be multiple and exhibit a low tendency for spontaneous sealing. In addition, the vessel is under pressure through the recanalized segment or, in case of unsuccessful recanalization, through the collaterals. Once the occlusion is successfully traversed, some authors recommend replacing hydrophilic guidewires with conventional ones. This is only feasible with non-Monorail systems and increases cost, an important issue with the clinically borderline indications often associated with chronic total coronary occlusions.

The laser wire has clearly disappointed in its overall performance in the only randomized trial comparing it with conventional wires.[62] Even without having really resorted to the top of the line mechanical wires in the conventional approaches during the trial, it was concluded that the laser wire should remain a last choice instrument for highly specialized centres and operators in light of its narrow edge over cheaper and less dangerous techniques. Although laser energy occasionally allows successful advancement of the wire where other wires get stuck (Fig. 5.12), this aggressiveness is accompanied by an increased risk for perforations and false channels.

Perforations are extremely rare with conventional coronary guidewires, even those of the extra-support type.[65,78] They are virtually non-existent with the ball-tipped Magnum wire.[61] Therefore, these wires should constitute the primary choice for the general attempt at chronic total coronary occlusions, reserving hydrophilic wires for failures or tough (e.g. very old) occlusions. Laser wires have no place in routine attempts.



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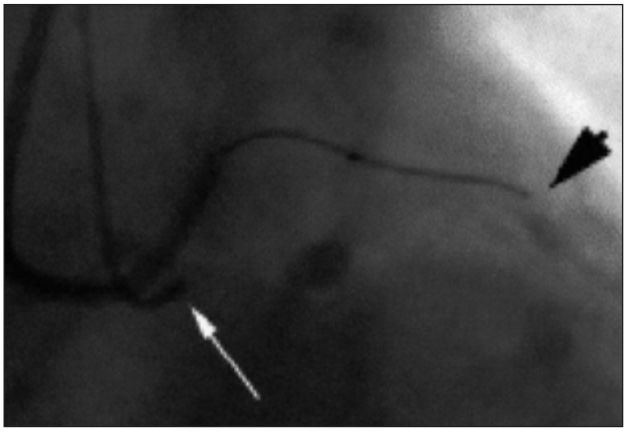

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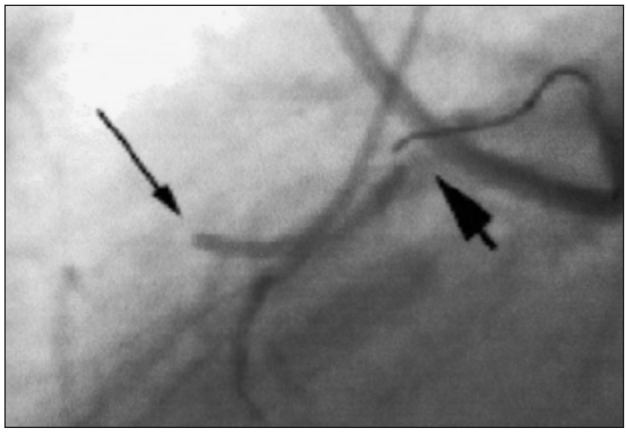

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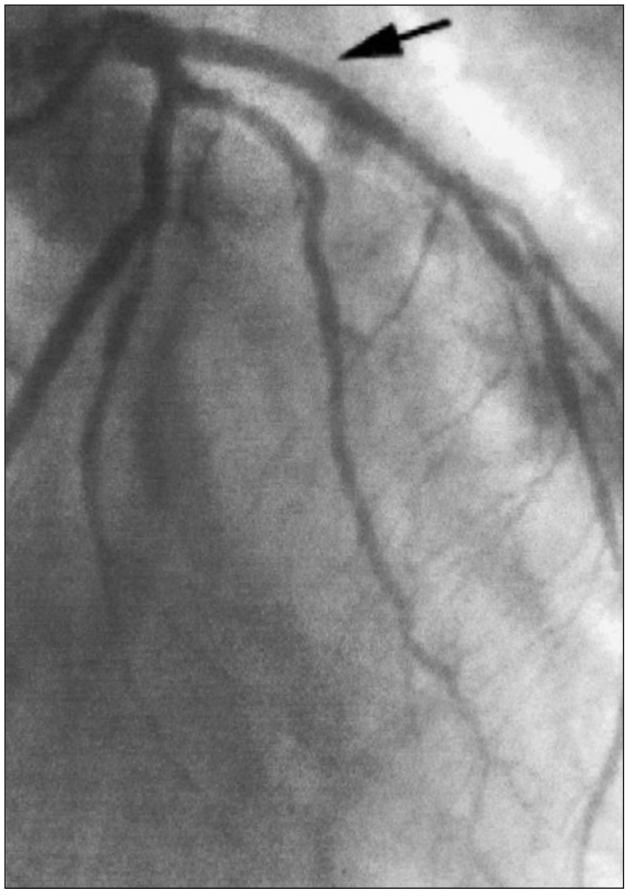

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Figure 5.12
Recanalization of a chronic total occlusion using a laser wire and simultaneous contralateral contrast medium injection. (a) Proximal occlusion of the left anterior descending coronary artery (arrow). (b) Maximal advancement of the laser wire without turning on the laser (arrow, right anterior oblique view). (c) Outlining of the distal left anterior descending coronary artery, and thus the direction into which to apply laser energy, by contrast medium injection into the right coronary artery through a 4 French right Judkins catheter introduced through the same femoral artery as the 7 French guiding catheter used for the contrast medium injection into the left coronary artery (thin arrow, left lateral view). (d) Result after laser recanalization and implantation of a Wallstent (arrow).

Special techniques

The naked wire is generally used to find and enter the stump of the occlusion. Passing the occlusion without support by a bracing catheter documents that the occlusion was very recent or extremely short. In the majority of cases, a support catheter will have to be advanced to stiffen the wire tip. Since this catheter is usually placed very distally at just a millimetre or two off the tip of the wire, the curve of the latter has to be shaped accordingly. The typical 4–5 mm commercial J-tip of conventional coronary guidewires will be straightened by this manoeuvre and steerability will be lost. Therefore, a second bend (usually into the same direction as the primary one) has to be added just 1–2 mm before the wire tip. This secondary J will afford steerability after bracing the coronary wire with the balloon catheter or after entering the occluded segment which also straightens the primary curve of the wire tip (Fig. 5.13).

A common technique to cross the occlusion is to advance the wire a few millimetres and then to follow with the balloon to reinforce it for further advancement. An alternative technique is to advance wire and balloon as a unit. In some situations if the conventional methods fail, it is safe to advance the balloon head first with the wire tip withdrawn inside the balloon. Additional last resort manoeuvres have been advocated and used with success by especially determined operators. The first consists of the inflation of the balloon in the most distal position achievable followed by powerful advancement of the wire, taking advantage of the excellent back-up support by the wedged inflated balloon. For this technique, the ball-tipped Magnum wire is the safest as it can hardly be pushed through the vessel wall. Other wires, particularly the hydrophilic ones, carry a significant risk of false, perhaps even extravascular, pathways. The second manoeuvre is only feasible with conventional over-the-wire systems. It entails the use of the coronary guidewire tail first to override an exceedingly resistant, yet straight and short, occluded segment. After advancing the balloon or support catheter through the crucial segment, the wire is again used tip first for the remainder of the intervention.

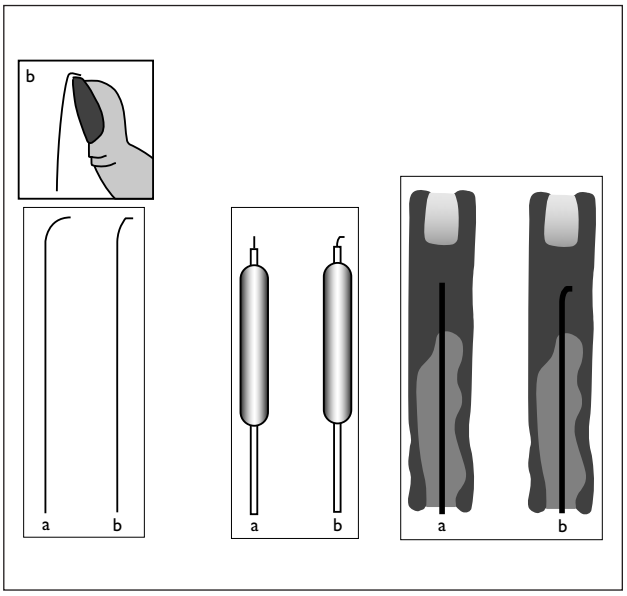

Figure 5.13
Custom shaping of guidewire tip for total occlusions. (a) Commercial J-curve resulting in loss of steerability in action because of straightening of the curve either by the balloon advanced for support (centre panel) or by the narrow passage in the occlusion (right hand panel). (b) Secondary J-curve, shaped with the aid of the thumbnail 1–2 mm proximal to the wire tip. This curve persists in the centre and right hand panel situations and maintains steerability.

During and after laborious attempts to force mechanical or laser wires through resistant occlusions, it is particularly important to assess the proper progress of the wire as well as its correct position in the true lumen beyond the occluded segment. For this purpose, it may exceptionally be advisable to employ a simultaneous injection into the contralateral coronary artery when insufficient ipsilateral collaterals are present. This method has been advocated as a routine for laser wire recanalizations and is exemplified in Fig. 5.12. The second catheter can be introduced through the same femoral artery using a second puncture and a tiny 4 French catheter may be used. Both puncture sites can subsequently be closed using a single pressure bandage or compression device.

It makes sense to use a balloon from the start that is adequately sized for the final dilatation. Most modern balloons feature an excellent crossing profile. Advancing the balloon rarely causes a problem, once the wire is safely in place in the distal third of the vessel to recanalize. If exchange to a smaller balloon becomes necessary, no material is wasted as the initially selected balloon will be reused for the final dilatation. Overall, this policy saves time and money.

In terms of overall strategy, the chronic occlusion should be opened first if angioplasty for more than one lesion is planned. This provides additional collateral support in case another lesion occludes abruptly. A failure may (but must not) be a reason to stop the entire procedure and perhaps recommend bypass surgery.

In summary, chronic total coronary occlusions are a common finding in patients undergoing diagnostic coronary angiography. They constitute about 15% of targets of coronary angioplasty. In symptomatic patients, the primary goal is symptom improvement and reduction of subsequent need for coronary artery bypass surgery. In asymptomatic patients, indications for a recanalization attempt may be derived from the hope for reactivation of hibernating myocardial territories and reversed collaterals in case of disease progression in other coronary arteries. Primary success rates have significantly improved with modern wires and more determined approaches. However, as for plain balloon angioplasty, randomized studies have unequivocally

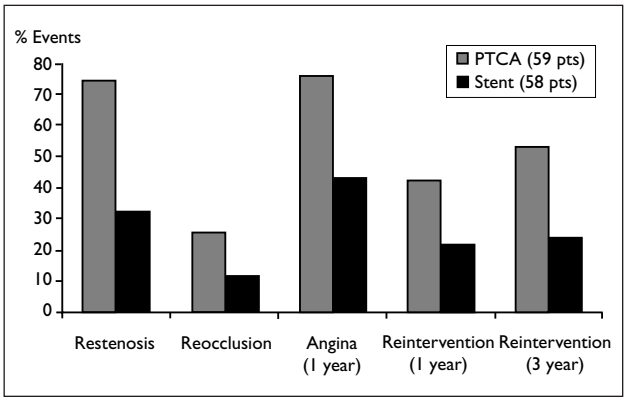

Figure 5.14
Major results of the SICCO (Stenting in Chronic Coronary Occlusion) study randomizing patients with successfully recanalized coronary arteries to plain balloon angioplasty or stent implantation. All differences are statistically significant.[86]

shown that stenting of successfully recanalized coronary segments is overall beneficial.[83–86] Stents reduce reocclusions, restenosis and other clinical events which are frequent problems with recanalized occlusions (Fig. 5.14). However, as with angioplasty for non-total stenoses, experienced operators will use stents judiciously—not routinely.

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6

Cutting balloon angioplasty

Olivier F Bertrand, David Meerkin and Raoul Bonan

Introduction

Since its introduction in 1977, balloon angioplasty has been limited mainly by early vessel closure and late restenosis.[1] The concept of the cutting balloon catheter (Interventional Technologies, San Diego CA, USA), developed by Peter Barath, hypothesized that a reduction in the acute vessel wall injury would allow a decrease in acute complications and late restenosis.[2] This chapter covers the proposed mechanisms of cutting balloon angioplasty and summarizes the current clinical experience and potential applications.

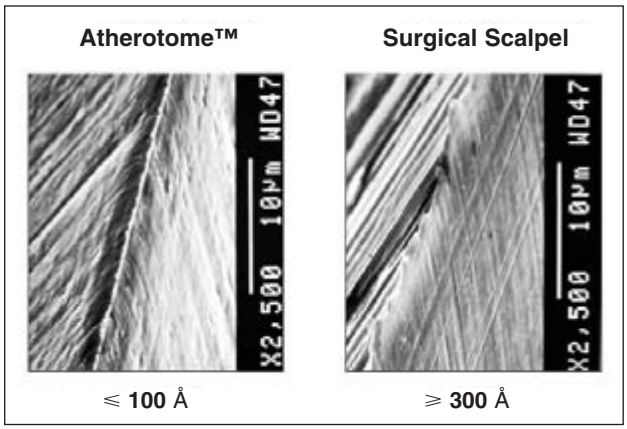


Figure 6.1
The cutting balloon blades are approximately five times sharper than a new surgical scalpel blade.

Device description and mechanisms of dilatation

The cutting balloon catheter was developed from a conventional balloon catheter.[3–6] The distinguishing feature is the presence of three micro-blades on smaller balloon sizes (2.0–3.25 mm) and four micro-blades on balloon sizes between 3.5–4.0 mm diameter. They are arranged lengthwise at 120°/90° radial intervals respectively and are approximately 0.25 mm in height. They are three to five times sharper than conventional surgical blades (Fig. 6.1). The balloon itself is made of polyethylene terephthalate (PET) and is non-compliant. The cutting balloon catheter (Fig. 6.2) is available with a range of inflation diameters from 2.0 to 4.0 mm in 0.25 mm increments and in 10mm and 15mm lengths. The blades are protected before inflation and theoretically after deflation by the folds of the balloon (Fig. 6.3). Unfortunately, the blades limit flexibility of the balloon around sharp bends. The shorter 10 mm length helps in this respect. Recently, a proprietary hydrophilic coating has been developed to improve the cutting balloon trackability (Cutting Balloon Ultra™), which also has a 2.9 Fr catheter shaft and a softer tapered tip.

Figure 6.2
The cutting balloon catheter. The cutting blades are only exposed during balloon inflation.

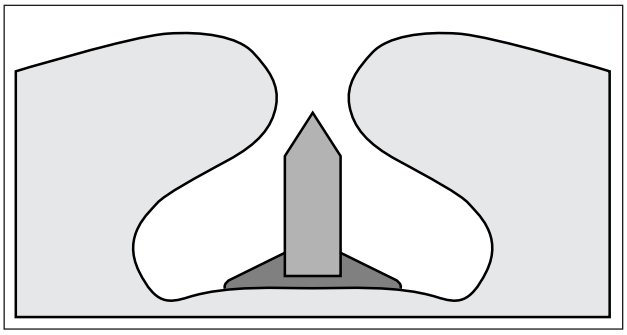


Figure 6.3
Cutting balloon folding action. The blades are shielded from view as they have a lower profile than the surrounding folded balloon.

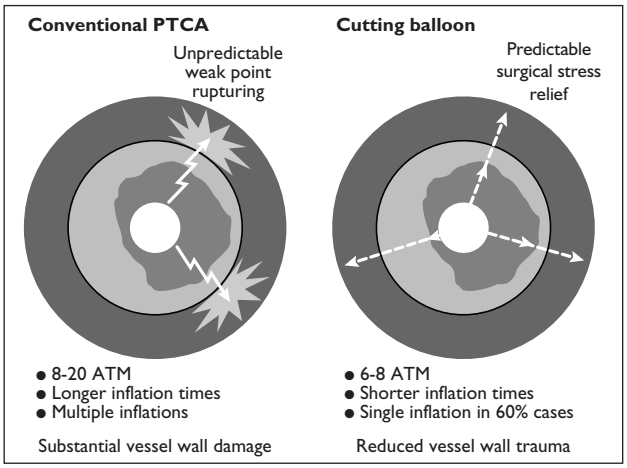


Figure 6.4
Conventional balloon and cutting balloon: comparison of mechanism of action.

The microsurgical dilatation concept combines conventional balloon angioplasty with advanced microsurgical capability. The concept is to 'cut' first and then dilate, resulting in a reduction in histological damage outside the cutting area compared to the standard balloon (Figs 6.4 and 6.5). The resultant lumen enlargement occurs due to widening of these initial cuts through the balloon inflation, relieving the 'hoop stress' of the vessel, thereby reducing the elastic and fibrotic continuity. Due to that peculiar mechanism of action, it should be emphasized that inflation pressure should be kept = 8 atm and the balloon/artery ratio should be targeted between 1.0 and 1.1 to avoid deep vascular wall incisions (Fig. 6.6). The indications for the use of the cutting balloon are listed in Table 6.1. The two main contraindications are tortuous/angled vessels resulting in difficult access due to balloon stiffness (although the shorter 10 mm balloon can be used in this situation) and a risk of rupture, and severely calcified lesions which may also result in wall perforation (but can be treated with the cutting balloon after adequate debulking by rotational atherectomy).

Cutting balloon preparation and use

Guiding catheter and guidewire selection is the same as with conventional PTCA. Good guiding catheter support is always recommended and the large lumen 7 Fr or 8 Fr guiding catheters are the catheters of choice. If the lesion is in the distal anatomy, in a tortuous vessel or severely stenosed, a support wire is recommended as with conventional PTCA.

In preparing the cutting balloon, only a negative preparation should be used to protect the blades. No air or fluid should be introduced until the first inflation. It is highly recommended that a stopcock is used to connect the inflation device to the cutting balloon. A maximum of 5 ml of contrast/saline solution is used in the inflation device to ensure that a maximum vacuum is obtained on deflation.

For the first inflation, a slow inflation rate starting at 1 atmosphere and counting to three between each atmosphere, up to the nominal pressure of 6 atmospheres is used. The normal inflation time is 90 seconds. If a second or further inflations are needed, there should be 3–5 second intervals between each atmosphere increase, to ensure that the balloon material unfolds from around the blades. Rapid inflations could result in puncturing a hole in the balloon. If the lesion is long or there are multiple lesions, always work distal to proximal.

Early clinical experience

In 1993, Unterberg et al reported the first clinical study of cutting balloon angioplasty.[7] In 12 patients out of 25, the cutting balloon was used as the sole device and stenoses were reduced from 84 ± 8% to 28 ± 11%. At 6 month angiographic follow-up, three restenoses were noted from 14 controlled patients. All restenoses presented in lesions that were either pre or post dilated with a conventional balloon and none were present in stand-alone cutting balloon procedures.

Table 6.1 Indications for the use of the cutting balloon.

Bifurcation lesions
Aorta-ostial lesions
Optimal pre-stent dilatation
Restenotic lesions
In-stent restenosis
Highly resistant lesions
Small vessels
Long lesions

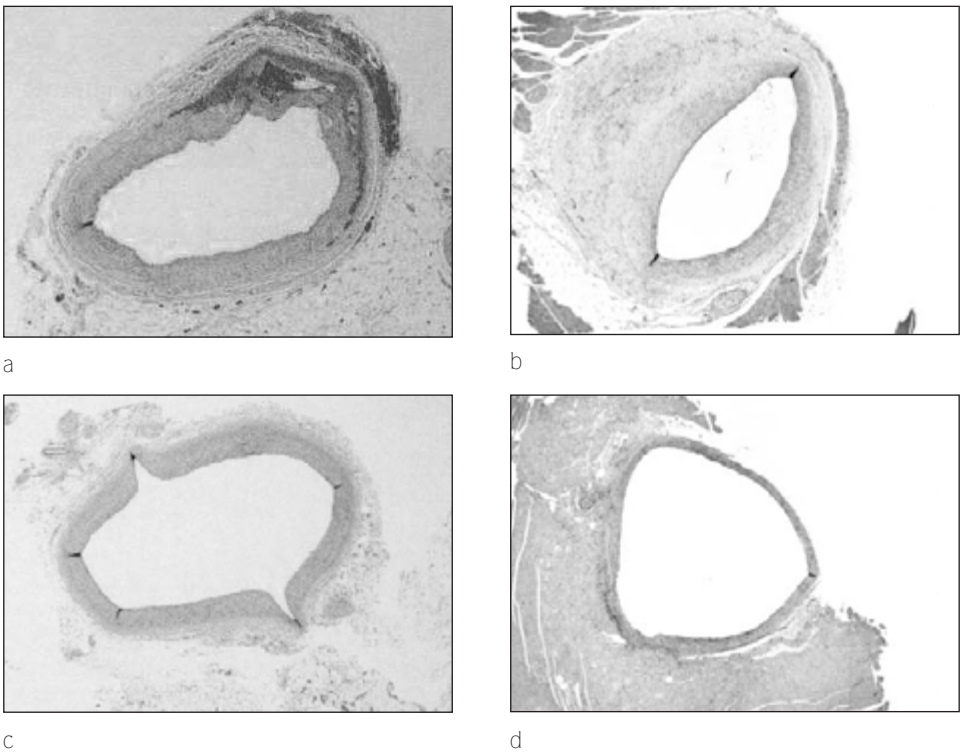


Figure 6.5
(a) Post dilatation PTCA using conventional balloon on normal porcine artery, showing intramural and perivascular haemorrhage. (b) Day 14 post PTCA showing marked neoproliferative changes. (c) Post dilatation with cutting balloon. The endothelium is not denuded and medial muscle cells not stretched. No intramural or perivascular bleeding is present. (d) Effect of cutting balloon angioplasty on normal porcine artery after 14 days showing minimal subintimal proliferation and complete endothelialization.

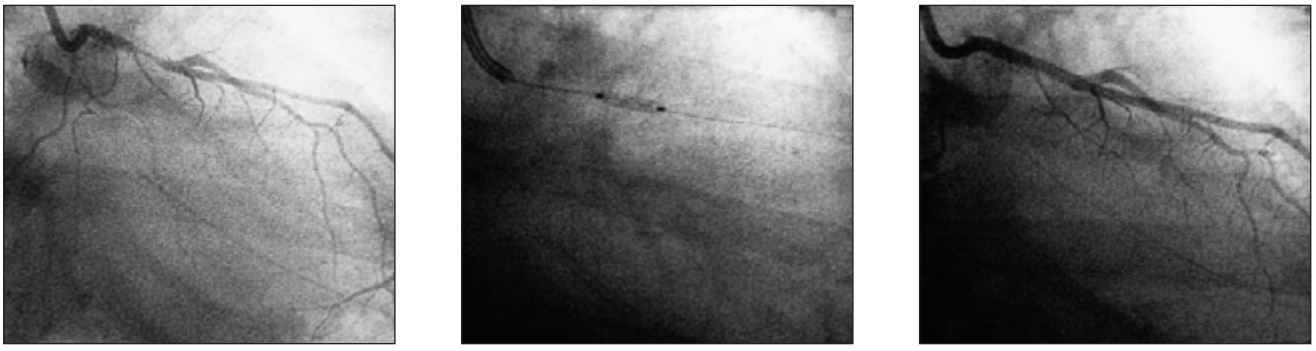


Figure 6.6
Example of cutting balloon result in a 46-year-old female patient with unstable angina who was found to have a severe concentric, tubular stenosis in the proximal LAD artery (a). A 3 mm cutting balloon inflated to 6 atmospheres (b) resulted in a good angiographic result (c). (Acknowledgment: Dr DR Ramsdale, Liverpool, UK.)

In 1996, Hosakawa et al reported their experience with cutting balloon angioplasty in 177 patients and 236 lesions.[8] Lesion characteristics included mostly type B (80%) and type C (16%). Minimal lumen diameter increased from 0.8 ± 0.3 mm to 1.6 ± 0.4 mm and percentage diameter stenosis decreased from 66% to 31%. Procedural success was obtained in 81% of stand-alone cutting balloon angioplasty and 90% after adjunctive conventional balloon angioplasty. No lesion characteristics were significantly associated with treatment failure. Of note, one coronary perforation occurred which was successfully treated by percutaneous pericardial drainage and prolonged inflation with an autoperfusion balloon catheter. Restenosis rate at 3 months was 36% in 36 patients. Extending their experience to 374 patients, the authors reported a restenosis rate of 31% with an acute gain of 1.05 ± 0.5 mm and a late loss of 0.55 ± 0.56 mm.[9]

Prior to initiation of a large randomized trial comparing balloon angioplasty and cutting balloon angioplasty, four non-randomized trials were performed.[10] These included a total of 333 patients with type A or B lesions (n = 314). Of these

lesions, 207 out of 314 (66%) were treated by the cutting balloon catheter as sole device whereas 107 out of 314 (34%) required additional devices. Patients were treated with a single cutting balloon inflation using up to 8 atm and inflation time up to 90 seconds. Overall lesion success after cutting balloon angioplasty was 249 out of 314 (79.3%). In 207 stand-alone cutting balloon procedures, success was obtained in 161 out of 207 (77.8%), and after additional balloon angioplasty in 107 cases, success was obtained in 88 out of 107 (82.2%). In these multicentre experiences, no deaths, emergency bypass surgery or Q-wave myocardial infarctions were reported during the hospitalization period. Non-Q-wave myocardial infarction occurred in 5 out of 333 (1.5%) patients. No vessel perforations were reported, while abrupt vessel closure was present in 5 out of 349 (1.4%) cases and type B dissections were seen in 50 out of 349 (14.3%).

Popma et al have analysed angiographic data from 150 lesions in the Global Learning Curve Registry.[11] Overall, reference diameters were 2.80 ± 0.42 mm. Minimal lumen diameter increased from 1.02 ± 0.3 mm to 2.01 ± 0.42 mm ($P < 0.001$) and diameter stenoses were reduced from 64 ± 9% to 29 ± 12% ($P < 0.001$). The minimal lumen diameter, after cutting balloon angioplasty alone ($n = 106$), was lower than after additional techniques ($n = 44$), 1.93 ± 0.37 mm versus 2.22 ± 0.46 mm, respectively. The average cutting balloon/artery ratio was 0.88 ± 0.12 (range 0.64–1.34). Interestingly, no difference in cutting balloon/artery ratio was found in lesions with type B dissections and those lesions without dissections (1.00 ± 0.11 versus 0.97 ± 0.13).

In the International Phase II Trial, the angiographic analysis of the 120 lesions (Core lab: Cardialysis) showed a late loss in the group treated by cutting balloon alone of 0.24 mm compared to 0.36 mm in the group requiring additional inflations.[10] In preliminary data comparing absolute and relative angiographic parameters from the International Phase II Trial with those from the CCAT study, a lower loss index was found after cutting balloon than after cutting balloon and additional angioplasty or directional atherectomy.[12] This in turn suggested that cutting balloon, by limiting the extent of vessel trauma, could reduce the neointimal formation and hence restenosis. From these data, it appeared that cutting balloon could be used as the sole device in about two-thirds of the cases with a primary angiographic success similar to that of balloon angioplasty. In these selected lesions, complications were kept low and initial angiographic follow-up suggested a possible advantage of cutting balloon angioplasty over conventional balloon angioplasty.

Table 6.2 The Global Randomized Cutting Balloon Trial: baseline demographic and clinical characteristics.

	CB	*PTCA*	*Total*
Patients	617	621	1238
Lesions	689	696	1385
Age (y)	59 ± 10	58 ± 11	59 ± 10
Male (%)	72	77	74
Diabetes (%)	13	12	13
Hyperlipidaemia (%)	45	47	46
High Blood Pressure (%)	34	37	36
Current smokers (%)	67	69	68
Prior MI (%)	37	39	38
Prior CABG (%)	3	3	3
LVEF (%)	60 ± 12	61 ± 12	60 ± 12

CB: cutting balloon.

Randomized studies comparing the cutting balloon with balloon angioplasty

The Global Randomized Cutting Balloon Trial was designed to compare acute procedural results and 6-month outcomes using 1245 patients treated with cutting balloon or conventional balloon angioplasty (Fig. 6.7). This represented the largest clinical trial comparing balloon angioplasty to a new device. The protocol targeted short, type A (15%), B_1 (39%), and B_2 (43%) lesions in native coronary arteries. Only 3% of type C lesions were recruited in each group. If the patient was allocated conventional balloon angioplasty, the operator was authorized to use multiple balloons and multiple inflations, as necessary. Furthermore, there was no restriction in terms of inflation pressure or duration. If the patient was assigned the cutting balloon, initial dilatation was performed with a single inflation (maximum 8 atm) for 90 seconds. The operator was strongly encouraged not to use subsequent conventional balloon angioplasty if the residual stenosis was ≤ 40%.

By 1996, 1238 patients had been enrolled at 30 centres in North America and Europe (Table 6.2).[13] There were seven patients deregistered after randomization but before receiving the assigned treatment, five in the cutting balloon arm and two in the PTCA arm. All patients were to undergo repeat angiography between 6 and 9 months post procedure. Among the remaining 1238 patients, follow-up angiograms have been performed on 1080 (88.7%) with qualified QCA data available on 1015 (83.3%). Clinical follow-up was performed at 6 weeks, 6 months and 9 months. The primary endpoint was angiographic binary restenosis rate at 6 months. The secondary endpoint was the 9 months clinically-driven target lesion revascularization rate. All major clinical events were adjudicated by a clinical events committee blinded to treatment assignment, and all end points were analysed on an intent to treat and on a per protocol basis.

In the intent to treat analysis, the acute and 6-month angiographic (Table 6.3) and clinical results (Table 6.4) were similar

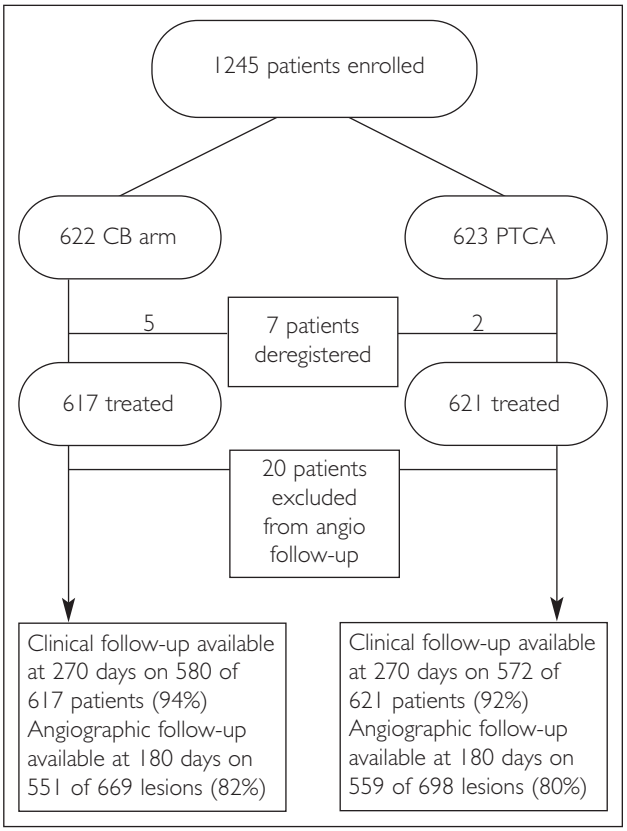


Figure 6.7
Flow chart of the Global Randomized Cutting Balloon Trial.

in both the cutting balloon and the PTCA arm. Procedural success defined as achievement of <50% residual diameter stenosis and freedom from MACE (death, Q-MI, emergency CABG or repeat TLR) was 92.9% in the cutting balloon arm versus 94.7% in the PTCA arm. MACE during the first month were noted in 3.7% in the cutting balloon arm and 2.7% in the PTCA arm. MACE > 30 days were noted in 10% of the cases in the cutting balloon arm versus 12.9% in the PTCA arm. The binary angiographic restenosis rate (>50% DS) was 31.4% for the cutting balloon versus 30.4% for PTCA. Interestingly, the 9 month freedom from target vessel revascularization was significantly higher after cutting balloon compared with PTCA, 88.5% versus 84.6% ($P = 0.042$), respectively. Vascular complications requiring surgical repair were also similar between the two groups, 0.3% for cutting balloon versus 0.2% for PTCA.

In the per protocol analysis, the binary restenosis rate was slightly smaller after cutting balloon versus PTCA, 28.8% versus 32.6% (P = ns). Furthermore, the 9-month incidence of freedom from TVR was significantly greater after cutting balloon compared with PTCA, 90.5% versus 85.1% ($P = 0.006$). Similarly, the incidence of freedom from target lesion revascularization was also significantly greater after cutting balloon compared to PTCA, 91.2% versus 85.8% respectively ($P = 0.021$).

Other randomized studies have also reported preliminary results. In the CUBA (CUtting Balloon versus Angioplasty) trial, 306 patients with de novo lesions in native coronary arteries were randomized to cutting balloon or PTCA. At 6-month follow-up, the incidence of MACE was similar between the two groups whereas the angiographic restenosis rate was 30% in the cutting balloon group versus 42% in the PTCA group ($P < 0.05$).[14] In the REDUCE-I (REstenosis reDUction by Cutting balloon Evaluation) study, 800 patients with de novo, type A and B_1 lesions were randomized to cutting balloon or PTCA. Procedural success rates were similar in the cutting balloon (90.7%) and PTCA groups (87.1%). Interestingly, fewer dissections occurred after cutting balloon compared with PTCA (25.2% versus 38.9%, $P < 0.0001$) and this was associated with a lower incidence of

Table 6.3 The Global Randomized Cutting Balloon Trial: angiographic results.

Measures	*CB arm* (*n* = 689)	*PTCA arm* (*n* = 696)	*All lesions* (*n* = 1385)
Ref diam pre (mm)	2.84 ± 0.49	2.87 ± 0.49	2.86 ± 0.49
Ref diam post (mm)	2.89 ± 0.49	2.93 ± 0.48	2.91 ± 0.49
Ref diam f-up (mm)	2.79 ± 0.46	2.83 ± 0.47	2.81 ± 0.47
MLD pre (mm)	0.96 ± 0.33	0.98 ± 0.34	0.97 ± 0.33
MLD post (mm)	2.05 ± 0.52	2.13 ± 0.53	2.09 ± 0.52
MLD at 6 months	1.63 ± 0.62	1.65 ± 0.61	1.64 ± 0.62
Lesion length (mm)	8.9 ± 4.2	8.9 ± 4.4	8.9 ± 4.3
% DS pre	66 ± 11	66 ± 11	66 ± 11
% DS post	29 ± 14	27 ± 13	28 ± 14
% DS at 6 months	42 ± 19	42 ± 19	42 ± 19
Restenosis rate (50% DS)	31.4	30.4	30.9
Loss index	0.36 ± 0.89	0.37 ± 1.52	0.37 ± 1.52

CB: cutting balloon; f-up: follow up; %DS: percentage diameter stenosis.

Table 6.4 The Global Randomized Cutting Balloon Trial: complications

Complications (%)	*CB*	*PTCA*	*All*
MACE (death, Q-MI, CABG, TLR)	13.6	15.1	14.4
Death	1.3	0.3	0.8
Myocardial infarction			
Q wave MI	1.5	1.1	1.3
Non-Q wave MI	3.2	1.8	2.5
Emergent CABG	1.0	1.0	1.0
TLR	11.7	14.8	13.2
Subacute closure	1.3	1.6	1.5
Clinical perforation	0.8	0.0	0.4

bail-out stenting (24% versus 38.9%, $P = 0.02$), respectively (Suzuki, pers comm). In the IVUS substudy, Shimodozono et al found that coronary dissections were more common after PTCA in calcified lesions whereas the cutting balloon produced a similar dissection area index in calcified and non-calcified lesions.[15] In the CAPAS study, 232 patients with type B or C lesions in vessels <3.0 mm were randomized to cutting balloon or PTCA. At 3 months, the restenosis rate after cutting balloon was 22% compared to 41% after PTCA ($P < 0.01$). However, at 1 year, the incidence of MACE (death, Q-MI, CABG and TLR) was similar between the two groups.[16]

Other applications of cutting balloon angioplasty

Resistant coronary lesions

Resistant coronary lesions remain a challenge for modern angioplasty. Using the cutting balloon catheter, we have reported our initial experience in six highly resistant lesions.[17] Three lesions were located in saphenous vein grafts and three lesions in native coronary arteries. Reference diameters were 3.30 ± 0.68 mm. Initial attempts using conventional balloons with a maximum balloon/artery ratio of 1.14 ± 0.27, maximum inflation pressure of 20 ± 3 atm and total inflation time of 11 ± 5 minutes failed. Using cutting balloon catheters and a balloon/artery ratio of 0.99 ± 0.23, a maximum inflation pressure of 8 ± 1 atm and a duration of 3 ± 0.6 minutes, minimal lumen diameters increased from 0.85 ± 0.63 mm to 2.49 ± 0.55 mm. Additional balloon angioplasty or stenting performed in five cases led to a final minimal lumen diameter of 3.16 ± 0.97 mm. Therefore, the cutting balloon angioplasty could be a useful device for the treatment of resistant coronary lesions.

Aorta-ostial lesions

Kurbaan et al reported similar success on aorta-ostial lesions when they used the cutting balloon before stenting in three native and five vein graft aorta-ostial lesions.[18] These lesions were resistant to conventional high pressure balloon angioplasty and responded to cutting balloon at a mean pressure of 7.5 ± 0.5 atm. All procedures were completed by stenting and displayed a 100% event-free survival.

Pre-stent dilatation

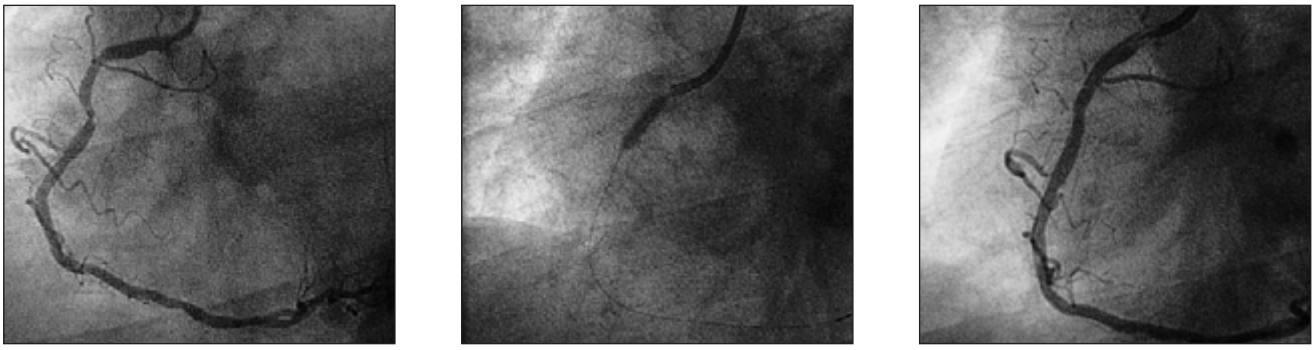
In a small randomized study involving 120 lesions in 107 patients, Park et al examined the potential impact of the cutting balloon prior to stenting on the rate of in-stent restenosis (using the GFX stent) compared with balloon angioplasty.[19] They found that the cutting balloon made no difference to restenosis rates (20% in both groups) and major adverse cardiac event rates were also similar. The CBBEST (Cutting Balloon BEfore STenting) study is also evaluating the effect of the cutting balloon as a predilatation method before stenting to reduce vascular trauma.

In-stent restenosis

Very recently, the cutting balloon was proposed for the treatment of in-stent restenosis (Fig. 6.8). Using intravascular ultrasound, Albiero et al suggested that the cutting balloon had greater capacity to extrude residual neointimal plaque outside the stent struts compared with conventional balloon angioplasty.[20] The long-term superiority of cutting balloon over balloon angioplasty for the treatment of in-stent restenosis is being assessed in the two randomized multicentre trials, the REDUCE II study (REstenosis reDUction by Cutting balloon Evaluation) in Japan and the RESCUT (REStenosis CUTting balloon evaluation) trial in Europe.

Conclusion

The cutting balloon represents a mechanical attempt to deal simultaneously with vascular recoil/remodeling and with smooth muscle cell proliferation. In microsurgical dilatation, stress fracture mechanics are employed to alter the vessel's contractile capabilities by scoring through the intima and into the media, while simultaneously reducing barotrauma by lowering inflation pressures, inflation times and the number of inflations through localized dilatation forces in small sections of the treatment area. In contrast to other devices, the cutting balloon is easily mastered by any interventional cardiologist.



a b c

Figure 6.8
Example of cutting balloon result in a 61-year-old man who underwent two stent implantations in the proximal RCA and presented with a recurrence of angina. Coronary angiography revealed two severe, discrete in-stent restenoses (a). These lesions were each dilated (single inflation at 8 atmospheres) with a 3.5 mm cutting balloon (b) and an excellent result achieved (c). The patient has subsequently remained free from angina. (Acknowledgement: Dr J Gunn, Sheffield, UK.)

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7

Coronary stenting I: intracoronary stents – form, function and future

David G Almond

Introduction

Not since the advent of coronary angioplasty itself has a technique developed in such a way as intracoronary stenting. While this procedure has come of age in the last decade, its origins go back much further.

The concept of an endoluminal scaffolding device to maintain lumen integrity in diseased vessels has been present since the pioneering work of Charles Dotter in the 1960s. Initially using sequentially sized dilating catheters and later early balloon catheters, he was able to reduce stenoses in peripheral vessels. However, he soon discovered that many of these vessels thrombosed at the site and became narrowed or occluded. To overcome this problem he initially inserted tubular prosthetic grafts that were 'pushed' in place from within a guiding catheter. In his initial study involving 25 dogs, he found that all the implanted grafts occluded within 24 hours. To overcome this, he developed coil springs of stainless steel wire wound on a mandril. Implanting three such grafts into heparin-treated dogs, he found that two of the three remained patent for over two years.[1] Despite this, it was almost 20 years before intracoronary stenting in humans became a reality. In 1986 both Sigwart in Switzerland and Puel in France implanted stents in human coronary arteries[2] and in the following year, the first coronary implants were performed in the United States by Roubin[3] and Schatz.[4] Early indications were as bailout devices for the treatment of acute and threatened closure for failed angioplasty and shortly thereafter for restenosis as well as the treatment of saphenous vein graft stenoses.

The first published results of observational multicentre trials utilizing the self-expanding Wallstent in Europe and the Palmaz–Schatz balloon-mounted stent in the United States occurred in 1991 and highlighted several key problems:

- the occurrence of subacute stent thrombosis, which occurred in 20% of patients in the European study;
- significant bleeding complications relating to the aggressive anticoagulation regimen employed; and
- problems of stent loss or embolization using the Palmaz–Schatz stent or malpositioning using the Wallstent.[5,6]

Despite this less than auspicious start, many believed that the concept of endovascular scaffolding remained sound and work continued on improvements in stent technology and periprocedural care. Over the last decade this has led to an exponential growth in the use of intracoronary stents as an adjunct to balloon angioplasty for the treatment of obstructive coronary artery disease (Fig. 7.1). From very few implants in 1990, an estimated one million stents were implanted worldwide in 1998,[7] with over half a million in the United States alone the following year.[8] Stents are now used in up to 80% of all coronary interventions.

Several factors have led to this rapid growth. Firstly, improved stent technology has led to more flexible, lower profile devices being delivered more easily in tortuous vessels. Secondly, new deployment strategies coupled with post-procedure antiplatelet therapy have significantly reduced the subacute thrombosis rate, the incidence of vascular complications and the length of hospital stay. Additional factors include the reduced cost of intracoronary stents, the improved angiographic appearance post-procedure compared to balloon angioplasty and the results of randomized clinical trials which now support the use of intracoronary stenting in a variety of clinical and lesion-specific subsets.

In the remainder of this chapter the classification of stents will be discussed with emphasis on stent design and characteristics. This will include the results of some comparative trials and the recommendations for specific stent types in particular lesion morphologies. The indications for coronary stenting in a variety of clinical and lesion specific subsets will

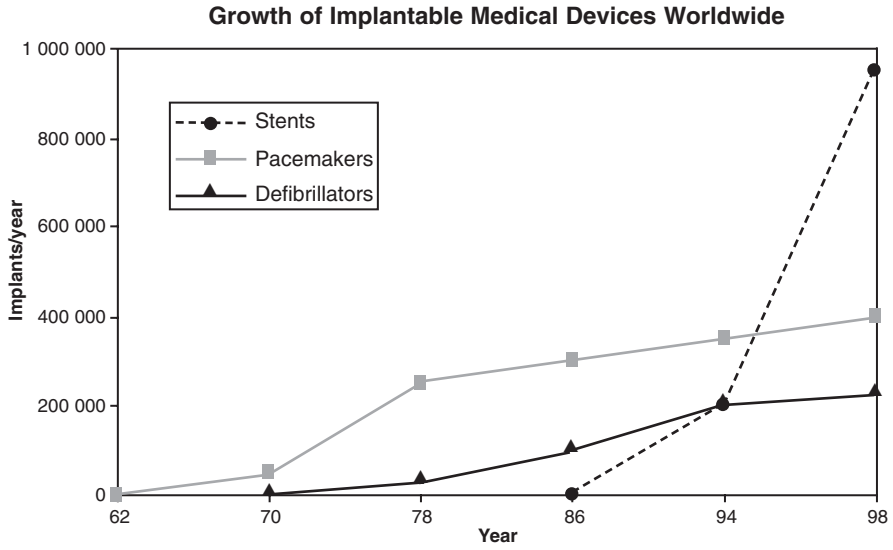


Figure 7.1
The dramatic growth of intracoronary stenting since its inception in the late 1980s compared to other implantable medical devices (courtesy of Medtronic, Canada).

be discussed as will the future directions of intracoronary stenting including drug delivery stents, covered stents, bifurcation stents, and brachytherapy.

Classification of stents

From the outset, researchers and stent manufacturers have been in search of the Holy Grail – the ideal coronary stent (Table 7.1). Several important characteristics must be considered and include mounted profile, flexibility, trackability, conformability, visibility, thrombogenicity, uniform expansion, radial force, vessel trauma and its effect on restenosis. This has led to the creation of a large variety of stents of varying designs and materials in the hope of achieving the ultimate goal. To date, we are still searching.

Table 7.1 Characteristics of an ideal stent.

- Low profile
- High longitudinal flexibility/trackability
- Secure attachment to delivery balloon
- Full and uniform expansion within the working range of the delivery balloon
- No foreshortening or recoil on expansion
- Adequate radial and axio-lateral strength for all lesion types
- Conforms to vessel shape without change in stent geometry
- Visible without obscuring lumen
- Biologically inert
- Non-thrombogenic
- High fatigue tolerance
- Can be used for primary stenting in the majority of cases
- Delivery balloon can be used to post-dilate
- Available in a variety of sizes and lengths
- Low cost

Although stents have been manufactured from a number of different metals such as tantalum and nitinol, the vast majority in clinical use today are manufactured from stainless steel. Tantalum stents, because of their marked radio-opacity, proved excellent for accurate placement. However, once deployed they obscured the lumen. Nitinol with its characteristic thermal memory and excellent flexibility remains promising, but has yet to be widely utilized. At present, steel has proven to be the most versatile in terms of cost, availability, tensile strength and tissue compatibility. Polymer stents, attractive because of their ability to degrade and act as drug delivery vehicles, have failed to fulfil their promise because of the technical difficulties of expansion and adequate radial support, as well as the intense inflammatory response that they create.

Stents can be characterized on the basis of their delivery system, self-expanding or balloon-expanded and, for the latter group, by their construction and design – coil, slotted tube or modular. Due to the large number of stents currently available in each category, individual descriptions are beyond the scope of this chapter. Instead, discussions regarding the general characteristics of each group will be presented.

Self-expanding stents

The prototype self-expanding stent remains the Wallstent™ (Fig. 7.2). This is a woven multi-filament stainless steel stent that is constrained on a delivery catheter by a rolling membrane

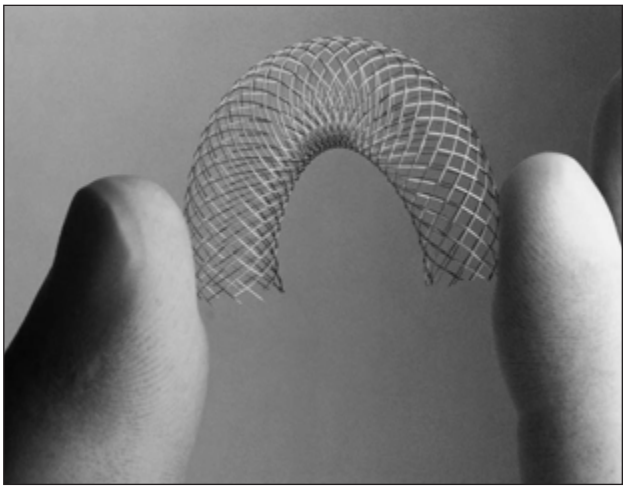


Figure 7.2
The self-expanding Wallstent™ (Boston Scientific).

sheath. Once positioned over a guide wire, the outer sheath is retracted allowing the stent to expand to its preformed diameter. The latest version, the Magic Wallstent™, incorporates modifications of the braiding angle as well as improvements to the delivery system. This has resulted in a device which is much easier to deliver, can be recovered by the outer membrane if less than 50% of the stent has been deployed and which demonstrates more flexibility and less shortening on expansion than its predecessor. Coupled with advances in peri and post procedural anticoagulation, significant improvements in outcome have now been reported, with clinical success, subacute closure and angiographic restenosis rates similar to results obtained with other stents.[9–12] It is available in lengths up to 50 mm and for vessel diameters up to 5.5 mm, making it ideal for long, diffuse lesions, larger vessels and saphenous vein grafts, where it can be deployed without predilatation. A major disadvantage remains the relatively high surface coverage (up to 20%) which may limit access to side branches.

The SciMed Radius™ stent is a self-expanding nitinol stent composed of multiple zigzag segments attached to each other at three sites (Fig. 7.3). Like the Wallstent™, it is constrained on a delivery catheter by an outer membrane that is withdrawn to deliver the stent. The material and design results in a very flexible stent (making it well suited to lesions in tortuous vessels) with virtually no shortening (<5%) on expansion. Early observational studies have shown excellent 1-month event free rates.[13] Like the Wallstent™, side branch access may be limited due to similar surface coverage.

Unlike balloon-expandable stents, self-expanding stents do not appear to reach their nominal diameter at implantation despite recommended post-dilatation. The long-term benefit may therefore depend in part on continued expansion after initial implantation. Studies have reported late stent gains of 0.5 to 0.6 mm over follow-up periods of 6 to 8 months. While the extent of expansion appears to correlate with the amount of neo-intimal proliferation, these competing forces appear to balance each other, as there seems to be little effect on late lumen loss.[14,15]

Balloon-expandable stents

This category can be divided into three basic types: coil, slotted tube and modular stents.

Coil stents

These are nearly all balloon-mounted stents created from a single continuous filament of wire shaped into a specific design (eg sinusoidal wave, helical coil and fishscale). It is this design that primarily differentiates the stents, although a variety of metals are also used. While stainless steel remains the most common (Gianturco–Roubin II™, Cook Inc. (Fig. 7.4a); Crossflex™, Johnson & Johnson/Cordis; Freedom™, Global Therapeutics Inc.), others included tantalum (Wiktor™ stent,

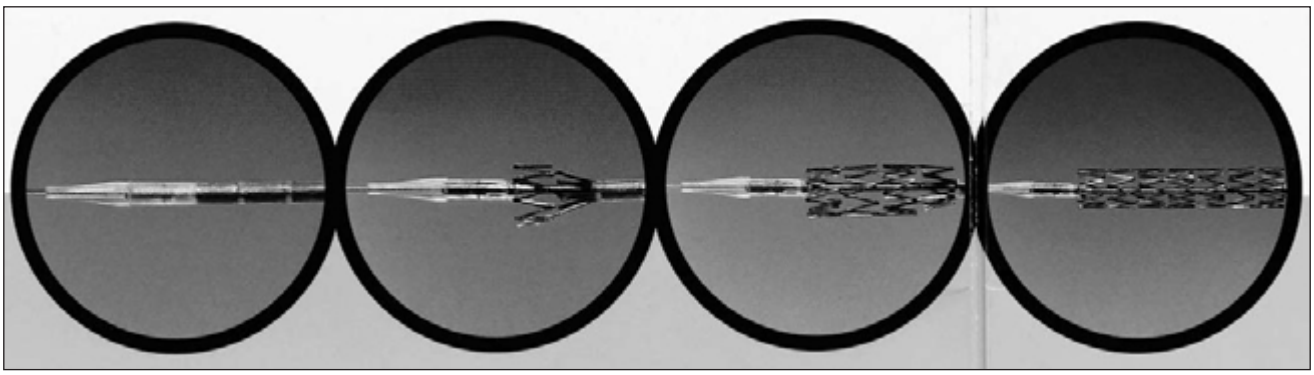
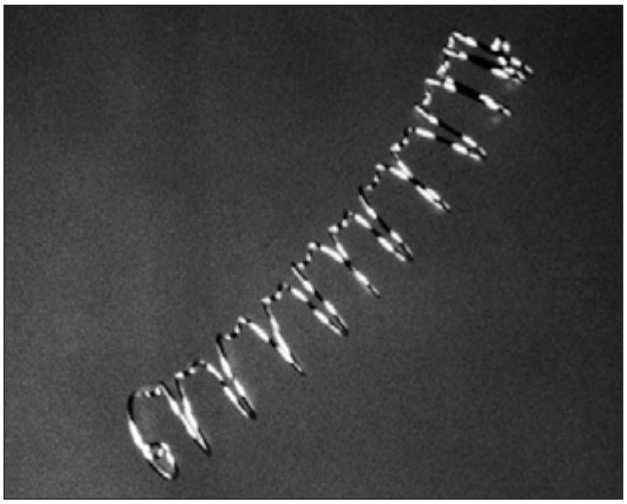


Figure 7.3
The self-expanding Radius™ stent (Boston Scientific).



a

b

Figure 7.4
Examples of coil stents: (a) Gianturco–Roubin II™ (b) Wiktor I™.

Medtronic Corp. Fig. 7.4b), platinum/iridium (Angiostent™, Angiodynamics) and nitinol (Cardiocoil™, Medtronic InStent). Because of their coil design, all share the features of excellent flexibility, trackability and conformability, making them potentially useful in tortuous vessels and angulated lesions. They also tend to have lower metal to surface ratios (7–10%) allowing for better access to side branches.

However, these design 'advantages' may also prove to be problematic in certain circumstances. The relative lack of longitudinal support can lead to distortion if significant resistance is met during stent advancement ('accordianing'). In addition, studies have demonstrated that in general these designs tend to have less radial strength than slotted tube or modular stents. Moreover, comparative studies have shown a tendency to greater chronic recoil and, possibly, restenosis (particularly in chronic total occlusions and vessels <3 mm in diameter) as compared to other stent types.[16–18] This latter phenomenon may be due in part to the relatively low metal to artery ratio and larger inter-strut distances allowing for greater tissue prolapse into the lumen with its subsequent deleterious effects.[19,20] These factors may therefore limit their application in hard, calcified lesions (particularly in tortuous vessels) as well as chronic total occlusions and ulcerated or dissected lesions where plaque burden is high and flaps may already be present therefore increasing the risk of prolapse.

Despite these potential shortcomings, individual evaluations of coil stents have demonstrated acceptable and comparable clinical and angiographic outcomes in a variety of settings.[21–24] In addition, a randomized equivalence trial of the Gianturco–Roubin II™ and Palmaz–Schatz™ stents in favourable lesions showed similar clinical and angiographic outcomes at 9 months for optimally deployed stents.[25] Despite this, few coil stents remain available.

Slotted tube stents

These stents share the common characteristics of being either laser cut or chemically etched from a solid piece of metal tubing, cleaned, electropolished and mounted on a delivery balloon. They differ primarily in strut design, shape and thickness. As with coil stents, the vast majority are made with 316L stainless steel, although the NIRoyal™ is also electroplated with 24K gold to improve visibility. The major exceptions were the Paragon™ stent (Progressive Angioplasty Systems, Inc) which was composed of martinsitic nitinol and the tantalum TENSUM™ stent (Biotronik GmbH).

Since the prototype Palmaz–Schatz™ stent (Fig. 7.5) was first released, numerous technical advances have been made to both the stents (cell design, strut shape and thickness) and the delivery balloons. This has greatly improved crossing profiles (allowing a greater role for primary stenting) and longitudinal flexibility (and hence trackability) while maintaining excellent radial support (Figs 7.6 and 7.7). Significant advancements have also been made in stent securement using a variety of proprietary techniques that has greatly decreased the incidence of detachment and embolization (Fig. 7.8).

In general, these stents provide greater surface coverage (averaging 15–18%) and radial force than coil stents, making them better suited to prevent tissue prolapse associated with ulcerated and dissected lesions, as well as minimizing recoil in calcified and aorta-ostial lesions. These benefits are balanced by the slight reduction in longitudinal flexibility that may limit their use in extremely tortuous or rigid vessels.

As with coil stents, single centre and registry evaluations have shown excellent and comparable short and intermedi-

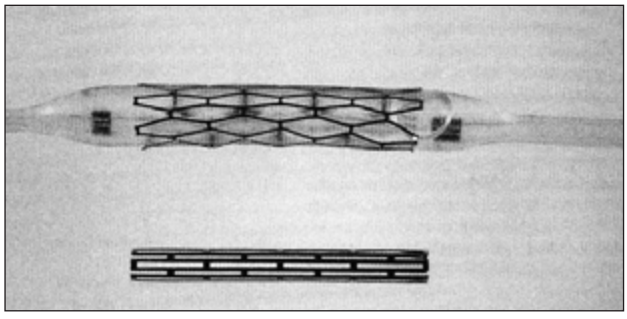
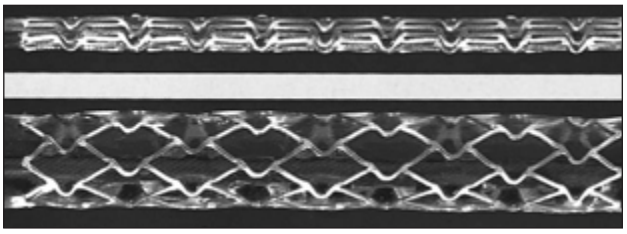


Figure 7.5
The original Palmaz–Schatz™ stent.



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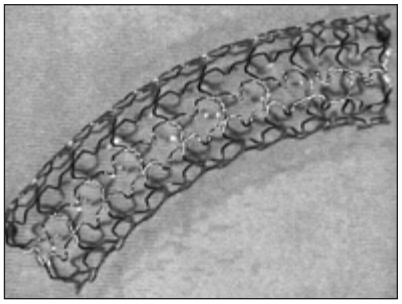

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Figure 7.6
Examples of slotted tube stents: (a) NIRoyal™ (b) Bestent 2™.

ate term clinical and angiographic outcomes.[26–28] A small number of randomized trials have been performed comparing the new generation stents to the original Palmaz–Schatz™ stent. These have demonstrated similar or slightly superior clinical and angiographic outcomes at both early and late follow-up.[29,30] However, it must be kept in mind that these were equivalence trials that were not designed to show superiority. To date, there are few data to differentiate one stent from another in this category and the decision as to which to use must be based largely on the experience of the interventionist and the nature of the vessel and lesion to be treated.

Modular stents

Recognizing the superior flexibility of coil stents and the greater radial support of slotted tube designs, modular stents were developed in an attempt to capture both of these characteristics in one stent. In general, they are composed of a series of discrete zigzag modules of 316L stainless steel laser welded to either a flexible spine (Bard XT™ coronary stent)

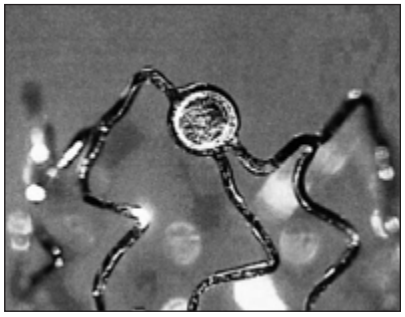
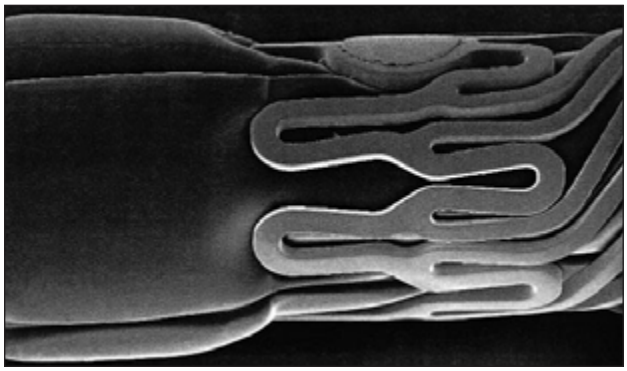


Figure 7.7
A gold marker at each end of the Bestent 2™ allows for better visualization and more accurate placement, especially in ostial lesions.



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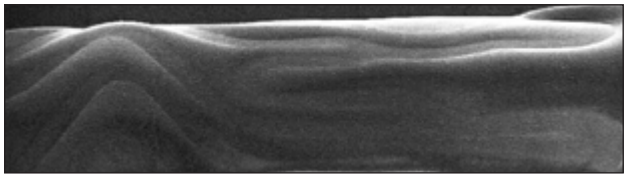

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Figure 7.8
(a) and (b) Example of stent securement of the Bestent 2™, demonstrating 'pillowing' of the stent into the balloon material achieved by a combination of heat and pressure.

or to successive modules (AVE Microstent™, Medtronic/AVE GFX™ (Fig. 7.9), S540™ and S670™ stents) resulting in a stent with excellent flexibility and radial support similar to slotted tube designs.[16,17]

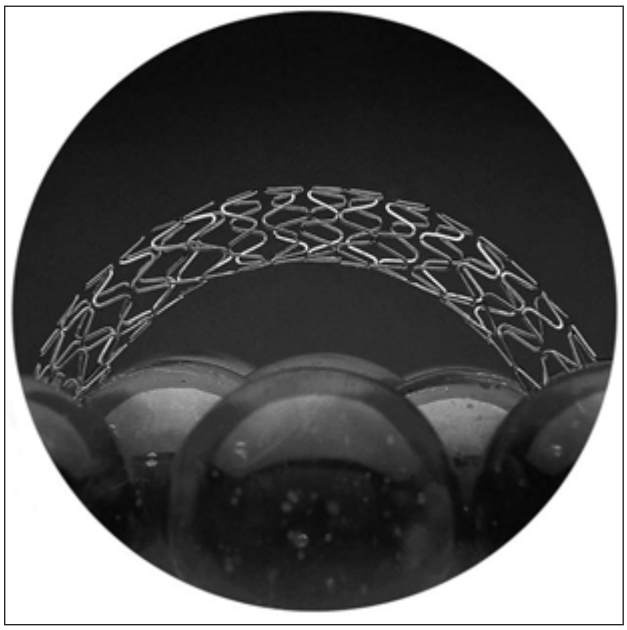


Figure 7.9
The GFX II™ stent. An example of a modular design with continuously connected elements.

Like coil stents, early modular designs had relatively large interstrut distances allowing for potential tissue prolapse and often leaving a 'scalloped' angiographic appearance following implantation. More recent developments, however, have increased the number of crowns per module as well as shortening the module width, thereby providing greater scaffolding with minimal loss of longitudinal flexibility and improved post-deployment angiographic appearance.

Early registry results demonstrated comparable clinical and angiographic outcomes as compared to the Palmaz–Schatz™ stent.[16,17,31] As with the other stent types, few randomized trials have been reported and are limited to comparisons of the AVE Microstent™ with the Palmaz–Schatz™ stent. These have again demonstrated similar clinical and angiographic outcomes both acutely and at 6-month follow-up.[32,33] Whether newer modular stent designs will show greater benefit remains to be seen. However, there is experimental evidence in animal models that corrugated ring stents produce less vascular injury, intimal hyperplasia and thrombosis as compared to slotted tube stents and that this appears to be due to a smaller number of strut–strut intersections with this design.[34]

Indications for coronary stenting

Perhaps no other area within the field of coronary stenting has generated as much controversy as have its clinical indications. Much of the early growth in stenting was based on improved post-procedure appearance and, as with balloon angioplasty itself, occurred without the benefit of randomized clinical trials. Even when data became available regarding its benefits in favourable lesion morphologies,[35,36] growth continued in clinical and lesion subsets where no such evidence existed. This was due to a number of reasons: advances in stent technology allowing for the delivery of lower profile, more flexible stents to a wider variety of lesions; improved ancillary care with high pressure stent deployment[37] and the replacement of Coumadin with antiplatelet agents resulting in reduced local vascular complications, subacute stent closure and shortened hospitalization;[38,39] as well as a gradual reduction in the cost of stents.[40]

However, over the last few years a clearer picture of the role of coronary stenting has emerged based on the results of clinical trials and collective experience. This has led to an attempt to define better the current indications for coronary stenting.[41–43] Both the American College of Cardiology as well as the Cardiac Care Network of Ontario (Canada) have developed guidelines based on a consensus process.[42,43] The latter group employed the methodology of the consensus development process followed by the Canadian Cardiovascular Society in which levels of evidence are generated based on the scientific merits of the published information (Table 7.2).[44,45] Using this methodology and a more rigid approach of randomized trial data only (level I and II evidence), recommendations for stenting in the following clinical and lesion subgroups can be made.

Table 7.2 Definitions of levels of evidence.

Levels of evidence	*Description*
I	Large unconfounded randomized trials with low false positive (α) and low false negative (β) error rates
II	Small unconfounded randomized trials with high false positive (α) or high false negative (β) error rates[a]
III	Non-randomized concurrent cohort study
IV	Non-randomized historical cohort study
V	Case series

a Based on previous consensus documents, published abstracts of randomized trials were classified as level II evidence regardless of the false positive or false negative error rate[43].

Favourable lesions

While the definition of this lesion subset remains variable, in general it describes single, discrete, de novo stenoses in vessels greater than 3 mm in diameter with the absence of adverse features such as angulation, vessel tortuosity, excessive calcification or thrombus. These lesions would be characterized as type A or B_1 in the modified American College of Cardiology/American Heart Association lesion classification. They were the first lesions to be subjected to randomized clinical trials and both the STent REStenosis Study (STRESS) and the BElgium NEtherlands STENT (BENESTENT I and II) trials demonstrated a significant reduction in 6-month angiographic restenosis rates as well as clinical event rates when compared to balloon angioplasty.[35,36,46] In addition, the START trial, while demonstrating similar 6-month outcomes, has shown a significantly reduced need for target lesion revascularization at 4 years (12% versus 25% in the angioplasty group; $P = 0.0006$) although there was no significant difference in either mortality or non-fatal myocardial infarction.[47] As such, there is clear evidence of benefit for stenting in this lesion subgroup.

However, less clear is the question of whether all such lesions should be treated with stents (universal stenting) or whether it should be reserved for those lesions with a less than optimal result following balloon angioplasty (provisional

stenting). A number of small observational and randomized studies have demonstrated similar clinical event rates between stenting and balloon angioplasty when the latter approach produces an 'optimal' result (generally described as less than 25–30% residual stenosis by quantitative coronary analysis).[48–50] The importance of obtaining a 'stent like' result with balloon angioplasty is underscored by the study of Knight et al who randomized patients with as little as 15–20% residual stenosis by QCA following balloon angioplasty to either stent placement or no further therapy. Six-month angiographic restenosis was 22% in the stented group compared to 45% in the balloon group.[51] While this question may become less important as the overall costs of stenting decrease, a strategy of provisional stenting for suboptimal balloon results in favourable lesions (ie less than 15% diameter stenosis visually or less than 25% by on line QCA) appears to be supported. Perhaps the only exception to this would be lesions in diabetic patients and those in the left anterior descending artery as both have been shown to derive even greater benefit from coronary stenting because of a significantly increased risk of restenosis with balloon angioplasty alone.[52–55]

Restenotic lesions following balloon angioplasty

While this is becoming less of a problem because of the reduced rates of stand-alone balloon angioplasty, there is evidence that restenotic lesions following balloon dilatation may behave differently from de novo lesions with regard to the risk of subsequent recurrence following intervention. This would be supported by the work of Mittal et al who demonstrated a significantly higher recurrence rate when restenotic lesions were stented as compared to de novo lesions (27.1% versus 22.9%).[56] Two subsequent randomized trials have demonstrated a 20% reduction in recurrence rates when restenotic lesions underwent stenting as opposed to repeat balloon dilatation.[57,58] As such, there appears clear evidence that restenotic lesions following balloon angioplasty benefit from intracoronary stenting.

Chronic total occlusions

This subgroup accounts for up to 10% of all cases undergoing percutaneous intervention and has long been problematic with regard to primary success as well as high restenosis and reocclusion rates. While primary recanalization remains problematic, a number of trials have now demonstrated a significant benefit of stenting as compared to balloon dilatation alone. These studies have demonstrated not only reduced restenosis and reocclusion rates but also a reduced need for target vessel revascularization, lower average CCS angina scores and improved left ventricular function.[59,60] In addition, the clinical benefits appear to be maintained for at least 2 years.[61] While the limitations adherent to any form of percutaneous recanalization of a chronic total occlusion demand a rational approach to case selection, provided the occlusion can be crossed, stenting is clearly indicated.

Saphenous vein grafts

Early experience with balloon angioplasty in saphenous vein grafts proved disappointing with consistently high clinical event rates and restenosis of around 60%. With the advent of stenting, non-randomized observational trials suggested a reduction in restenosis and subsequent randomized trials have now confirmed the clear benefit of stenting in vein graft stenoses with significant reductions in both angiographic restenosis and clinical event rates.[62] Unlike native coronary artery lesions, it would appear that an optimal balloon angioplasty result is not equivalent to stenting. Abhyankar et al demonstrated 35% one-year target lesion revascularization and 54% event free survival with balloon dilatation as compared to 5% and 88% respectively with stenting.[63] Coronary stenting is therefore clearly indicated for all saphenous vein graft lesions felt to be amenable to a catheter based approach.

Acute or threatened closure

In the era prior to stenting, acute or threatened closure was one of the major complications of coronary angioplasty, occurring in approximately 4–8% of cases and being associated with a 40% incidence of myocardial infarction and a 5% in-hospital mortality.[64] Several large cohort studies demonstrated significant success rates for bailout stenting with marked reductions in the need for emergency bypass as well as for both myocardial infarction and death.[65,66] These results have made randomized trials difficult to perform and in fact one major trial, the Gianturco–Roubin™ stent in Acute Closure Evaluation (GRACE) trial, attempting to compare stenting with conventional perfusion balloon for threatened or acute closure, was discontinued because of lack of enrolment. A small Canadian Trial (TASC II) randomized patients with acute or threatened closure to either perfusion balloon or intracoronary stenting. Primary success occurred in 90% of the stent patients but only 45% of the perfusion balloon group.[67] As such, despite the lack of randomized clinical trials, there appears to be significant (level II) evidence of benefit for intracoronary stenting in this clinical subgroup.

Acute myocardial infarction

While direct infarct angioplasty is clearly indicated for patients with contraindications to thrombolytic therapy, its role in the treatment of all infarcts continues to be evaluated and is beyond the scope of this discussion. However, where angioplasty is indicated, there is growing evidence of the additional benefit of intracoronary stenting. Several randomized trials have demonstrated significant reductions in both clinical events (primarily target lesion revascularization) and angiographic restenosis.[68–70] Therefore, whilst there is clear evidence of benefit for intracoronary stenting over balloon angioplasty in the setting of direct infarct angioplasty, it must be stressed that these findings may not be applicable to the setting of failed thrombolytic therapy where more data are required.

'Difficult' anatomy

While the above indications for coronary stenting are based on sound evidence, a number of other lesion subsets exist which are commonly stented but for which the evidence of benefit is not as strong.

Balloon dilatation of aorta-ostial lesions has long been associated with higher restenosis rates due largely to marked elastic recoil of the vessel. While no randomized comparison has been reported, several small observational trials have demonstrated marked reductions in restenosis and clinical event rates with the use of stenting.[71,72] One study, comparing balloon angioplasty, debulking (with either excimer laser, directional or rotational atherectomy) and stenting for ostial right coronary lesions, demonstrated that the need for late reintervention was lowest with stenting at 24% compared with 40% after debulking and 47% after balloon angioplasty.[73] As such, it would appear reasonable to consider stenting for clinically indicated aorta-ostial intervention (level III evidence).

Long, diffuse lesions (variably defined as greater than 15–20 mm in length) have also demonstrated significant complication and restenosis rates when treated with balloon angioplasty alone. Long balloons and debulking devices have done little to improve these results. Coronary stenting, in general, has demonstrated superior results compared to historical controls using balloon angioplasty alone, but restenosis rates remain higher than in shorter lesions. Predictors of restenosis appear to be lesion length, smaller vessel diameter and the use of multiple overlapping stents.[74,75] These factors must be kept in mind when considering stenting for long lesions and the relative risks and benefits weighed against those of medical therapy or bypass surgery (level III and IV evidence).

The additional feature of lesion calcification has long proven problematic to interventionists, with higher rates of acute complication and restenosis as well as reduced stent expansion compared to non-calcified lesions for any given balloon pressure. More recent studies combining stenting with rotational atherectomy appear promising.[76] One such study performed matched paired analysis of calcified lesions undergoing one of three treatment strategies: rotational atherectomy with adjunct balloon angioplasty, stent implantation without pretreatment and stent implantation following rotational atherectomy. The latter approach resulted in greater acute gain and final lumen diameters compared to the other two groups and at 6 months, target vessel revascularization was required in only 12.2% as compared to 24.5% in the stent alone group and 31.6% in the atherectomy and balloon angioplasty group.[77] While this approach may be reasonable (level III, IV and V evidence), there are insufficient data to recommend a definite treatment strategy in heavily calcified lesions. Operators must therefore be aware of the associated pitfalls of stenting in such situations (difficulty in stent delivery, inadequate expansion and higher periprocedural complication and long term restenosis rates) when making treatment decisions.

Future directions

Despite the advances seen in intracoronary stenting over the last several years, several anatomical and lesion specific situations remain problematic (Table 7.3). A number of exciting initiatives are currently underway which will hopefully address many of these areas.

Biological coatings

Although improved by new anticoagulation regimens and deployment strategies, subacute stent thrombosis remains a potentially life threatening problem in coronary interventions. Central to this process is platelet adhesion to both the metallic stent surface and the adjacent subendothelium. Application

Table 7.3 Lesion and vessel morphologies not ideally suited to stenting.

- Aorta-ostial lesions
- Bifurcation lesions
- Chronic total occlusions
- Intra-coronary thrombus
- Long/diffuse lesions
- Saphenous vein graft disease
- Tapering vessel diameters
- Vessels ≤ 2.5 mm and ≥ 4.5 mm
- Calcified vessels

of inert polymer materials to the stent has been shown to significantly reduce both platelet adhesion and thrombosis in animal models.[34,78,79] Similar animal studies have also demonstrated the ability of heparin-bonded stents to reduce thrombosis in vivo.[80] While heparin-bonded stents have been used in a number of clinical trials,[46,60,70] there is no clear evidence of benefit over conventional, non-coated stents. However, the development of this polymer bonding technology has opened the potential of using the stent as both a scaffolding device and a vehicle to deliver a variety of therapeutic agents, such as anticoagulant or antimitotic agents, directly to the local environment. At present, several trials are being designed to assess the benefit of a variety of compounds for both acute closure and restenosis.

Bifurcation stents

Treatment of bifurcation lesions has long been problematic and conventional stent technology has only partially addressed this. Designing a bifurcation stent is associated with unique problems, particularly in dealing with adequate stent coverage at the carina and addressing the issues of varying side branch angles and size. Various approaches to this problem have been devised.

The Bard XT Carina™ bifurcated stent (Fig. 7.10) was a balloon-expandable stainless steel stent made of discrete zigzag modules mounted on two flexible spines, each of which hold one limb of the bifurcation. The stent was premounted on two semi-compliant balloons that connect to a single shaft for simultaneous inflation. The main body of the stent was a single coil through which both balloons pass, diverging at the crux to pass separately into each limb. The stent can accommodate angles up to 120°.

The AVE™ bifurcation stent employs a similar design except that it consists of unconnected 2 mm length segments with each segment composed of six waves or crowns. The same balloon delivery system is used as was described for the Bard XT carina™ stent.

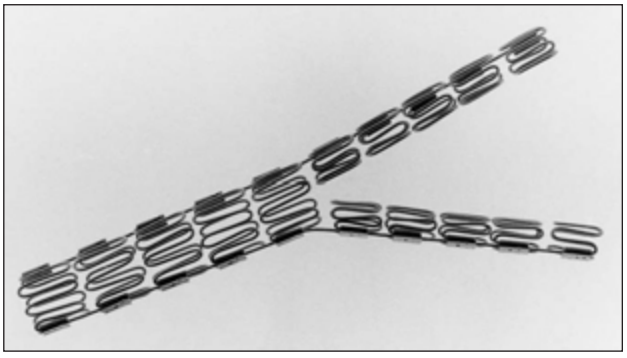


Figure 7.10
The BARD XT carina™ bifurcation system.

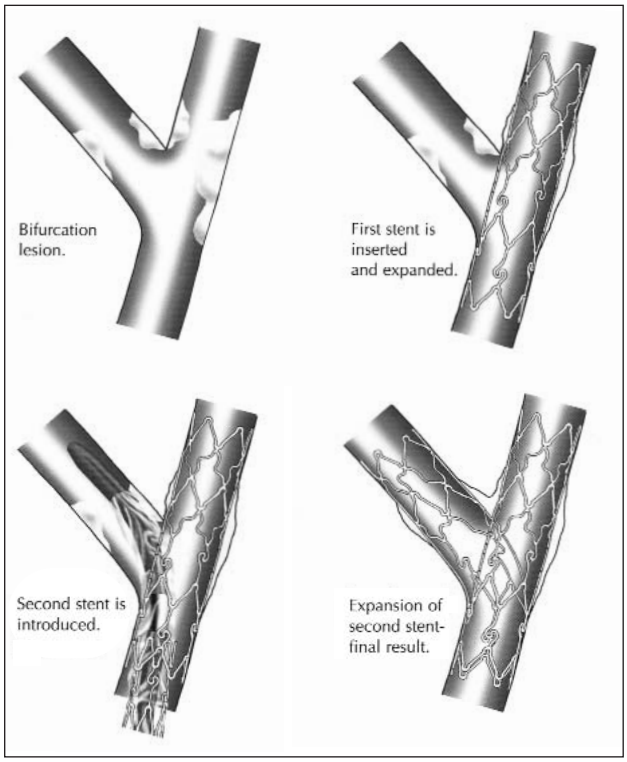


Figure 7.11
Diagrammatic representation of deployment of the JOSTENT bifurcation system.

The NIRoyal™ Side stent is similar in composition to a standard NIR except the proximal 5 mm consists of a nine cell circumferential design while the distal 11 mm consists of a seven cell design. This leaves a small 'gap' at the point of the cell change through which the tip of the side catheter of the delivery balloon is allowed to protrude during crimping. This gap can then be rotated into position over the side branch ostium allowing for easier passage of a subsequent balloon and stent should side branch dilatation be necessary. The gap can be expanded to 3 mm.

The JOMED stent system (Fig. 7.11) combines two separate stents, the JOSTENT 'bifurcation'™ and the JOSTENT 'side branch'™. Both are similar in that the distal portion of the stent is composed of a tighter cell design than the proximal or mid portion. The bifurcation stent is initially placed in the main vessel with the tighter weave beginning immediately beyond the side branch. The second stent is then passed into the branch and positioned with the tighter weave beginning at the side branch ostium. It is anticipated that the overlap of the looser weave segments in the main artery will provide adequate radial support.

While these approaches are all slightly different, with isolated case reports of their use,[81] no clinical results are available to indicate whether they offer a benefit over conventional approaches with regular stents.

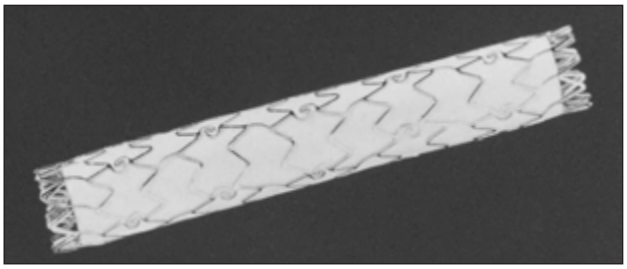


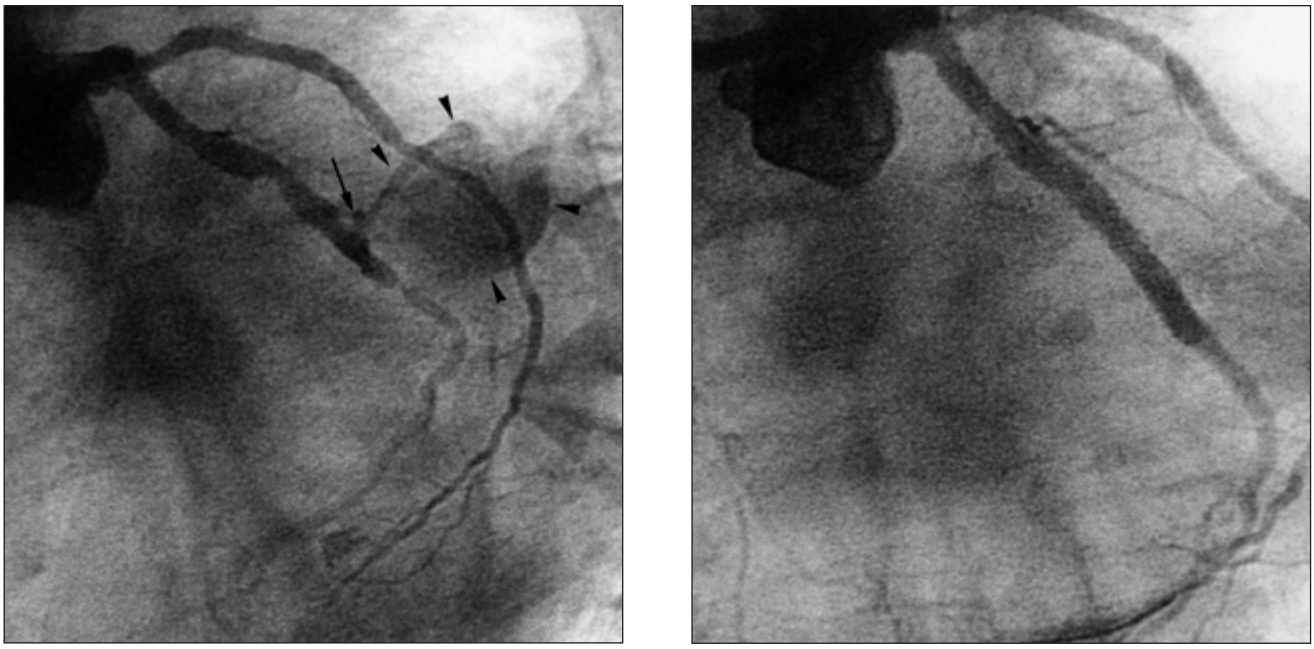
Figure 7.12
The JOSTENT® coronary stent graft.

Covered stents

These consist of a synthetic membrane attached to the outer surface of a stent or 'sandwiched' between two stents. An example of the latter design is the JOSTENT® coronary stent graft, which is composed of a thin layer of polytetrafluorethylene (PTFE) between two stainless steel stents (Fig. 7.12). A self-expanding PTFE stent is currently under development by Boston Scientific. Potential applications for these devices include degenerated vein grafts, where it may help reduce the risk of distal embolization, the sealing of coronary artery ruptures or perforations and covering aneurysms (Fig. 7.13). While anecdotal reports appear encouraging, few clinical data are yet available.

Radioisotope stents

Perhaps one of the more exciting developments in the area of restenosis prevention has been the development of brachytherapy to reduce restenosis in de novo lesions and to treat the emerging and vexing problem of in-stent restenosis. A number of small studies have been reported utilizing different energy sources and delivery techniques. One such approach is the use of radioisotope stents. These are currently produced by direct ion implantation with the beta particle emitter P^{32}. In animal studies, beta particle emitting radioactive stents reduced neointimal hyperplasia by inhibiting smooth muscle cells in a dose dependent manner.[82,83] The first human trial using a beta emitting stent was the Isostent for Restenosis Intervention Study (IRIS), a non-randomized, observational trial using lower radiation doses (0.5–1 microCi). This failed to show any benefit of radioisotope stents with respect to restenosis or clinical events compared to patients who received conventional stents.[84] Subsequently, the IRIS Feasibility Study was performed with stent activities of 0.75–1.5 microCi. At 6 months, 17% demonstrated angiographic in-stent restenosis.[85] More recently, a larger dose–response study demonstrated a dramatic fall in intrastent restenosis from 16% at doses between 0.75 and 3 microCi to 3% at 3–6 microCi and 0% at 6–12 microCi. However, restenosis at the stent edges was seen in 40–50%



a b

Figure 7.13
(a) Perforation (arrow) of the left circumflex coronary artery occurred after rotastenting to an undilatable calcified lesion. A false aneurysm was outlined by contrast (arrowheads).
(b) A 9 mm and 12 mm long PTFE covered stent (Jomed) were deployed in series to cover the perforation point and obliterate flow into the false aneurysm. (Acknowlegment: Dr DR Ramsdale.)

of cases in each group, possibly due to lower activity levels at the edges of the stent combined with an aggressive approach to stenting.[86] This phenomenon has been termed the 'candy wrapper' effect. While these initial results are clearly encouraging, much work remains to be done. The 'candy-wrapper' effect must be overcome and the longer term effects of radioisotope stents must be evaluated, ideally in the setting of randomized clinical trials.

Adjunctive therapies

Several emerging treatments and technologies may further improve the outcomes of coronary stenting. The use of distal embolization devices may reduce the risk of percutaneous intervention in degenerated saphenous vein grafts where distal embolization of particulate debris remains problematic. Rotational atherectomy has already been mentioned as an adjunct to coronary stenting in calcified lesions. There is now a growing body of evidence that it may also be beneficial in the treatment of diffuse in-stent restenosis, with lower target lesion revascularization rates as compared to repeat balloon angioplasty or re-stenting.[87]

As previously mentioned, coronary brachytherapy holds the promise of being a powerful tool in the prevention and treatment of restenosis, particularly in-stent restenosis. One of the more powerful randomized studies assessed the benefits of an iridium[192] (a gamma emitter) source wire following successful stent implantation. This demonstrated a significant reduction in 6-month in-stent restenosis as compared to the group who were not irradiated (8% versus 39%).[88] In addition, these benefits were maintained for 3 years with restenosis rates of 33% in the irradiated group versus 64% in the non-irradiated group and target lesion revascularization rates of 15.4% and 48.3% respectively.[89]

Finally, with the release of the EPISTENT data, there would appear to be significant additional benefit from the platelet glycoprotein IIb/IIIa receptor antagonist, abciximab (ReoPro) at the time of stenting, with a 51% reduction in the composite endpoints of death, myocardial infarction and urgent revascularization as compared to stenting alone.[90] Whether this benefit will extend to other IIb/IIIa antagonists awaits the results of ongoing trials.

Summary

While we have clearly not yet reached the Holy Grail of an ideal stent, there is little doubt that coronary stenting has been the greatest advance in the percutaneous treatment of coronary artery disease since the balloon itself. A 3-year, prospective study of almost 10 000 patients in British Columbia, Canada, demonstrated a clear association between the increased use of stents and a significant reduction in major cardiac events at one year, due entirely to a 30% reduction in target vessel revascularization.[91] No other device has had such an impact on clinical outcomes.

Lest we become complacent, however, there is still much work to be done. Stent technology must continue to improve to better address current problems such as difficult anatomy, subacute thrombosis and restenosis. The role of ancillary therapies must be further evaluated and ongoing clinical trials are required to determine the most cost effective strategies and define the optimal role for intracoronary stenting.

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8

Coronary stenting II

Antonio Colombo and Evangelia Karvouni

Introduction

The introduction of coronary stenting has changed the approach to the percutaneous treatment of coronary artery disease. In most interventional centres, stents are used in over 50% of all coronary angioplasty procedures.[1] The main reasons for this expansion are firstly that stents can now be implanted without the need for systemic anticoagulation, secondly they have made angioplasty safer, with a sharp decline in the need for emergency bypass surgery, in particular since the availability of new generation stents and finally they have resulted in a significant decrease in restenosis rates.

Indications for stenting

Coronary stenting, which achieves a greater acute gain and provides effective lumen scaffolding, is associated with better short- and long-term outcomes in lesions within large native coronary arteries.[2,3] The positive results of a few randomized trials have been enthusiastically applied to almost every other patient and lesion subcategory. However, these favourable results do not apply to all coronary lesions treated with catheter-based interventions in daily practice.[4] For long lesions,[5] small vessels,[6,7] chronic total occlusions[8,9] ostial[10,11] and bifurcation lesions[12] restenosis after stenting still remains a problem.

The unequivocal indications for stenting are currently only those few that have been supported by observational and randomized trials (Table 8.1), and are limited to very few lesion types. The definitive evidence for the use of stents for other clinical indications is still lacking and the results of many ongoing randomized trials are eagerly awaited.

The American College of Cardiology has recently updated its initial paper published in 1996,[13] providing an Expert Consensus document where the current indications for coronary stenting are discussed.[14] The most important aspects of stent usage, which reflect current interventional practice, are discussed in detail in the following sections.

Abrupt and threatened vessel closure (Fig. 8.1)

Despite improvements in catheter technology and operator experience, abrupt closure continues to limit the safety and efficacy of coronary angioplasty. The aetiology of abrupt closure is multifactorial and includes arterial dissection, elastic recoil, thrombus formation and intraluminal haemorrhage.[15] The rationale for using stents as a bail-out technique in abrupt or threatened closure is based not only on their ability to scaffold the vessel from its endoluminal surface and hence restore flow down the dissected or occluded artery but also to reduce elastic recoil. Numerous studies have demonstrated the favourable impact of stenting for abrupt or threatened vessel closure.[16–21] In the first randomized stent trials[2,3] stenting was successful in the acute setting. Although these good results were overshadowed by a high rate of subacute thrombosis and restenosis, better deployment techniques and improved designs have allowed stent deployment to be safely performed even in the setting of acute myocardial infarction or in thrombus-rich lesions.[22] Results following stenting for acute coronary closure are now comparable to those obtained following elective stenting.

Two randomized trials (TASC II and STENT-BY)[23] have compared prolonged balloon inflation or CABG versus stenting for the treatment of abrupt closure following PTCA, and

Table 8.1 Randomized stent trials.

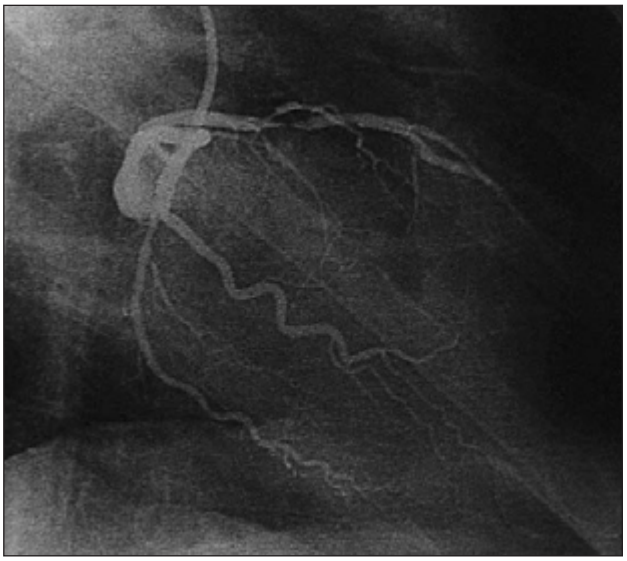
Acronym	*No of pts*	*Objective*	*Results*
TASC II	43	Treatment of abrupt closure during PTCA with prolonged balloon inflation vs stenting	Acute success 42% vs 90% ($p = 0.002$) Final MLD 1.5 ± 0.3 mm vs 2.2 ± 0.4 mm ($p = 0.002$)
BENESTENT I	520	Balloon angioplasty vs stent in native lesions	Restenosis 32% vs 22% ($p = 0.02$) 6-month MACE 29.6% vs 20.1% (RR = 0.68)
BENESTENT II	827	Heparin coated JJIS stent vs balloon angioplasty in native lesions	Restenosis 16% vs 31% ($p = < 0.05$) 6-month MACE 12.8% vs 19.3% ($p < 0.05$)
STRESS	410	Balloon angioplasty vs stent in native lesions	Restenosis 42.1% vs 31.6% ($p = 0.04$) 6-month MACE 23.8% vs 19.5% ($p = 0.16$)
STRESS I-II (Small Vessel Substudy)	331	Palmaz–Schatz stent vs balloon angioplasty in small vessels	Restenosis 34% vs 55% ($p = < 0.001$) 1-year event free survival 78% vs 67% ($p = 0.01$)
SICCO	119	Palmaz–Schatz stent vs balloon angioplasty in CTO	Restenosis 31.6% vs 73.7% ($p < 0.001$) 6-month TLR 22.4% vs 42.4% ($p = 0.02$)
GISSOC	110	Stent vs balloon angioplasty in CTO	Restenosis 32% vs 68% ($p < 0.0008$) 6-month TLR 5.3% vs 22% ($p = 0.03$)
SPACTO	47	PTCA vs Wiktor stent in CTO	Restenosis 74% vs 32% ($p < 0.001$) 6-month MACE 17% vs 8% ($p = 0.04$)
TOSCA	410	Balloon angioplasty vs heparin coated stent in CTO	6-month MACE 23.1% vs 15.8% ($p = 0.08$) Failed target vessel patency 19.5% vs 10.9% ($p = 0.02$)
SAVED	220	Balloon angioplasty vs stent in SVGs	Restenosis 46% vs 37% ($p = 0.24$) 8-month MACE 39% vs 26% ($p = 0.04$)
REST	383	Balloon angioplasty vs stent in restenotic lesions after PTCA	Restenosis 32% vs 18% ($p = 0.03$) Event-free survival 72% vs 84% ($p = 0.04$)
EPISTENT	2399	Stent + placebo vs PTCA + abciximab vs stent + abciximab	Death, MI and urgent revascularization at 30 days 10.8% vs 6.9%* vs 5.3%** (*$p = 0.007$, **$p < 0.001$)

MACE: Major Adverse Cardiac Event.
TLR: Target Lesion Revascularization.
MI: Myocardial Infarction.
PTCA: Percutaneous Transluminal Coronary Angioplasty.
SVG: Saphenous Vein Graft.
CTO: Chronic Total Occlusion.

the results have demonstrated the benefit of stenting. The technique of stenting any acute or impending closure was so profoundly beneficial in clinical practice, that it has precluded any other study addressing this issue from being performed. The disadvantage of using stents to treat angioplasty complications is that the incidence of acute myocardial infarction remains higher than with elective stenting—even following successful reopening of the occluded vessel.[20,21] Routine elective stenting and primary stenting are new concepts which might help diminish the need for bail-out stenting.

While there is solid evidence for stenting obstructive dissections following balloon dilatation (Fig. 8.1), the question of whether we should stent all dissections has not yet been fully answered. Recent studies suggest that post-PTCA dissections which do not diminish antegrade blood flow are not associated with an increase in acute and long-term events or restenosis.[24,25] Although, the prognostic significance of even transient vessel closure after balloon angioplasty alone is still not clear, a recent study showed that transient abrupt vessel closure during otherwise successful angioplasty and emergency stenting were predictors of adverse clinical outcome at 6 months.[26]

In conclusion, although coronary stenting is the treatment of choice for occlusive dissections following balloon dilatation, the role of stenting non-occlusive dissections still remains unclear.



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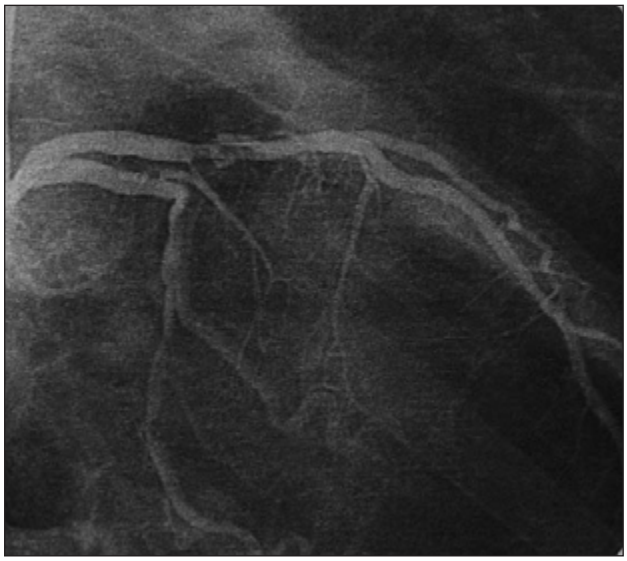

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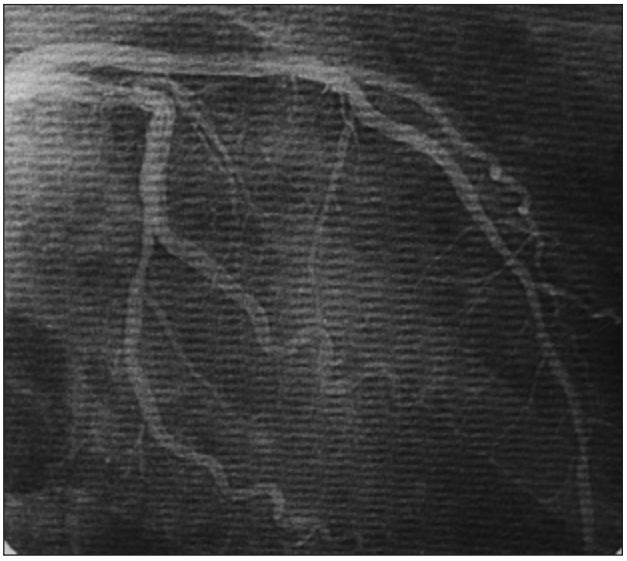

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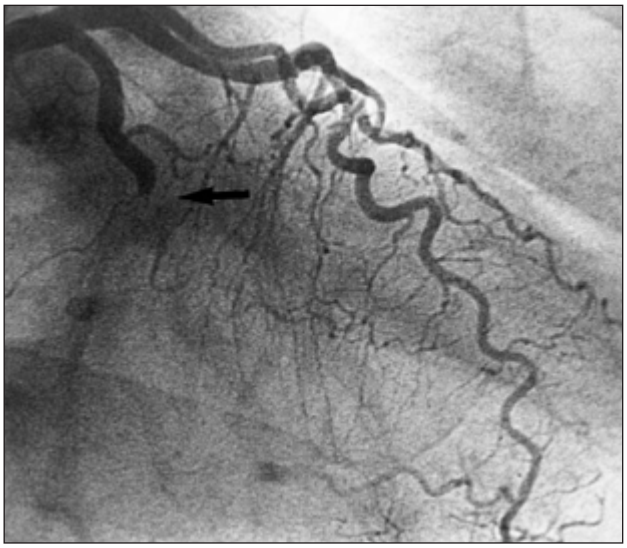
Figure 8.1
(a) This severe proximal LAD stenosis was dilated with a 3.0 mm balloon but (b) the suboptimal result puts this vessel at significant risk of abrupt closure. (c) Result after deployment of a 3.5 mm 15 mm long Multilink™ stent (Guidant). *(Courtesy of Dr D Ramsdale.)*

Prevention of restenosis

Lesions in native vessels with reference diameter >3 mm and <15 mm in length

The practice of coronary stenting in this lesion subset is supported by the results of the BENESTENT[2] and STRESS[3] randomized trials, which showed that elective stenting of selected lesions resulted in lower restenosis rates than balloon angioplasty. The conclusions of these trials were further strengthened by the fact that the superiority of stenting was demonstrated despite suboptimal stenting and suboptimal post-stenting antiplatelet therapy. In addition, long-term follow-up data after stenting showed favourable outcomes in native coronary lesions.[27,28] For these reasons, it is appropriate that every lesion that satisfies the criteria of these two trials should be stented. However, this practice ignores the fact that, despite the better outcome with stenting, balloon angioplasty is still effective in selected cases.[29] Considering the difficulty that interventionists face in dealing with in-stent restenosis and the higher procedural costs of stenting, the question arises as to which lesions can be treated just as effectively by balloon angioplasty as with stenting. The recently completed multicenter DEBATE (Doppler Endpoint Balloon Angioplasty Trial Europe)[30] study addressed the issue of provisional stenting, assessing the final angio-



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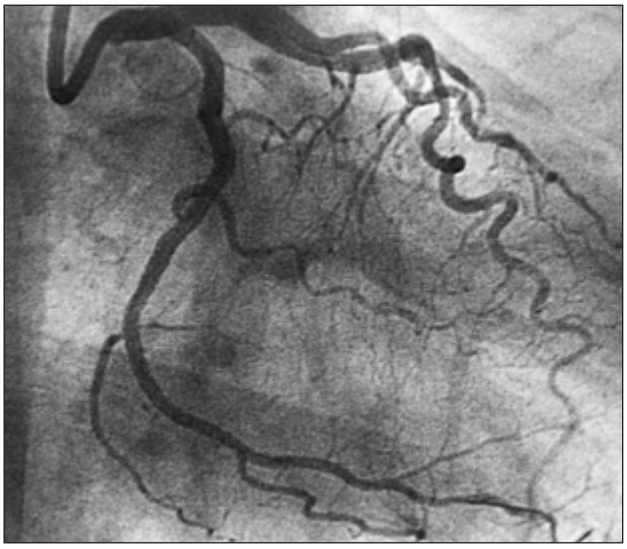

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Figure 8.2
(a) Occluded left circumflex coronary artery (arrow). (b) Appearance after PTCA and deployment of a 3.0 mm 15 mm Multilink™ stent. *(Courtesy of Dr D Ramsdale.)*

graphic result after optimal balloon angioplasty with intracoronary Doppler measurements. The combination an optimal angiographic result (<35% diameter stenosis) and a coronary flow reserve greater than 2.5 was associated with a favourable clinical outcome at 6 months. Three randomized trials tested the hypothesis of elective stenting versus balloon angioplasty with provisional stenting (DEBATE II, DESTINI, FROST),[31–33] using the Doppler Flow Wire and quantitative angiography as tools to evaluate an optimal angioplasty result. Preliminary results from these trials show that when optimal angiographic and physiologic endpoints are met after PTCA, early and late clinical outcomes are comparable to outcomes observed after elective stent implantation. However, it is important to note that in the PTCA arm only 43% of patients achieved the predetermined endpoints.

One interpretation of these results is that as optimal PTCA is as good as elective stenting, it is not worth spending additional time and effort to achieve an optimal PTCA result when the same outcome can be reached with direct stent implantation. However, if one looks at the outcome of the subgroup of patients with an optimal PTCA result in the DEBATE II trial, who underwent a further subrandomization to stenting, this group did better than those left without any additional intervention. The conclusion from these studies and from current clinical practice is that provisional stenting is no longer a reasonable alternative to elective stenting in lesions which meet the inclusion criteria adopted in most of the above studies.

In conclusion, in patients with focal native artery stenosis, stenting has been definitively proven to reduce restenosis compared to conventional balloon angioplasty and is the treatment of choice.

Chronic total occlusions (Fig. 8.2)

The treatment of chronic total occlusion (CTO) with conventional PTCA has been limited by the inability to cross the occlusion and to decrease reocclusion and restenosis rates. Restenosis rates after balloon angioplasty for CTO range from 49% to 68%.[34,35] One of the most important findings is that after successful PTCA of a CTO, the reocclusion rate is approximately 20% and this can be prevented by stenting. We have reported on stenting of CTO with and without anticoagulation.[36,37] Subacute thrombosis occurred in 5% and 2%, and restenosis in 20% and 25% respectively. Mori et al found a restenosis rate of 28% in patients with CTO receiving stents compared to 57% in patients treated with PTCA alone ($p = 0.005$).[38] A prospective randomized trial (SICCO) (Stenting In Chronic Coronary Occlusion) showed that stenting improves the angiographic outcome after PTCA of CTO, with a reduction in the 6-month restenosis rate from 74% to 32% in the group with additional stent implantation compared with the group treated with angioplasty only.[39] Other recently completed randomized trials (GISSOC, SPACTO, TOSCA)[40–42] have confirmed the superiority of stenting after recanalization of totally occluded coronary arteries over PTCA, reporting restenosis rates of between 32% and 55%.

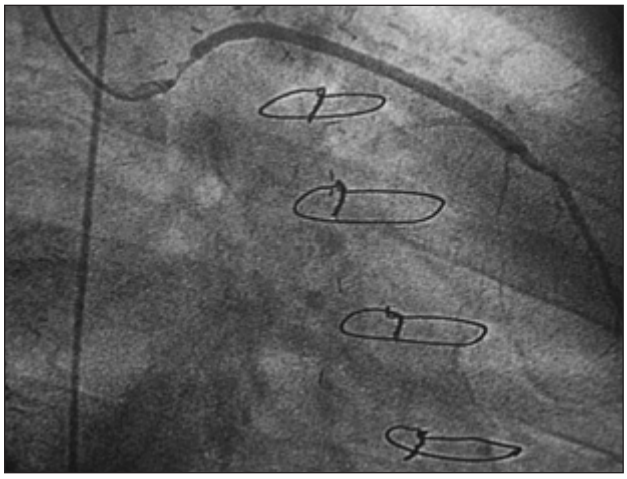
In conclusion, CTO studies have demonstrated significant reduction in restenosis rates and improvement in long-term outcomes and support the use of stenting.

Saphenous vein grafts (Fig. 8.3)

Conventional balloon angioplasty of complex saphenous vein graft (SVG) lesions is limited by frequent periprocedural complications such as distal embolization and high rates of late clinical recurrence.[43,44] Adverse events are more common in older, degenerative and complex, thrombus-containing SVGs.[44,45] Stents have been used successfully in patients with symptomatic SVG disease.[46–49] Advantages of stents in this setting include the ability to scaffold the friable SVG surface with a potential risk reduction of distal embolization. In a non-randomized study,[50] comparing stenting with balloon angioplasty in treatment of old SVGs, stenting was associated with a marked improvement in the acute angiographic result and a trend towards lower in-hospital major events. At one year, the incidence of major adverse events was reduced by 50% in the stent group with a decrease in the need for repeat target vessel revascularization. The multicentre randomized trial SAVED (Saphenous Vein Graft De Novo Study)[51] compared Palmaz–Schatz stents with PTCA in de novo SVG lesions requiring no more than two stents. The mean vein graft age was 10 years with a mean diameter of 3.19 mm. Technical success (<50% stenosis by quantitative coronary angiography) was 97% in the stent group compared with 86% in the PTCA group ($p < 0.01$). Postprocedural MLD was 2.81 mm after stenting versus 2.16 mm after PTCA ($P < 0.001$). Clinical success was 92% after stenting and 69% for PTCA ($p < 0.001$). There was a trend toward the occurrence of fewer non-Q wave myocardial infarctions (MI) in patients treated with stents (2 versus 7 patients, $p = 0.1$), whereas Q-wave MI, death or need for bypass surgery occurred at similar rates in each group. At 6 months, late loss with stents was greater (1.04 mm versus 0.68 mm, $p = 0.01$), but net gain remained significantly larger (0.85 mm versus 0.54 mm, $p = 0.002$) in favour of stents. The major cardiac event rate (death, MI, need for repeat revascularization) at 6 months was 26% after stenting versus 39% after PTCA ($p = 0.04$). However, there was no difference in angiographic restenosis: 37% with stents, 46% with PTCA ($p = 0.24$).

Despite the absence of a device for solving the numerous problems present in SVG intervention, some progress may be on the horizon. This includes the introduction of stents dedicated to SVG implantation (Fig. 8.4), distal protection devices[52] and the use of platelet IIb/IIIa receptor antagonists[53,54] which may improve the safety of stenting. We have recently reported the outcome of 15 degenerated SVGs (18 lesions) treated with stenting and a dedicated device (PercuSurge™ GuardWire™) developed to prevent distal embolization.[52] No distal embolization was observed, and there were no major in-hospital adverse clinical events, including Q-wave or non-Q wave MI, emergency CABG or death.

The role of IIb/IIIa agents in this type of intervention is less clear. Despite the intuitive value to use this type of pharma-



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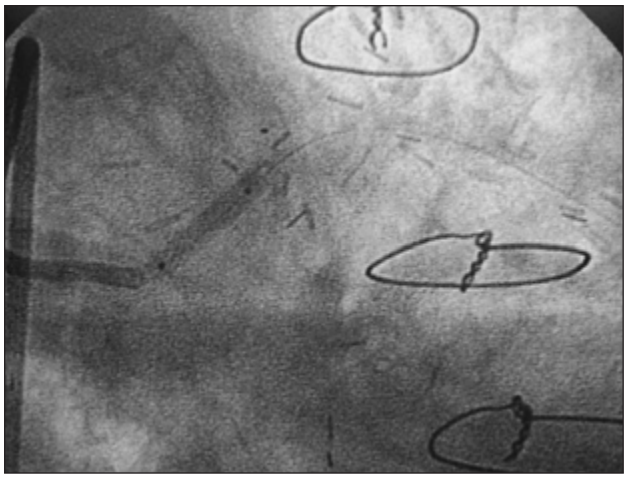

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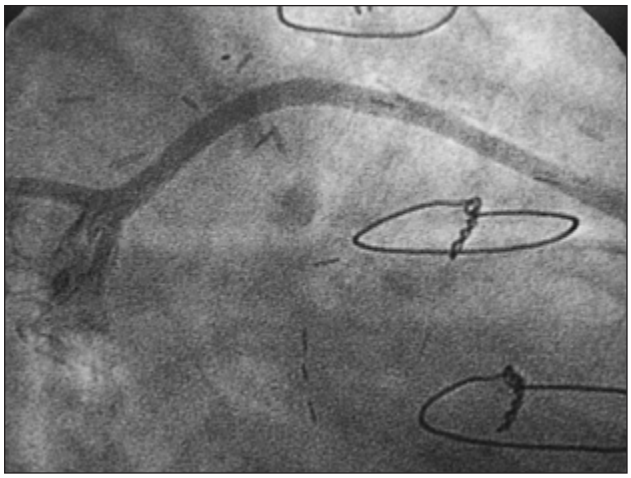

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Figure 8.3
(a) LAD SVG with a severe ostial stenosis extendng over a 10–12 mm segment. (b) A 3.5 mm 15 mm long Palmaz–Schatz™ stent (Johnson and Johnson) is deployed after predilatation by PTCA. (c) Final result. *(Courtesy of Dr D Ramsdale.)*

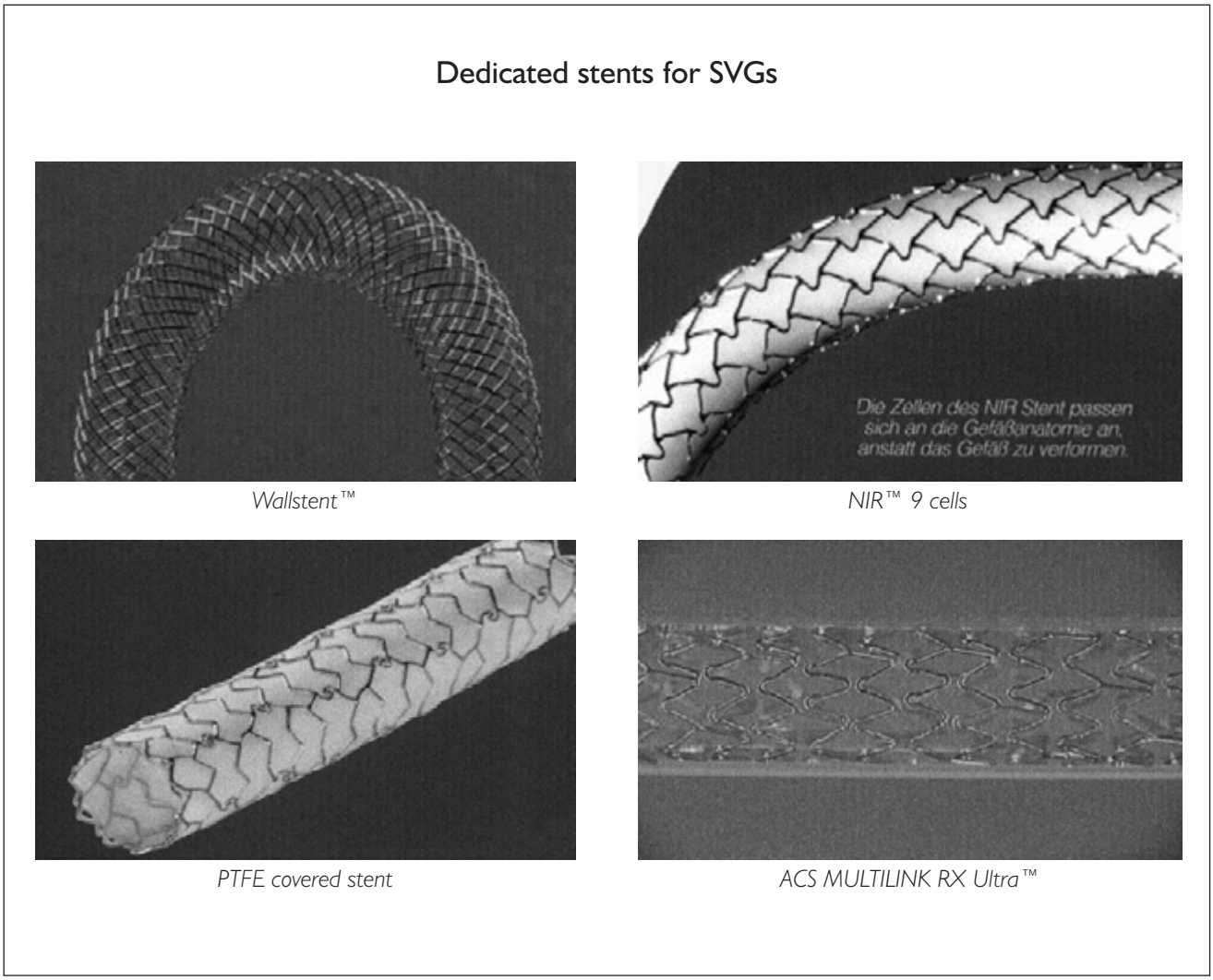


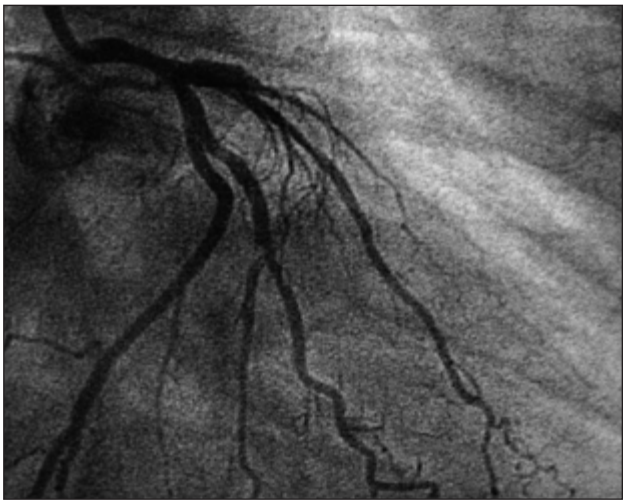
Figure 8.4
Stents with superior scaffolding potential, best suited for SVG application.

cological protection in a setting where distal embolization appears to be the major problem, a recent study reported SVG lesions as the only ones which did not benefit from routine usage of abciximab.[55] The problem of long lesions and degenerated SVGs remains unsolved. Preliminary data seem to negate the role for extensive stenting with graft reconstruction.[56]

In conclusion, in selected patients and lesions, stents in SVGs result in improved initial success rates and a larger acute angiographic gain. However, the restenosis rate remains high compared to stenting in native coronary arteries. Old grafts with degenerative disease remain a difficult problem.

Stenting in acute myocardial infarction (Fig. 8.5)

Mechanical reperfusion in the setting of acute MI has been shown to reduce in-hospital mortality, reinfarction, recurrence of ischemia and stroke compared with thrombolytic therapy. However recurrent in-hospital ischaemia still occurs in 10–15% of recanalized patients, and at 6 months a 15% reocclusion rate and 40% restenosis rate have been reported.[57] In the PAMI II trial,[58] residual stenosis >30% and the presence of a dissection after primary angioplasty were predictive factors for recurrent ischemia and occlusion. Now that the problem of thrombotic stent occlusion has been markedly reduced by a combination of aspirin, clopidogrel and optimal stent deployment, stenting can be effectively



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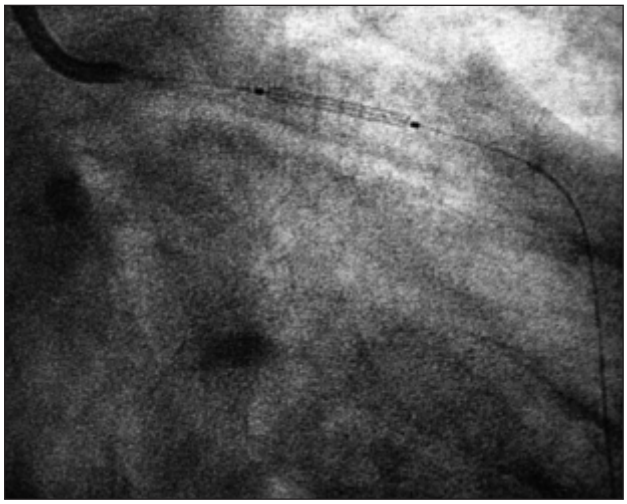

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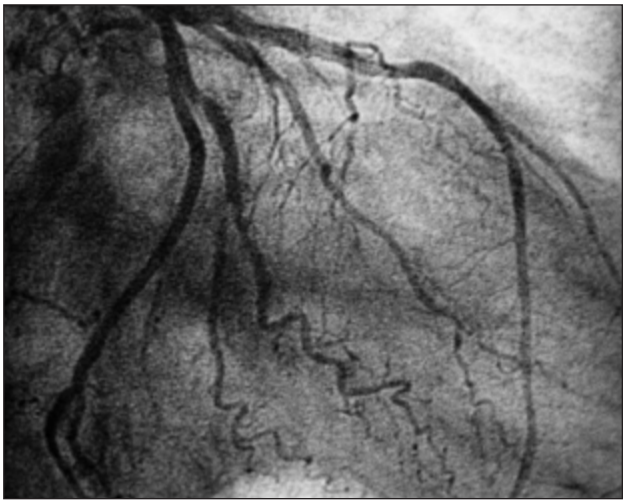

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Figure 8.5
(a) Acute occlusion of the proximal LAD causing anterior MI. (b) The occlusion is crossed with a 0.014 floppy guidewire and stented with a 3.5 mm 18 mm long Microstent™ (AVE). (c) Final result was associated with immediate improvement of left ventricular function. *(Courtesy of Dr D Ramsdale.)*

used to address the problem of a suboptimal result following PTCA in acute MI. Stenting can even be utilized as a tool to improve clearance of a thrombus by establishing a better forward blood flow. In the last 2 years an impressive number of studies have evaluated the role of stenting for mechanical reperfusion in acute MI (STENT PAMI randomized, STENTIM 2, GRAMI, FRESCO, PASTA)[59–64] (Table 8.2). The results of these completed randomized trials which compared primary stenting with balloon angioplasty show a lower incidence of repeat target vessel revascularization in the stent groups compared with the angioplasty groups, and support the elective stent usage in patients with acute MI. In addition, a strategy of bail-out stenting for failed PTCA in patients with AMI appears to be inferior to a primary stenting strategy.[65]

The superiority of primary stenting in acute MI compared to thrombolytics was shown in the STAT (Stent versus Thrombolytics in Acute myocardial infarction Trial) trial. Data from this trial, presented at the American Heart Association Meeting 1999 in Atlanta, showed that TIMI III flow could be achieved in 92% of patients randomized to stenting, and that a target vessel revascularization rate of 11.3% was significantly lower than 47.5% in patients receiving a thrombolytic agent ($p < 0.05$).

Recent data suggest that the glycoprotein IIb/IIIa receptor blockers reduce the occurrence of acute complications during percutaneous revascularization procedures and improve long term outcome.[66,67] In the setting of acute myocardial infarction, use of glycoprotein IIb/IIIa receptor blockers confers additional benefit in mechanical reperfusion in terms of the maintenance of vessel patency and recovery of microvascular perfusion.[68,69] The synergistic action of stents with GP IIb/IIIa blockade may further improve the outcome of patients with

Table 8.2 Randomized trials of stenting in acute myocardial infarction.

Acronym	*No of pts*	*Objective*	*Results*
STENT PAMI	900	Primary stenting vs balloon angioplasty	Restenosis 20% vs 32% ($p < 0.05$)
STENTIM 2	211	Primary stenting vs balloon angioplasty	Restenosis 25% vs 40% ($p < 0.05$)
GRAMI	104	Primary stenting vs balloon angioplasty	In-hospital MACE 3.8% vs 19.2% ($p = 0.03$) Event-free survival at 1 year 83% vs 65% ($p = 0.002$)
Suryapranata et al	227	Primary stenting vs balloon angioplasty	6-month TLR 4% vs 17% ($p = 0.001$) Cardiac event-free survival 95% vs 80% ($p = 0.01$)
FRESCO	150	Primary stenting vs optimal balloon angioplasty	6-month death, MI, TLR 9% vs 28% ($p = 0.003$) 6-month restenosis or reocclusion 17% vs 43% ($p = 0.001$)
PASTA	136	Primary stenting vs balloon angioplasty	In-hospital MACE 6% vs 19% ($p = 0.02$) 6 month TLR 18.6% vs 37.6% ($p = 0.009$)
STAT	123	Primary stenting vs thrombolysis	Death, recurrent MI, stroke and TVR at 6 weeks 19.4% vs 52.5% ($p < 0.05$)
CADILLAC	2081	PTCA vs PTCA + reopro vs stent vs stent + reopro	See Table 8.3

MACE: Major Adverse Cardiac Event. MI: Myocardial Infarction.
TLR: Target Lesion Revascularization. TVR: Target Vessel Revascularization.

acute myocardial infarction. In the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angiographic Complications) trial, in which patients with acute MI were randomized to PTCA with or without abciximab versus stenting with or without abciximab, there was less early recurrent ischaemia in groups receiving abciximab, whereas the lowest rate was observed in the group of stenting with abciximab (1.2%) (Table 8.3). Following recent results from the TIMI 14 study,[70] which supports the combined use of tPA and abciximab (Fig. 8.6), could the association of a percutaneous intervention bring patency rates and TIMI 3 flow in the infarct-related artery close to 100%?

Table 8.3 CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angiographic Complications) – 2081 patients randomized.

	PTCA	*PTCA + ReoPro*	*Stent*	*Stent + ReoPro*
% of Stents	20	15	All	All
Stent length (mm)	—	—	23	23
Final MLD (mm)	2.19	2.12	2.67[a]	2.72[a]
Ref diameter (mm)	2.98	2.95	2.96	3.00
TIMI 3 (%)	94.8	95.5	92.1	96.1[a]

[a] $p < 0.005$ compared to stent without ReoPro.

In conclusion, stenting is recommended as a primary strategy of mechanical reperfusion in acute MI. Optimal mechanical resolution of plaque disruption and inhibition of platelet aggregation are key elements in the treatment of an infarct-related vessel.

Restenotic lesions after balloon angioplasty

Restenotic lesions after balloon angioplasty are associated with a high rate of recurrence when treated with repeat balloon dilatation.[71,72] The scaffolding properties of stents appear to be a reasonable way to prevent early recoil and late vessel wall constriction which are mainly responsible for restenosis after balloon angioplasty[73,74] We have reported on 125 patients treated with stents for restenosis after PTCA. The acute success rate was 98%, with an angiographic restenosis rate of 25%.[75] In a randomized trial (REST), which compared stents with balloon dilatation for treatment of restenotic lesions post PTCA, stenting resulted in a significant reduction of recurrent restenosis (18% versus 32%, $p = 0.03$).[76]

In conclusion, in vessels of appropriate size and in lesions of a suitable length, coronary stenting appears the treatment of choice for restenotic lesions following balloon angioplasty.

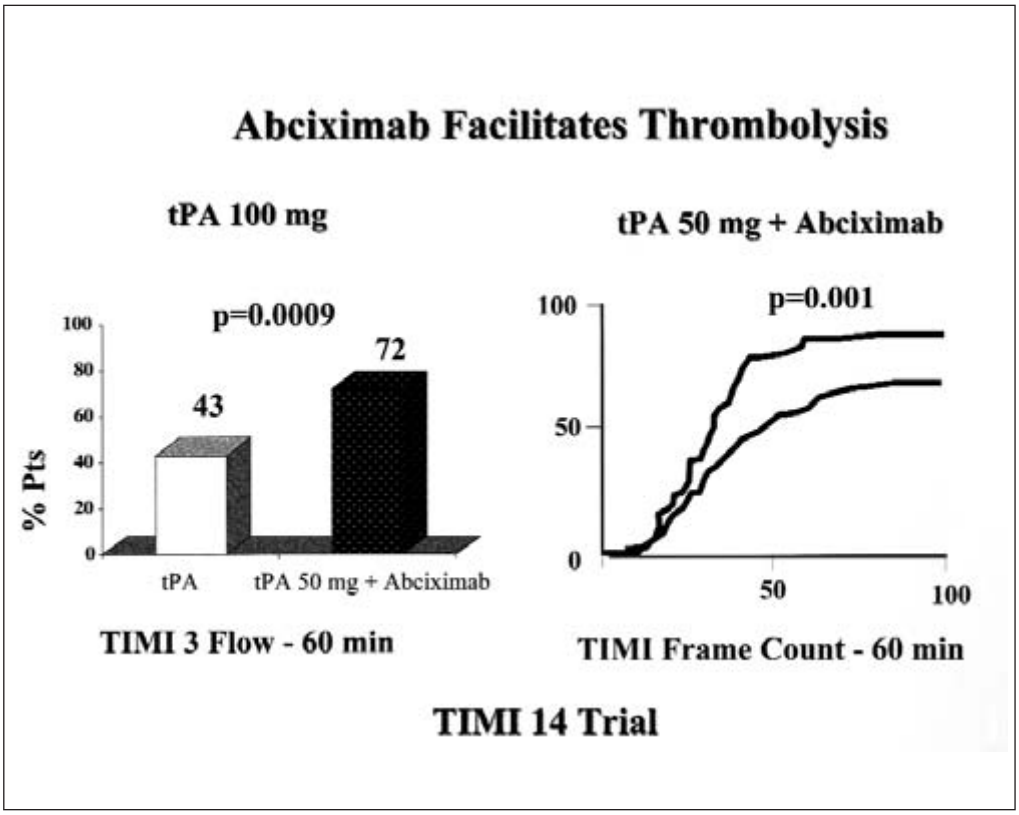


Figure 8.6
Abciximab in addition to tPA improves flow in acute myocardial infarction (TIMI 14 trial).

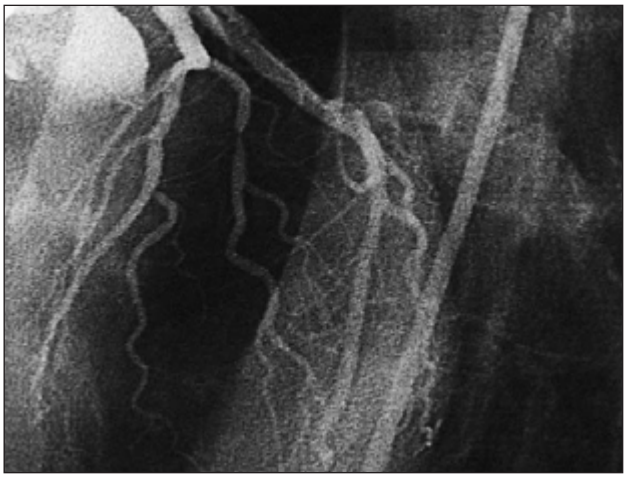
Contraindications to stenting

The only absolute contraindication to coronary stenting is in situations where antiplatelet therapy (aspirin, ticlopidine or clopidogrel) cannot be taken. Although we do not have randomized studies addressing this issue, one observational study reports that a regimen with ticlopidine only is safe.[77] However, as indications for coronary stenting continue to broaden, stents are implanted in complex lesions where we still do not have hard data to support the presence of a clear benefit compared to angioplasty or surgery. The results following stent implantation outlined below are not uniform and expert opinion as to the effectiveness remains divided at the present time.

Lesions in small vessels (<2.5 mm) (Fig. 8.7)

Percutaneous revascularization procedures in coronary vessels with small reference lumen diameter have been associated with low rates of procedural success and higher incidence of acute major complications.[78] In addition, for both balloon angioplasty and stenting, small reference lumen diameter is one of the most important predictors of restenosis.[79,80] IVUS studies showed that the absolute lumen loss caused by neointimal proliferation is similar in arteries with different diameter, but the same volume of neointimal proliferation is more likely to induce greater diameter stenosis in small coronary arteries.[81] Moreover, one study reported a higher loss index following stenting of vessels smaller than 3 mm in diameter (0.56 for vessels <3 mm versus 0.45 for vessels ≥ 3 mm, $p = 0.0006$).[7]

Although the early randomized stent trials required by protocol design the inclusion of vessels with a reference vessel diameter ≥ 3.0 mm only, core laboratory analysis identified that a large number of vessels treated with stents were <3.0 mm.[2,3] Savage et al[6] analysed a subgroup of 331 patients from the STRESS I and II trials with a vessel diameter <3.0 mm, measured by quantitative coronary angiography after randomization to stenting or conventional balloon angioplasty. This study showed that both procedural success and restenosis rates were more favourable after stenting than after balloon angioplasty (100% vs 92%, $p < 0.001$ and 34% vs 55%, $p < 0.001$, respectively). Similar results were recently reported at the 1999 American Heart Association meeting by Niazi et al, who presented a randomized trial of a heparin-coated stent versus balloon angioplasty in vessels smaller than 2.5 mm in reference diameter.[82] However, in a meta analysis of the BENESTENT-I and STRESS I and II studies, stenting did not show an advantage in either clinical events or restenosis over conventional PTCA when the two techniques were applied to



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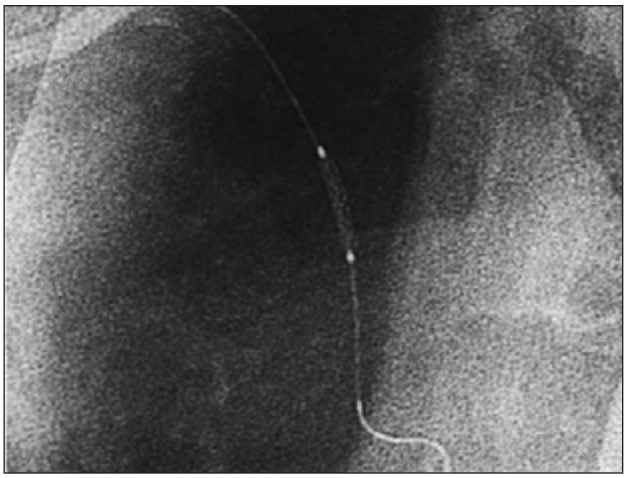

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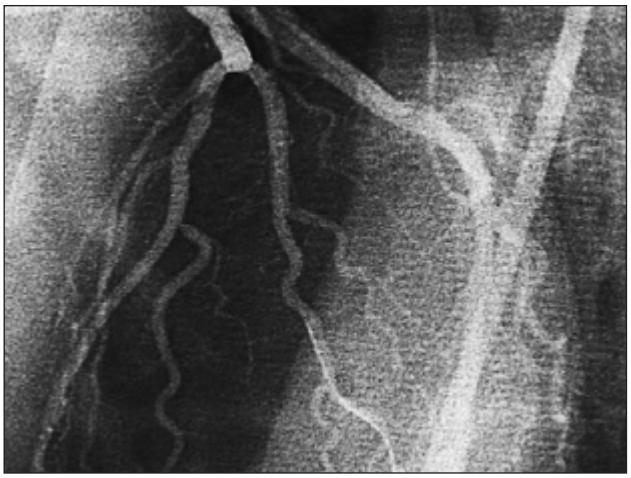

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Figure 8.7
(a) Severe discrete stenosis in the middle third of a 2.5 mm diameter diagonal branch of LAD. (b) After predilatation with a 2.5 mm balloon, a 2.5 mm 12 mm Microstent II™ (AVE) is deployed. (c) Final result. *(Courtesy of Dr D Ramsdale.)*

vessels <2.6 mm in diameter.[83] Akiyama et al[7] compared the outcome of coronary stenting in small (<3 mm) and large (≥ 3 mm) vessels. Although there was no difference in short-term outcome between small and large vessels, stenting in small vessels was associated with higher restenosis rates compared to stenting in larger arteries (32.6% versus 19.9%, $p < 0.0001$). The low incidence of stent thrombosis in this study is supported by other studies[84,85] and may be explained by aggressive stent expansion (with IVUS guidance in 70% of cases) as well as effective post-stenting antiplatelet therapy. Recently, Morice et al[86] showed favourable results following stenting of lesions located in vessels with a reference size ≤ 2.5 mm. The authors report high procedural success (98%), low stent thrombosis rate (2.6%) and a 24.5% repeat intervention rate.

However, an important question arises when examining the meaning of a 'small vessel' as defined by angiography. The fact that atherosclerosis is frequently a diffuse process may explain the finding that a diffusely diseased artery is labeled as a small 'healthy' vessel with a focal narrowing when evaluated by coronary angiography. The tomographic images of the coronary arteries provided by intravascular ultrasound (IVUS) allow us to obtain an accurate measurement of vessel and lumen dimensions. It permits identification of arteries which are small because of a large plaque burden and those non-diseased arteries with a true small lumen. In addition, IVUS demonstrates the result of the natural reaction of the vessel to the presence of plaque, expressed as positive or negative remodelling. In our experience of 365 vessels consecutively treated with stent implantation, the average vessel diameter (external elastic lamina to external elastic lamina) assessed by IVUS was 3.64 mm, while the angiographic lumen was <3.0 mm in all cases (mean angiographic diameter 2.65 mm).[87]

For these reasons we should be aware that the interventional studies involving angiographically defined small vessels may include two different groups of arteries. One group includes vessels which are small because of a large plaque burden, the other group includes vessels with no plaque. Despite the theoretical value of this distinction, we do not know its practical implications. Perhaps small vessels with a large plaque mass and positive remodelling may benefit from debulking and stenting or from stenting with a balloon sized to IVUS-measured dimensions. According to the study by Akiyama et al,[7] this second hypothesis is unlikely to be the case as the authors reported a high restenosis rate despite the use of IVUS-guided balloon sizing.

New dedicated stents for small vessels (reduced strut thickness and number of cells per row, lower metal-to-artery ratio, increased flexibility) may provide a solution to this problem and results of randomized clinical trials have been recently reported (Table 8.4). While the results of these trials did not settle the issue, preliminary results from prospective registries are fostering the use of stenting small vessels on the basis of selected observations.[88,89] Results from the SOPHOS Registry (Study Of PHosphorylcholine coating On Stents)[88] showed a beneficial

Table 8.4 Results of randomized trials of PTCA vs. stent in small vessels.

Study	*Number of patients*	*% Restenosis rate*		*p*
		PTCA	*Stent*	
ISAR-SMART[a]	404	37.4	35.7	NS
BeSmart[b]381	45.5	22.7	0.001	
SISA[c]	351	32	28	NS
RAP[d]	426	37	27	0.04

[a]ISAR-SMART: Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries. A. Kastrati, A. Schömig, J. Dirschinger et al. *Circulation* 2000; **102**: 2593–8.
[b]BeSmart: BeStent in Small Arteries. R. Koning, K. Khalife, P. Commeau. http://www.tctmd.com/expert-presentations/slides.html
[c]SISA: Stenting in Small Arteries. S. Doucet, M.J. Schalij, M. Vrolix. http://www.tctmd.com/expert-presentations/slides.html
[d]RAP: Restenosis en Arterias Pequeñas. E. Garcia. http://www.tctmd.com/clinical-trials/breaking

effect of the BiodivYsio stent (phosphorylcholine-coated) in reducing restenosis rates in small vessels. In another study, the use of the Mini BeStent (a slotted tube stent with a unique serpentine design, available in 2.5 mm diameter) resulted in a target lesion revascularization rate of 12.6% when implanted in small vessels.[89] Results from a randomized study comparing the heparin-coated JoStent versus balloon angioplasty in vessels with a diameter less than 2.5 mm showed a restenosis rate of 30% vs 49% respectively ($p = 0.0009$).[82] However, our experience with two dedicated stents (NIR 5 cells and Mini stent) showed high restenosis rates.[90]

Our view is that an understanding of the plaque mass and vessel remodelling is important for the initial design of any prospective study, in order to allow better interpretation of the results. In addition to stenting, competing technologies may be of value: balloon angioplasty, balloon angioplasty with cutting balloon, stenting, debulking and stenting. Any of the above techniques can be supported with IVUS or angiographic guidance. As we can see the menu in the small vessel 'restaurant' is quite diverse (Table 8.5). The appealing solution of simple angioplasty or direct stenting followed by brachytherapy will certainly be explored very soon in a randomized trial.

Table 8.5 Options for intervention in small vessels.

- Plain old balloon angioplasty (POBA)
- IVUS guided angioplasty with spot stenting
- IVUS guided angioplasty with cutting balloon and spot stenting
- Stenting alone with or without IVUS
- Debulking (device to be defined) followed by stenting with our without IVUS guidance
- Use of dedicated small vessel stents

Alternatives
Angioplasty or stenting followed by brachytherapy

In conclusion, the current available data on treatment of small vessels indicate that stenting is safe but does not result in improved long-term outcome when compared with conventional PTCA—provided that angioplasty dilatation gives a satisfactory initial result. Stents remain useful in this setting if the results of conventional PTCA are suboptimal with persistent significant residual stenosis.

Long lesions

Long lesions have been shown to have a poor acute and long-term outcome when treated with plain balloon angioplasty.[91] In addition, initial reports using coronary stents in long lesions (a strategy where full lesion coverage is performed) indicate improved acute outcome, but still high restenosis rates.[92–94] Since both stent length and number of stents implanted in long lesions are independent predictors of restenosis,[95–97] the strategy of 'spot stenting' was conceived. In the classical view of coronary stenting this procedure has been performed with the intent to cover the lesion entirely, anchoring the stent in a normal part of the vessel. Small dissections or haziness may ensue during stent deployment at the edge of the plaque or at the margins of the stent. These angiographic imperfections or complications are usually stented with the aim of completely sealing any edge dissection which may compromise inflow or outflow. The view that a stent is a prosthesis and needs to be anchored on a normal segment of a blood vessel is the basis of this concept.

In the large stent studies like BENESTENT I[2] and STRESS[3] most of the stents were 15 mm long and they were employed to cover lesions shorter than 10 mm. In the

BENESTENT I study the average lesion length in patients who underwent stenting was 7.06 mm and in the STRESS study the average lesion length was 9.6 mm (with a minimal stent length of 15 mm). The concept supporting this strategy was to minimize inflow or outflow obstructions which predispose to stent thrombosis. At that time stent thrombosis was the most important problem affecting the 'survival' of coronary stenting.

Our group in Milan was a major proponent of this concept in the years 1993–5 and this strategy minimized the risk of stent thrombosis by sealing any residual peri-lesion dissection: a condition firmly associated with a higher risk of thrombosis. Manufacturers and operators have reacted to this operative concept by marketing and implanting stents of different lengths—up to 40–60 mm. At this point an assumption and a conclusion were made: prevention of thrombosis may translate into prevention of restenosis. Full plaque coverage, introduced as a tool to lower thrombosis, became (for unknown scientific reasons and without any supporting data) an operative tool to limit restenosis. The proponents of this concept based their perceptions on the occasional findings of edge or articulation restenosis, claiming that incomplete lesion coverage was the basis for this unfavourable event.

Articulation restenosis may well be used as an example of incomplete lesion coverage or incomplete vessel scaffolding at a site where most of the plaque is present and where incomplete dilatation is likely to occur. Even if this assumption is correct, the results obtained from a number of stent vs stent trials in which the Palmaz–Schatz stent was compared to other stents failed to support this concept. Thus, the lack of incomplete coverage at the centre of the lesion is only a minor or modest determinant of restenosis.

The same considerations apply to edge restenosis. Most of the time, edge restenosis is not associated with the presence of significant plaque at that site prior to stenting.[98] In general, edge restenosis is a minor problem within the whole area of in-stent restenosis. All these considerations are necessary to support the idea that full lesion coverage by the stent does not appear to lower restenosis after percutaneous interventions. As a matter of fact it is the opinion of some interventionists that the introduction of long stents may have increased the risk of restenosis and in particular the risk of diffuse in-stent restenosis. A number of factors may contribute to the increased risk of tissue growth:

- more metal and therefore an increased foreign body reaction;
- a change in the dynamics of blood flow secondary to vessel straightening which occurs following stenting with an unfavourable change in shear stress.

The stent is no longer perceived as a bridge to fully replace a segment of diseased coronary artery. The stent is a support device for the vessel segment in which lumen collapse following angioplasty is severe. The stent becomes a 'pillar' rather than a 'bridge'. A pillar needs the integrity of the structure being supported while a bridge replaces the structure.

Intravascular ultrasound allows the operator to make decisions, to find out where to place the pillars and where the vessel lumen is sufficiently patent to be left as such. An unsatisfactory angiographic result, which would normally lead to additional stenting, may be considered acceptable when evaluated by intravascular ultrasound. This decision is based on true lumen evaluation rather than on angiographic silhouette assessment. How does this approach translate into an operational strategy? These are the steps:

(1) Determine whether the lesion needs spot stenting. Spot stenting may be a laborious and time-consuming approach, and should only be used when necessary. We empirically state that this approach should be used in lesions 15 mm or longer because this lesion length frequently demands the implantation of a stent longer than 15 mm. The cut-off point of 15 mm is taken because the 15 mm stent is the traditional length utilized in the major randomized trials for lesions <15 mm. Considering the number of 18 mm long stents now on the market we may increase the value by 3 mm.
(2) If the lesion needs spot stenting the first step is to perform intravascular ultrasound to determine the optimal balloon size to perform angioplasty. Intravascular ultrasound is necessary due to the fact that these lesions are frequently located within a diffusely diseased vessel. This situation leads to an underestimation of the true vessel size when angiography is used to make the assessment. Dilatation of a lesion with an undersized balloon may lead to a suboptimal result. When this suboptimal result is associated with the presence of a dissection, flow compromise is more likely to ensue.

The decision to spot stent within a diffusely diseased artery depends on IVUS evaluation, provided there is no impending occlusion or an angiographic stenosis of $>50\%$ in luminal diameter. If the residual stenosis at any point of the treated segment does not satisfy the following IVUS criteria, this segment should be stented:

- a minimum lumen cross sectional area $>50\%$ of the vessel cross sectional area;
- a minimum lumen cross sectional area >5.5 mm^2.

We have evaluated the outcome of two strategies in treating long coronary lesions. The IVUS-guided provisional and spot stenting approach was compared with the conventional approach of stenting the entire lesion length. We concluded that, for large vessels there was no significant difference in restenosis rates between the two strategies, in contrast to small vessels. This means that for long lesions in large vessels 'full lesion coverage' with stenting remains a good choice, while in small vessels the strategy of 'spot stenting' may be more efficient in reducing restenosis. At present there is no ongoing randomized study to test this hypothesis. The

COSST study, which was originally designed to compare the angiography-guided complete stenting versus the IVUS-guided spot stenting approach, has been halted, probably because of the high restenosis rate seen with long stents in the recently-completed ADVANCE trial.

In conclusion, treatment of long coronary lesions with stenting still remains problematic. The strategy of IVUS-guided spot stenting seems a promising alternative.

In-stent restenosis (Fig. 8.8)

In-stent restenosis seems to be a distinct entity in terms of its pathophysiology and treatment.[99] The persistence of a residual stenosis and of a hazy appearance within the stent after initial implantation as well as the presence of dissections at the stent ends are frequent after initial stent implantation and may result in 'pseudorestenosis'.[100] The rationale for the elective use of a second stent to treat in-stent stenosis is the presence of collapse of the initial stent, or plaque prolapse not correctable with PTCA. These conditions may occur in coil stents as well as for slotted tubular stents implanted in very calcified segments or in ostial locations.

Deployment of a new stent inside a restenotic stent 3–12 months after the initial procedure is an approach currently under evaluation for the treatment of in-stent restenosis. Although this 'sandwich' of neointima may be effective for early reintrusion of tissue after balloon dilatation,[101] its effectiveness in prevention of recurrent restenosis is not well established. Recent studies with stenting for treatment of in-stent restenosis report recurrent restenosis rates of between 14% and 44%.[102–104] However, the drawbacks are conceptually obvious: a longer segment than the initial stent length is stented and extreme stretching is imposed on the outer vessel wall, inducing a new powerful stimulus to hyperplasia in a patient whose artery is prone to neointimal proliferation.

Exclusion of the proliferative neointimal tissue behind PTFE-covered stents has also been tried, but restenosis was often observed at the stent edges, possibly because of the incomplete tissue coverage at the extremities of this device or from trauma in an area not covered with stent sealing.[105]

In conclusion, stenting as a strategy to treat in-stent restenosis has no clear role at the present time. Exceptions are restenotic lesions where gross plaque prolapse is present following the initial lesion dilatation.

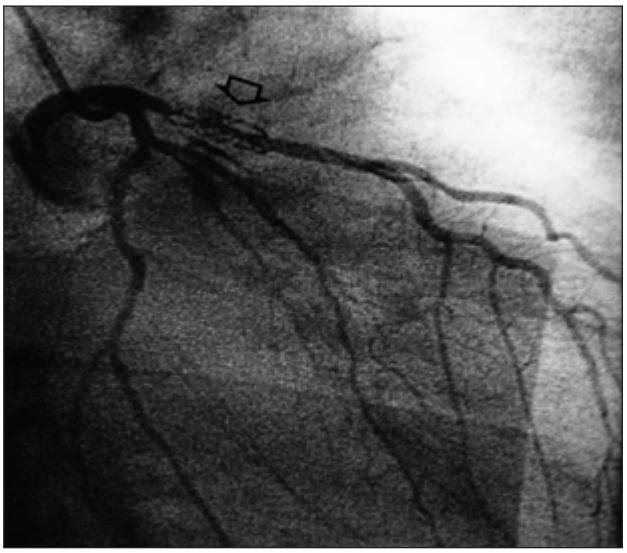


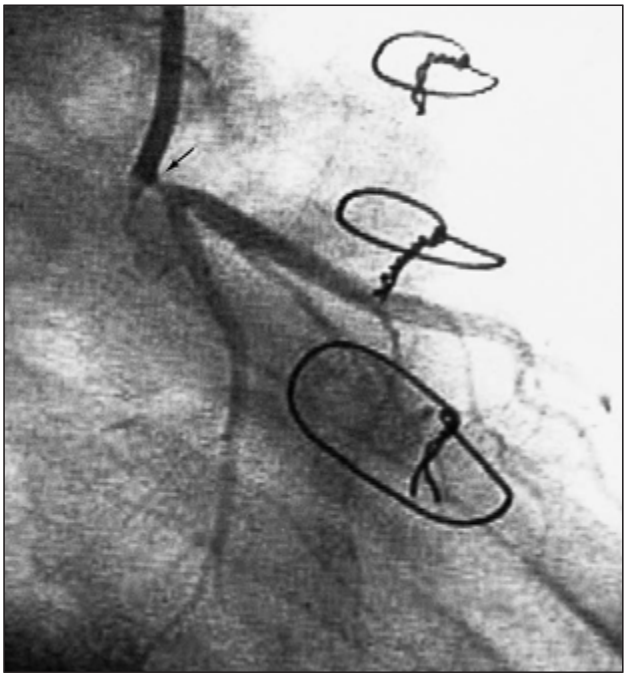
Figure 8.8
Severe in-stent restenosis inside a 3.5 mm Wiktor™ (Medtronic) stent in the LAD. *(Courtesy of Dr D Ramsdale.)*

Left main stem disease (Fig. 8.9)

Left main coronary artery (LMCA) stenosis is a widely accepted indication for bypass surgery[106] and stenting is usually reserved for patients with prohibitive surgical risks or for bail-out situations.[107–109] In the last few years, however, a number of studies have reported elective stenting of unprotected LMCAs in a wide range of patients.[110–112] Their findings indicate that stenting is a safe and effective alternative to CABG, since it is associated with an acceptably low rate of death, myocardial infarction or repeat revascularization at long-term follow-up. Park et al[111] report a restenosis rate of 22% at 6 month follow-up. In addition, IVUS-guided stenting of LMCA stenoses has been associated with a low target lesion revascularization rate of 7%, when the final lumen area was >7.0 mm^2.[112] Less optimistic results have been published in a multicentre registry involving 26 patients treated with stenting who had a 9-month survival of 68%.[107] Of the clinical variables which affect mostly the long-term outcome following LMCA interventions, the baseline ejection fraction appears to be the most important.[107,111] Of the procedural factors, the lack of involvement of the distal LMCA without the need to treat the left anterior descending and left circumflex bifurcation appears to be a favourable lesion characteristic. For these reasons, appropriate case selection is at the present time, one of the most important factors to guide interventions on the unprotected LMCA.

Our approach in the treatment of patients with unprotected left main stenosis is to select only lesions located at the ostium or in the body of the left main. A bifurcational left main lesion is treated only if it is technically feasible to debulk the lesion with directional atherectomy on both branches or at least the vessel where most of the plaque is present. Whenever possible, we prefer to debulk the lesion with directional atherectomy and then to stent. We are not aware of any ongoing randomized study testing the efficacy of stenting unprotected LMCA lesions versus the surgical solution.

In conclusion, in selected patients, stenting of LMCA stenoses appears to be a safe and efficient alternative to CABG



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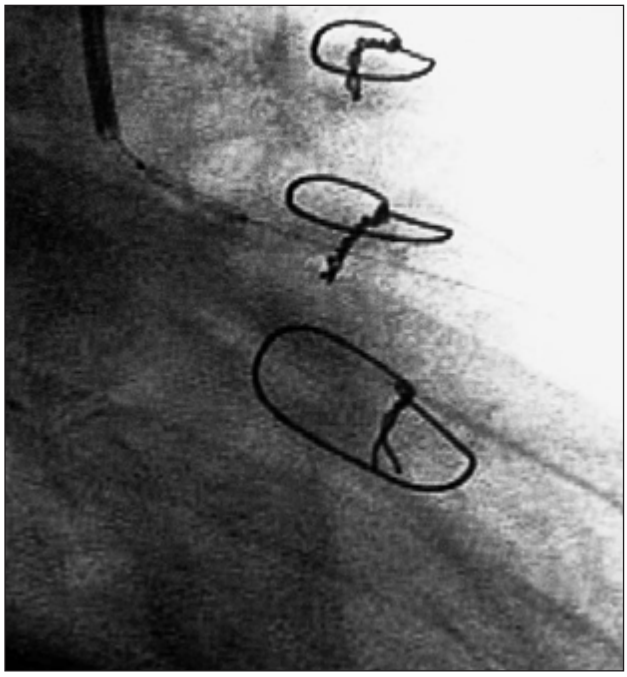

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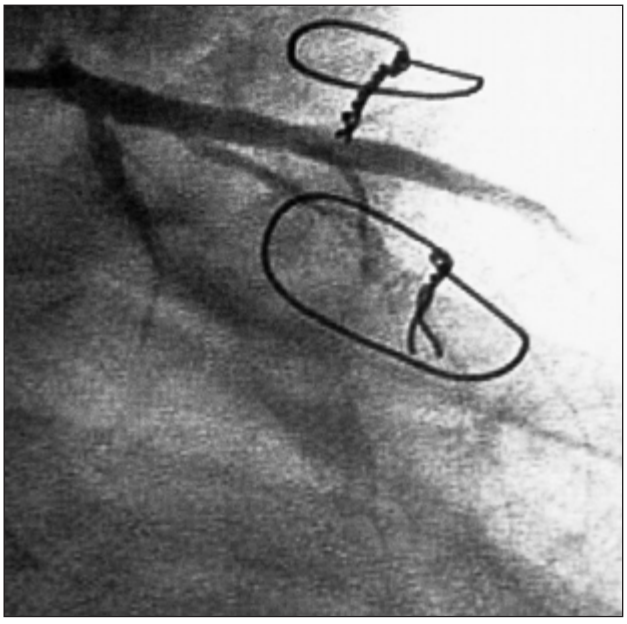

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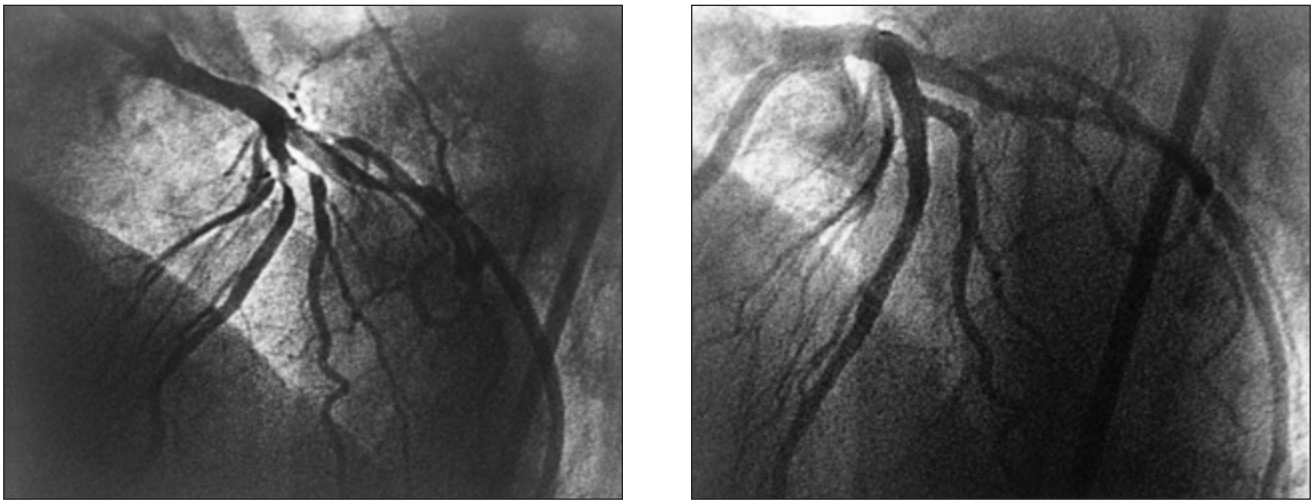
Figure 8.9
(a) Severe stenosis of the left main coronary artery (arrow). (b) A 3.5 mm 12 mm long stent is deployed with the guiding catheter disengaged. (c) Final result after post-dilatation with a 4.0 mm Finale™ (Guidant) balloon. *(Courtesy of Dr L Morrison, The Cardiothoracic Centre, Liverpool.)*

and is associated with a favourable long-term outcome. Until results of randomized trials or large registries become available, caution should be exercised in unprotected LMCA percutaneous interventions. It should only be considered in patients and lesions associated with a good clinical long-term outcome and in those unsuitable for CABG surgery.

Bifurcation lesions (Fig. 8.10)

Treatment of bifurcation lesions with balloon angioplasty carries a risk of side branch occlusion because of plaque redistribution (the 'plaque-shift', 'toothpaste' or 'snow-plough' phenomenon).[113] To lower the risk of plaque shift,



a b

Figure 8.10
(a) Severe stenosis of the bifurcation of LAD and first DG.
(b) Final result after deployment of a 3.0 mm 26 mm long JoStent™ (Jomed) in the LAD and a 2.5 mm 12 mm long GFX™ (AVE) stent at the ostium of the DG in 'T' stenting fashion. *(Courtesy of Dr D Ramsdale.)*

the 'kissing balloon' technique was developed.[114] However, the results following balloon dilatation of bifurcation lesions are frequently suboptimal with a high incidence of complications and restenosis.[115,116] The use of coronary stents has improved the treatment of bifurcation lesions, although technical challenges and a risk of compromising the branch vessel are still present.[117–119] Stent implantation on both the main and side branch ('kissing stents') is a useful technique for maintaining maximum expansion of both branches and minimizing plaque shift with the achievement of pristine immediate results.[120] These results are obtained using dedicated techniques for stenting bifurcation lesions ('T stenting', 'V stenting', 'Y stenting' and the 'Culotte technique').[121,122] Despite the continuing evolution of the above techniques and the availability of new dedicated stents for bifurcation lesions,[123,124] the long term results expressed as angiographic restenosis and need for a second intervention remain suboptimal.[125,126] For these reasons our recommended current strategy is to stent only the main branch with kissing balloon angioplasty on the side branch. Results of the recently completed AMIGO trial, which has included bifurcational lesions, will help to clarify the role of directional atherectomy followed by stenting.

In conclusion, stents have a role in the treatment of bifurcational lesions. Where possible, a strategy which limits the amount of metal coverage of both branches seems advantageous.

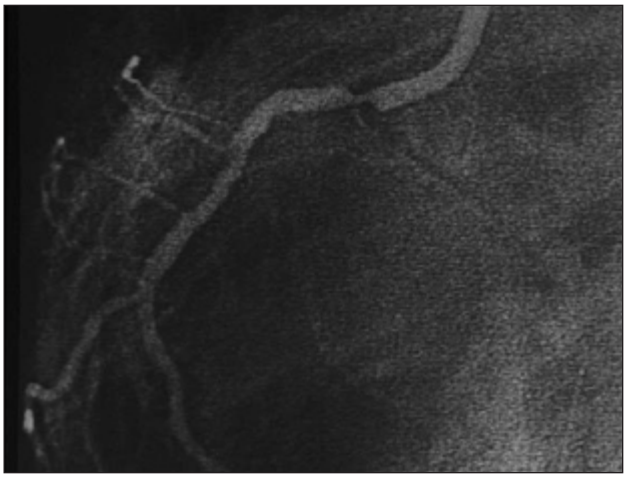
Ostial lesions (Fig. 8.11)

Ostial lesions respond poorly to conventional PTCA with inadequate dilatation and elastic recoil. Stents can be an excellent treatment for elastic recoil. There are a few reports on stenting of ostial lesions,[127–129] which have confirmed the effectiveness and safety of stents in this unfavourable lesion subset. Stent implantation must be precise, as if the stent is positioned too proximally the device may protrude into the aorta and make repeat catheterization difficult, or may compromise access to a branch vessel. A combination of stenting with other treatment modalities (cutting balloon, directional atherectomy) has been tried in ostial lesions.[130,131] At present, the ideal catheter-based intervention for these lesions has not yet been defined.

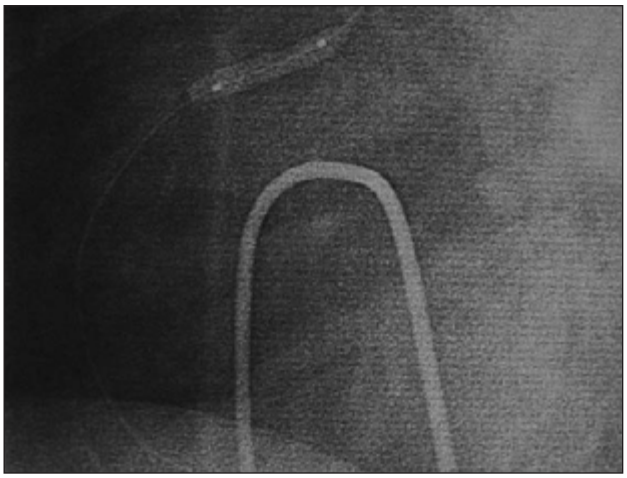
In conclusion, stenting in ostial lesions is feasible, but stents need to be accurately positioned. Despite excellent immediate outcomes and low complication rates, the incidence of restenosis and target lesion revascularization is still high and alternative or adjunctive solutions are needed.

Calcified lesions

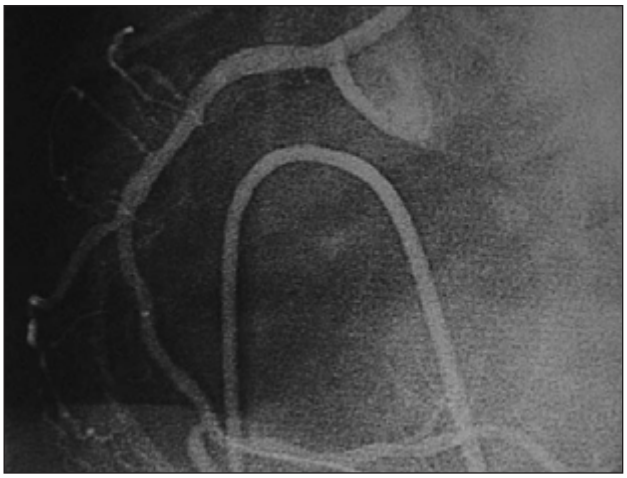
Moderate to severe lesion calcification has been associated with low procedural success and high complication rates after balloon angioplasty.[132,133] It has also been shown that lesion



a



b



c

Figure 8.11
(a) A critical stenosis at the ostium of a large RCA. (b) After predilatation with a 2.5 mm balloon, a 3.0 mm 12 mm long Multilink™ stent is deployed with the tip of the guiding catheter disengaged. (c) Final result. *(Courtesy of Dr D Ramsdale.)*

calcification limits stent expansion.[134] An approach of combined rotational atherectomy and stenting seems to improve outcome in this lesion subset.[135] Using this combined approach, we have reported the outcome after the treatment of complex, calcified lesions, with a procedural success rate of 96% and a restenosis rate of 22.5%.[136]

The availability of very low profile and high pressure balloons limits the need for rotational atherectomy to a very small subgroup of lesions with extensive superficial calcification. In our laboratory, rotational atherectomy prior to stenting in 1999 was limited to 2.7% of the treated lesions. The results of the recently completed SPORT trial, which compared rotational atherectomy prior to stenting with stenting alone, may change our conservative approach in favour of more calcium debulking.

In conclusion, stents are the preferred tools to scaffold calcified lesions which frequently dissect following balloon dilatation. Use of rotational atherectomy is reserved only for severely calcified lesions in which stent expansion without prior plaque modification may be suboptimal.

Complications associated with stenting

Stent thrombosis

Since the early days of stents, thrombosis has been a great concern to interventionists. Early studies showed significant platelet activation after stenting, which is not suppressed by anticoagulation therapy.[137,138] These in vitro findings explain the incidence of stent thrombosis (approximately 3.5%) in the early randomized stent trials (BENESTENT, STRESS)[2,3] despite the use of warfarin. In addition, intense anticoagulation with warfarin increased hemorrhagic complications (up to 10%), prolonging in-hospital duration and hence increasing hospital costs.[139]

In 1995, it became clear through our work[140] that incomplete expansion of the stent (documented by intravascular ultrasound) was a major contributor to the risk of stent thrombosis. Intravascular ultrasound performed following traditional stent placement helped in understanding the issue of stent 'underdilatation'. The use of high-pressure post dilatation (12–20 atm), full-sized balloons and the addition of ticlopidine to aspirin as an antiplatelet regimen lowered stent thrombosis rates to 1–2%. Our results were reproduced by the French registry, in which stent thrombosis occurred in 1.8% of patients receiving aspirin and ticlopidine, even without intravascular ultrasound guidance.[141] In vitro data confirmed that aspirin plus ticlopidine effectively controls activation of coagulation after percutaneous coronary interventions.[142] These findings led to changes in clinical practice after stent implantation (although evidence from randomized

trials was still lacking). Meanwhile, randomized trials were devised to compare the new combined antiplatelet therapy versus anticoagulation with warfarin. Today, data from these randomized trials have established that antiplatelet therapy with ticlopidine and aspirin combined with optimal stent placement with full expansion and no in-flow or out-flow obstruction is essential for successful stent implantation.[143–146] The incremental benefit of ticlopidine over aspirin alone after coronary stenting has been studied by Albiero et al.[147] In a series of 801 consecutive patients assigned to receive either aspirin alone or a combination of ticlopidine and aspirin after successful IVUS-guided stent implantation (in most cases), there was no significant difference in stent thrombosis between aspirin alone (1.9%) versus aspirin and ticlopidine (1.9%), despite the presence of more risk factors for thrombosis in the ticlopidine group. However, these findings may indirectly point out the superiority of the combined regimen versus aspirin alone. Results from the MUSIC study, in which the stent thrombosis rate was 1.3% in patients treated with aspirin alone after optimal IVUS guided coronary stenting, support this concept because all the patients included in this registry were at low risk for stent thrombosis.[148]

Despite a possible role of monotherapy with aspirin alone in selected cases, the overwhelming superiority of combined therapy is beyond doubt. However, the major concerns regarding the safety of ticlopidine are adverse effects such as skin rash, nausea, diarrhoea and the very rare but most serious neutropenia.[149] Ticlopidine-induced neutropenia occurs in approximately 1% of patients treated for longer than 2 weeks, whereas it has not been described in patients treated for less than 2 weeks.[150] In a recent study, the discontinuation of ticlopidine therapy 2 weeks after stent placement was associated with a very low frequency of stent thrombosis and other adverse events.[151] This approach could be an alternative for reducing adverse effects while maintaining antiplatelet protection.

Clopidogrel, a new platelet inhibitor similar to ticlopidine, has emerged as an alternative to ticlopidine after stent implantation. A loading dose of 300 mg of clopidogrel can achieve platelet inhibition more rapidly and with fewer side effects when compared with ticlopidine.[152,153] Recent studies have shown that clopidogrel combined with aspirin is an effective antiplatelet regimen after stent implantation.[154–157] The recent CLASSICS trial randomized patients after stenting to ticlopidine plus aspirin versus clopidogrel plus aspirin. The results showed a better outcome in the clopidogrel plus aspirin group (mainly due to a lower incidence of side effects) with similar effectiveness in the prevention of stent thrombosis.[158] The effectiveness of substituting clopidogrel for ticlopidine has been confirmed in a recent registry and in a randomized trial comparing clopidogrel and aspirin versus ticlopidine and aspirin.[154–157] However, some concern exists about the possible lower efficacy of clopidogrel. The higher thrombosis rate in the clopidogrel group (2%) reported in the randomized trial from Germany[157] may not have reached statistical significance due to the sample size.

The importance of maximizing protection against stent thrombosis should be emphasized. Recent data from the RISE (Registro Impianto Stent Endocoronarico) study suggest that stent thrombosis, despite adequate stent expansion and the use of antiplatelet drugs, still occurs in 1.4% of patients treated with coronary stents.[159] New potent antiplatelet drugs with a faster and more direct action on the final mediator of platelet aggregation, such as GP IIb/IIIa platelet receptor blockers, may further reduce this unfavourable complication. Evidence from the recently completed EPISTENT trial supports the use of abciximab in association with coronary stenting by showing a significant reduction in major adverse events at 30 days after stent implantation.[66] It is interesting to note that no abrupt closure occurred in the 794 patients randomized to stent plus abciximab treatment.

Bleeding and vascular complications

In the era of new antiplatelet therapy after stent implantation, bleeding complications have been considerably reduced and range between 1.7% and 5.5%.[144–146] Attempts to further reduce bleeding and vascular complications after coronary stenting include the radial approach and the use of closure hemostatic devices. A comparative study between transradial, transbrachial and transfemoral PTCA performed with 6F guiding catheters showed that major access site complications were less frequent with the transradial approach.[160]

Percutaneous closure devices (collagen plug devices, percutaneous suture closure) have also been used in patients undergoing stent implantation via the femoral route in an attempt to reduce vascular complications and promote early ambulation.[161–164] A recent study compared vascular sealing devices (Vasoseal and Perclose) with aided manual compression (Femostop) in patients receiving abciximab. The results showed that these devices do not seem to add any benefit in the reduction of vascular complications compared with manual compression.[165] However, data from a randomized trial comparing the strategy of delayed sheath removal by manual compression with immediate sheath removal and a collagen plug device (Angioseal) in patients at high risk for local complications showed that the latter strategy reduced complications and resulted in early ambulation.[166]

Cost issues of coronary stenting

Early data on economic aspects of coronary stenting from the STRESS trial showed an increase in total 1-year medical costs

compared with balloon angioplasty.[167] In addition to higher catheterization laboratory costs, total cost was increased because of increased vascular complications and a longer hospital stay.

The economic impact of the elimination of anticoagulant therapy following stenting became manifest in the BENESTENT II trial assessing the cost effectiveness of heparin-coated stents versus balloon angioplasty.[168] The balance between costs and effectiveness at 12 months was addressed by calculation of the incremental cost-effectiveness ratio (the average 1-year cost per patient with stent implantation minus the average 1-year cost with balloon angioplasty divided by the percentage reduction in event-free survival after 1 year) and the average cost-effectiveness ratios (the average costs per patient divided by the percentage of event-free survivors) for both stenting and angioplasty. The initial costs were significantly higher for the stent implantation group than the balloon angioplasty group. The differences in the cost of the initial procedure were mainly related to the use of balloons and the cost of the stent itself. Part of the initial higher cost was offset during the follow-up period, as there were significantly fewer revascularizations in the stent group. The average cost-effectiveness ratio at 1 year was 21 309 Dutch guilders (95% CI 18 348–24 105) for balloon angioplasty versus 21 073 Dutch guilders (95% CI 18 638–23 263) for stents. (One US dollar approximates to two Dutch guilders). It has also been shown that in-hospital costs associated with coronary stenting declined by 20% in the new era of antiplatelet regimens.[169,170]

The follow-up of the patients randomized in the ARTS trial, which compared the treatment of multivessel coronary artery disease with stenting or coronary bypass surgery, has been completed (European Society of Cardiology Meeting, Barcelona 1999). This study demonstrated that the stent strategy was associated with a lower total procedural cost (6464 Euros) compared to the surgical revascularization (10 742 Euros, $p < 0.0001$). This cost advantage was maintained at 12 months with a total cost per patient of 10 680 in the stent group versus 13 645 in the by-pass group ($p < 0.0001$).

These advantages are probably related to the use of stents and in particular to stenting with antiplatelet agents only and a short hospital stay. A recent study addressing the issue of cost implications of coronary stenting showed that although the mean in-hospital cost for patients receiving a stent was higher than in those patients who underwent balloon angioplasty, stent patients were less likely to be rehospitalized or to undergo repeat revascularization within 6 months of the procedure. Consequently, mean cumulative costs at 6 months and 1 year were similar for the two strategies.[171] In a fee-for-service environment, stent-use drives up procedural costs while lowering downstream revenue from repeat procedures. From a socio-economic point of view, stents provide better long-term patient outcome (fewer symptoms and repeat revascularizations) at a similar or possibly lower expense compared to balloon angioplasty.

Future trends

The surface properties of stents can be modified by different coatings. Synthetic polymers (biodegradable or not) have been used to modify stent surfaces, but most of the polymers tested in animal models have induced a marked inflammatory reaction.[172] More favourable results have been shown with high molecular weight poly-L-lactic acid, a polymer that was well tolerated in an animal model.[173]

Heparin-coating was the first to be successfully used in clinical practice in two large randomized studies.[42,168] The first trial was conducted in the setting of elective coronary stenting and the other was conducted in the setting of acute MI (STENT PAMI trial). In the two elective stenting randomized trials (BENESTENT II, TOSCA) enrolling 616 patients in the stent arm, stent thrombosis occurred only in one patient in the BENESTENT II trial (0.2%). In the STENT PAMI trial, which randomized 452 patients in the stent arm, stent thrombosis occurred in 7 patients (0.8%). Despite these encouraging results in short term outcome, no data are available to support any role for heparin coating in the prevention of restenosis.

Carbon-coating is another form of metal passivation used mainly to decrease platelet activation and to isolate some components of stainless steel such as nickel and chromium, which may trigger an inflammatory reaction in some patients. The Sorin Biomedica carbofilm-coated stent,[174] the AMG carbon-coated stent, the Biotronic Tenax silicon carbide-coated stent[175] and the Phytis diamond-coated stent[176] are all available on the European market and utilize different types of carbon-coating. It has been claimed from registry experience that these stents have a superior long term outcome in terms of reduced thrombogenicity and a lower restenosis rate compared to bare stainless steel stents.[177]

The phosporylcholine (PC)-coating, which mimics the cell membrane lipophilic–hydrophilic interface, has been used to cover the metal surface of stents.[178–180] The fact that PC-coating does not seem to increase the inflammatory reaction is already an important achievement.

Data from the SOPHOS trial which tested this type of stent were encouraging, with a 17.7% restenosis rate in a registry with 200 patients mostly with single vessel disease and all with a single short lesion.[88] It is claimed that the 20% angiographic restenosis rate found in vessels with a reference size <2.7 mm needs to be further evaluated in a separate study. An interesting new application of this PC-coating is its potential as a drug delivery vehicle.[181] Metallic stents coated with potent antiproliferative drugs such as paclitaxel (Taxol), its derivates and rapamycin (Sirolimus) have been extensively tested in animals[182,183] and are now being evaluated in man.

It is conceivable that the next step will be the evaluation of more specific compounds, which manifest their inhibitory effect only on proliferative cells or on the messengers involved in the restenotic process. A more selective activity will preserve the survival of many cell lines involved in posi-

tive regulatory systems present in blood vessel walls. In this category, drugs such as angiopeptin[184] or antisense oligonucleotides[185] are the ones with the largest preclinical data.

Finally, biodegradable stents, made of polymers which gradually degrade, are emerging as a new alternative to 'traditional' metal coronary stenting.[186] These devices may ultimately become the gold standard for drug delivery, disappearing from the vessel wall following completion of their task.

Conclusions

Coronary stenting has improved the outcome of percutaneous interventions and has almost eliminated the need for emergency surgery. Since the introduction of GP IIb/IIIa antagonists and their combined use with stenting, acute vessel closure has become a rare problem for the interventional cardiologist. Prevention of restenosis, however, has been successful only in a few lesion subsets. Despite this persistent limitation, the possibility for stents to 'freeze' a mechanical result with a predictable immediate lumen diameter would be an achievement of enormous importance. A new decade of work will concentrate on a better understanding of the biology of in-stent restenosis which will be important in addressing future therapeutic solutions. Unfortunately, only limited information can be obtained from past studies where the restenotic model was angioplasty with a combination of vessel recoil and tissue proliferation. Despite their effectiveness, alternative therapeutic modalities such as brachytherapy or anti-tumour drug-coated stents may divert useful resources away from finding the specific answer to the restenosis phenomenon.

Appendix

Clinical Trials Acronyms

ADVANCE	ADditional VAlue of NIR stents for treatment of long Coronary lEsions
AMIGO	Atherectomy before Multilink Improves lumen Gain Outcome
ARTS	Arterial Revascularization Therapy Study
BENESTENT	BElgium NEtherlands STENT
BESMART	BEstent in SMall ARTeries
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CLASSICS	CLopidogrel ASpirin Stent International Cooperative Study
COSST	COmplete Stenting versus IVUS-guided conditional Spot stenting Trial
DEBATE	Doppler Endpoint Balloon Angioplasty Trial Europe
DESTINI	Doppler Endpoint STenting INternational Investigation of Coronary Flow Reserve
FRESCO	Florence Randomized Elective Stenting in acute Coronary Occlusions
FROST	French Randomized Optimal Stenting Trial
GISSOC	Gruppo Italiano di Studio Sullo stent nelle Occlusioni Coronariche
GRAMI	GRII Stent in Acute Myocardial Infarction
MUSIC	Multicentre Ultrasound Stenting In Coronary arteries
PAMI II	Primary Angioplasty in Myocardial Infarction – II
PASTA	Primary Angioplasty and STent implantation in Acute myocardial infarction
RAP	Restenosis in Arterias Pequenas
REST	REstenosis STent study
SAVED	SAphenous VEin De novo Trial
SICCO	Stenting In Chronic Coronary Occlusion
SISA	Stenting In Small Arteries
SOPHOS	Study Of PHosphorylcholine coating On Stents
SPACTO	Stent vs PTCA After Chronic Total Occlusion
SPORT	Stent POst Rotational atherectomy Trial
STAT	Stents vs Thrombolytics in Acute myocardial infarction Trial
STENT BY	STENT versus BYpass for closure after PTCA
STENT PAMI	Primary Angioplasty in Myocardial Infarction Stent Trial
STENTIM 2	Elective Wiktor STENT In acute Myocardial infarction
STRESS	STent REStenosis Study
TASC II	Trial of Angioplasty and Stents in Canada
TIM1	Thrombolysis In Myocardial Infarction
TOSCA	Total Occlusion Study of CAnada

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9

Directional coronary atherectomy

David R Ramsdale and Ever D Grech

Introduction

Percutaneous transluminal coronary angioplasty is limited by a 3–5% incidence of abrupt coronary artery closure,[1,2] indifferent clinical and angiographic results in complex or balloon-resistant lesions and a 25–35% incidence of restenosis occurring in the first six months, requiring further intervention.[3–5]

Directional coronary atherectomy (DCA) involves the selective excision and retrieval of atherosclerotic material from diseased coronary arteries.[6–8] By debulking such arteries it was anticipated that improved results could be obtained in lesions with complex morphology, non-dilatable lesions and those in sites associated with higher complication and restenosis rates. Furthermore, it was hoped that retrieval of material might help in understanding the pathology of coronary atherosclerosis and restenosis after PTCA and perhaps also result in lower restenosis rates. Some of these hopes have been realized, but not all.

History

The first successful coronary atherectomy was performed in February 1987. After the initial 50 clinical cases were performed at Sequoia Hospital, 11 other institutions in the USA joined a multicentre investigation in June 1988. Based on an 85% success rate and low complication rate in 1032 lesions up to November 1989, the FDA subsequently approved the device made by DVI (Devices for Vascular Intervention, Guidant Ltd, CA, USA) in September 1990[9] and by mid 1992 more than 33 000 procedures had been carried out in over 670 centres in the USA.[10] The Simpson AtheroCath® has since been refined with the original surlyn-covered device (SCA–1™) being replaced by the more streamlined SCA-EX™ device in 1992. Other devices such as the ShortCutter, the GTO® Atherocath and the Bantam™ were subsequently released for clinical use to overcome some of the shortcomings of the original design. Improved guiding catheters and guidewires have also helped to make the procedure more user friendly and less daunting.

Indications

Directional coronary atherectomy is ideal for complex, bulky, focal, de novo lesions in the proximal portions of large (>2.5 mm), non-calcified, non-tortuous vessels but the indications have expanded as the equipment has developed and more practical experience has been gained.[7,8,11–13] Cases should be selected on the basis of the operator's experience, lesion location and morphology (Table 9.1).

Table 9.1 Ideal indications for DCA.

Vessel	*Lesion*
Large (>2.5 mm)	Focal (<10 mm)
Non-tortuous	De novo or restenosis
LAD>RCA>LCX	Morphologically complex
Proximal/mid	– bulky concentric/eccentric
Non aorta-ostial (LAD, LCX branches)	– ulcerated, flap-like
	– local dissection
Aorta-ostial (LM, RCA, SVG)	– mild/no calcification
	– PTCA resistant
	Discrete tubular

RCA, right coronary artery; LCX, left circumflex artery; LM, left main artery; SVG, saphenous vein graft; LAD; left arterior descending artery

Operator experience

Case selection guidelines for DCA have been published by DVI (Guidant) and should be adhered to.

Lesion location

Lesion location is an important factor since accessibility is limited by the size, profile and rigidity of the device.

- Left main coronary artery lesions should only be addressed if the left main is protected by patent bypass grafts.
- Lesions in the proximal or mid-left anterior descending coronary artery are usually accessible unless its takeoff is high or there is marked tortuosity.
- Generally, only lesions in a left circumflex with a shallow takeoff (<30°) or a short left main should be attempted.
- Lesions in the proximal or mid right coronary artery are suitable as are more distal lesions before the crux in large, non-calcified vessels.
- Aorta-ostial lesions are technically demanding.[14–18] Ostial left main and vein graft stenoses are easier than ostial right coronary disease, but all should only be attempted by experienced operators.
- Ostial LAD and left circumflex lesions can be effectively treated by DCA.[19,20] It is important that a minority of the cutting window is in the left main with most being in the LAD or LCX and that the guiding catheter is disengaged once the atherectomy device is correctly positioned in order to allow perfusion of the uninvolved vessel.
- Bifurcation lesions can be treated by sequential DCA in order to remove the 'shifting atheroma' seen during PTCA.[21,22] Both branches should ideally be 2.5 mm or more in diameter. The side branch should not be protected by a standard angioplasty guidewire, otherwise guidewire fracture and embolization are possible. Dauerman et al[23] reported improved acute angiographic results and reduced target vessel revascularization with atherectomy and adjunctive PTCA compared to PTCA alone.

Lesion morphology

Ideal lesions for DCA are those which are ideal for PTCA (type A). However, DCA offers a higher success and lower complication rate for morphologically complex lesions (Types B and C).[11,24,25]

- Eccentric lesions are ideal for DCA. The window of the housing can be directed towards the eccentric plaque without damaging the 'normal' vessel wall in close proximity.
- Lesions with complex morphology, such as ulcerated, bulky, flap and membrane-like lesions are better treated by DCA than PTCA.[24,25]
- Tough, resistant plaque which has failed to respond to PTCA can often be removed by DCA, as can restenotic lesions.[10,26]
- Minor but potentially occlusive dissections can also be removed by 'rescue' DCA, although extensive or spiral dissections should be avoided.[26–31]
- Mildly calcified lesions can be excised, but data suggest that procedural success is reduced and complication rates are higher.[9,32]
- Complex lesions with associated thrombus, as seen in unstable angina, can be effectively excised by DCA,[33,34] but vessels containing large amounts of clot should be avoided because of an increased risk of acute closure.[35]
- Saphenous vein graft (SVG) stenoses can be effectively removed by DCA, but restenosis rates are higher than in native arteries.[36–39]

Contraindications

Contraindications to DCA include those for PTCA and are shown in Table 9.2.[40]

- Some coronary anatomy can make DCA impossible and this includes Shepherd's crook RCA, high take-off LAD and LCX exiting from left main stem at an angle of >60°.
- Severe peripheral vascular disease can make it impossible to deliver a suitable guiding catheter to the aortic root and marked dilatation of the ascending aorta or unfolding frequently prevents satisfactory engagement

Table 9.2 Contraindications to DCA.

Contraindications for PTCA	Moderate and severely calcified lesions/vessels
Shepherd's crook RCA	Large branches requiring protection
Long left main	Diffuse disease
LCX exiting left main stem at >30°[a]	Small vessels (< 2.5 mm)
Long lesions (>20 mm)	Tortuous vessels
Distal lesions	Degenerated SVGs
Bend lesions >45°[a]	Dissection—extensive spiral
Internal mammary arteries	Severe peripheral vascular disease

[a]ShortCutter takes a bend up to 60–70°.
RCA: right coronary artery.
LCX: left circumflex artery.
SVG: saphenous vein graft.

and stable alignment of the guiding catheter, which is essential for success.
- Old, degenerated saphenous vein grafts containing much friable, grumous material should be avoided because of the risk of embolization.[41–44]
- Severe tortuosity proximal or just distal to the lesion is a contraindication to DCA because the rigid housing will not negotiate the curves and coronary dissection may result from aggressive manipulation.[8] Even moderate tortuosity with calcification will make it difficult to advance the device through the non-compliant segments.
- Calcification is a major adverse factor and calcified lesions cannot usually be excised by the current cutter.[45]
- Lesions on bends (>60°) should be avoided because of the risk of dissection and perforation by deep cuts across the angle. Less severe angulated lesions can be approached with the newer, lower profile Bantam™ device and the ShortCutter.
- Diffusely diseased vessels, small vessels and distal lesions should be avoided because the large profile of the device makes advancement difficult.[8]
- Excessively long (>20 mm) lesions are unsuitable and even those of intermediate length (10–20 mm) will require multiple cuts with device position adjustment along the length of the lesion.[46]
- Lesions in internal mammary arteries are inaccessible.

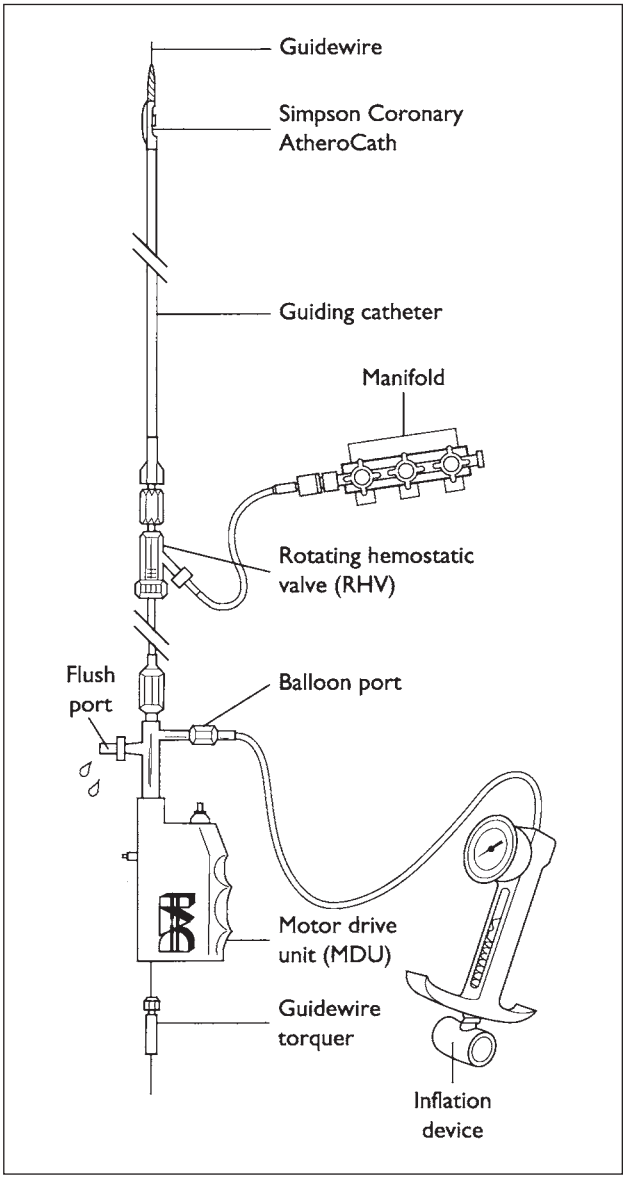


Figure 9.1
Schematic diagram of Simpson coronary atherectomy device (AtheroCath®). (Courtesy of DVI/Guidant Ltd, Santa Rosa, CA, USA).

Equipment

Simpson coronary AtheroCath®

The Simpson coronary atherectomy device is a coaxial over-the-wire catheter for use with a steerable 0.014 inch guidewire (Fig. 9.1). The distal portion of the device consists of a non-flexible, gold plated, stainless steel biopsy housing in which lies a cup-shaped cutter. This portion has a longitudinal window of a 120° arc (9 mm long) and a support PET balloon on its opposite side. Immediately distal to the housing is a tapered, flexible, stainless steel, braided nosecone that functions as a specimen collection chamber (Fig. 9.2). The braided shaft of the atherectomy catheter provides torquability—by rotation of the proximal assembly part. The proximal end of the device consists of a balloon inflation port, a distal flush port and a small lever, which is attached to the hollow

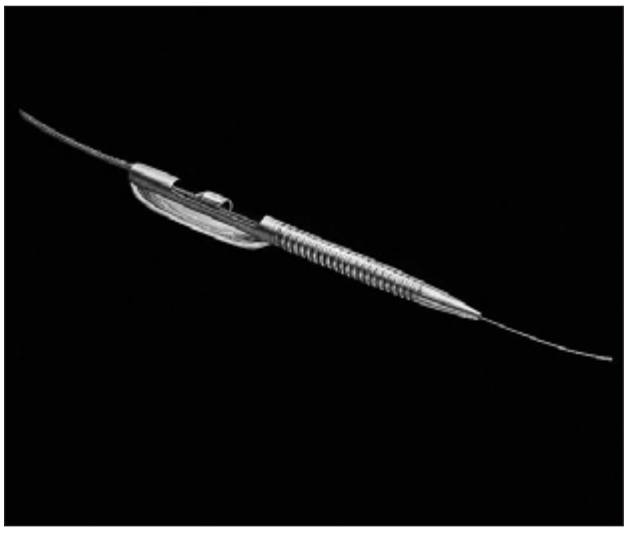
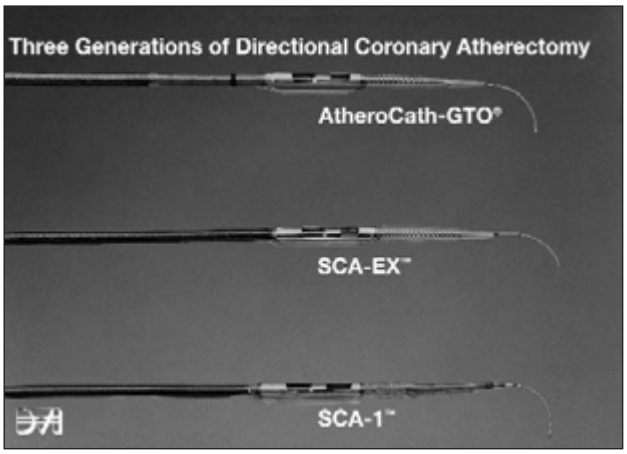


Figure 9.2
Distal end of Simpson Coronary AtheroCath® showing the flexible nosecone, the cutter within the housing window and the balloon. (Courtesy of DVI/Guidant Ltd, Santa Rosa, CA, USA).

drive cable that runs the length of the catheter and connects to the cutter. The 0.014 inch guidewire passes through the centre of the drive cable. A hand-held, battery-powered, motor drive unit (MDU) connects to the proximal end and once activated spins the cutter at 2000 rpm. The cutter is advanced and retracted manually by the lever. Balloon inflation and deflation are controlled by a low pressure indeflator attached to the balloon inflation port.

Choice of AtheroCath® (Table 9.3)

The vessel size is the major factor in selecting the size of the AtheroCath® device (5F–7F) to use, although vessel compliance/calcification, tortuosity and accessibility, lesion/vessel angulation, lesion severity and length are important. Until recently three devices were available – the SCA-EX™, the GTO® and the Bantam™ (Fig. 9.3) together with a 'ShortCutter'. The original SCA-1™ has been withdrawn.



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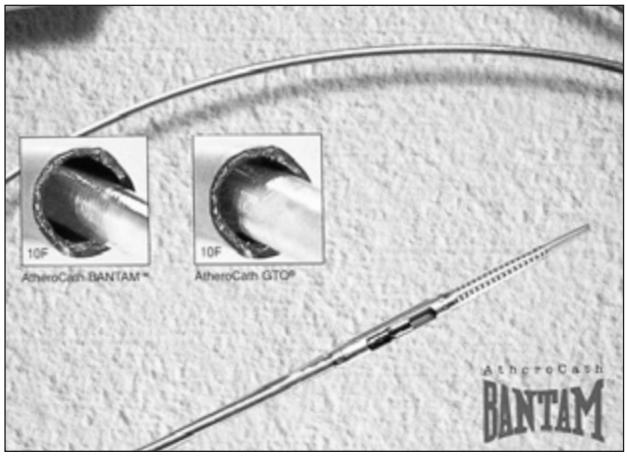

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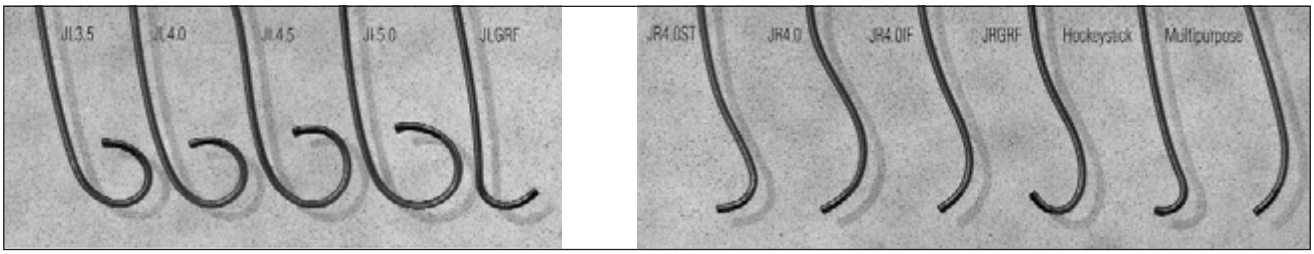
Figure 9.3
(a) The first three generations of Directional Coronary Atherectomy. (b) The more recent Bantam™ has a 'downsized' shaft that allows a 7F device to be used within a 9F Tourguide™ guiding catheter.

Table 9.3 Choosing the Atherocath®.

SCA-EX™, GTO® or Bantam™ device Indication	*SCA-EX™ ShortCutter Indication*	*SCA-EX™ 7FG Indication*
Most native vessels	Ostial lesions	Large native vessel
Tandem lesions	Focal (<5 mm) lesions	Aorta-ostial lesion
Distal tortuosity	Distal insertion lesions	SVGs
Tapering vessel	Acute take-offs	Calcified lesions
Distal disease beyond lesion site	Short radius turns	Bulky/long lesions
Device for vessel size		
AtheroCath®	*Size*	*Vessel diameter (mm)*
SCA-EX™ or Bantam™	5F	2.0–2.5
	6F	2.5–3.0
	7F	3.0–3.5
	7FG	3.5–4.0[a]
GTO®	5F	2.0–2.5
	6F	2.5–3.1
	7F	3.1–3.7

[a]7FG is not available as Bantam™.



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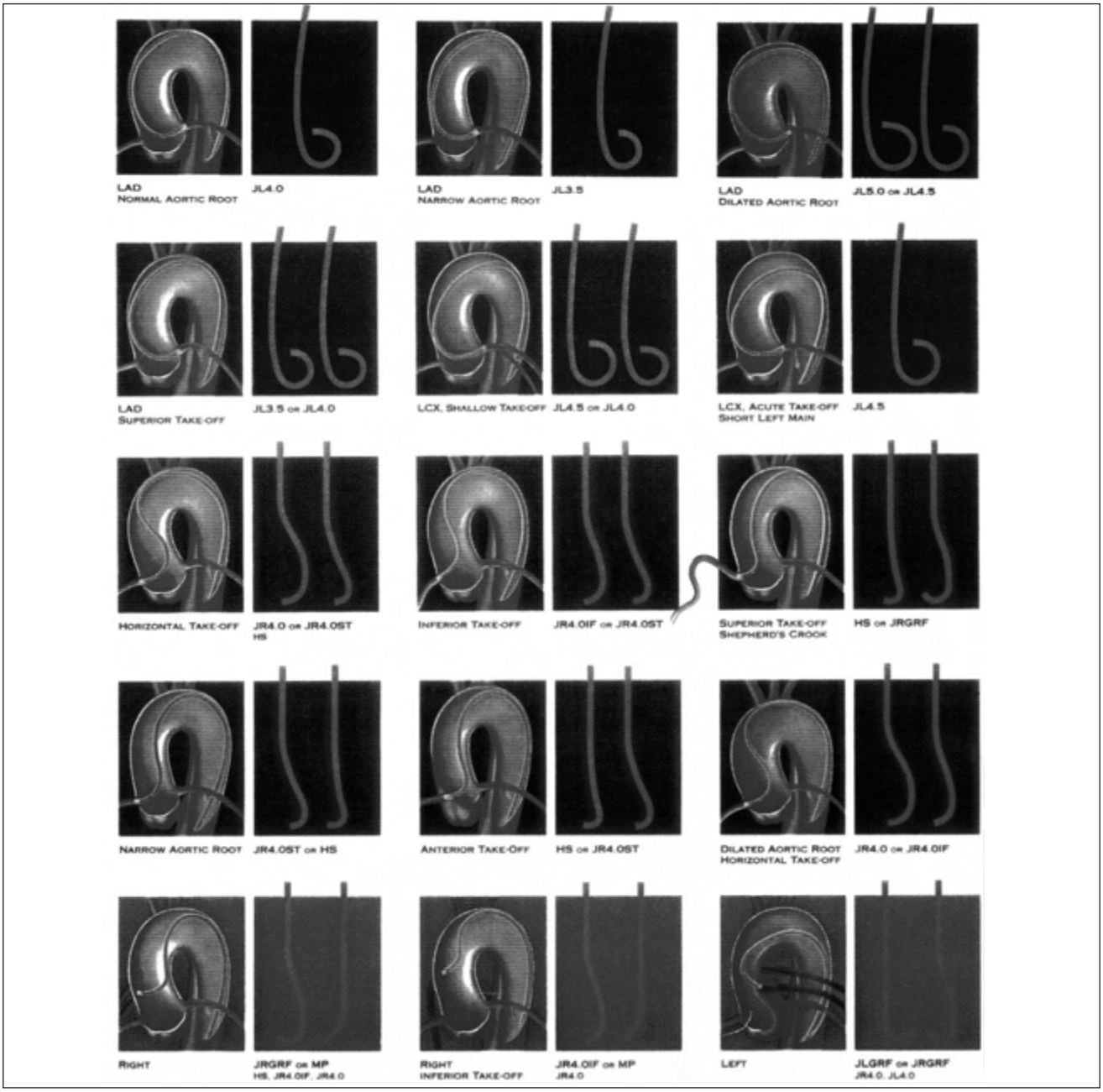

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Figure 9.4
(a) DVI guiding catheters (currently available). (b) Choice of guiding catheter depends on size and shape of aortic root and angle of take-off of coronary ostium or SVG.

- The SCA-EX™ (6F, 7F and 7FG) is designed to address the majority of anatomical challenges. The low profile reduces the need for predilatation and the springtip nosecone improves flexibility and trackability.
- The GTO® AtheroCath (5F, 6F and 7F) has a coaxial inflation lumen and a round shaft profile to allow greater torque output and improved stability of the device within the coronary artery.
- The Bantam™ (5F, 6F and 7F) has a small shaft profile which enhances contrast visualization of the vessels during the procedure, improves trackability and of course can be used within a 8F or 9F Tourguide® catheter.
- The ShortCutter (5F, 6F and 7F) offers 29% reduction in rigid housing length (12 mm), which widens its applications. The window is only 5 mm long and little tissue is retrieved per cut. It is ideal when the LAD or LCX has an acute take-off and for focal, ostial and distal lesions and stenoses in tortuous vessels.

Guiding catheter

Guiding catheters must have a large internal diameter and additional stiffness in order to provide support when delivering the AtheroCath® into the coronary artery.[47] DVI® and Tourguide® guiding catheters have soft distal tips and side holes and a range of shapes and sizes are available (Fig. 9.4a,b). Compatibility between the various AtheroCaths and the guide catheters is shown in Table 9.4.

The atherectomy device is inserted into the guiding catheter through a rotating haemostatic valve (RHV).

Guidewire

A 300 cm 0.014 inch, teflon-coated, high torque, floppy guidewire is ideal, but one of intermediate or standard stiffness can also be used. An 'extra support' wire (Guidant, USA) may aid delivery of the AtheroCath® into and along the coronary artery.

Table 9.4 Tourguide/AtheroCath® compatibility.

	AtheroCath®	*Tourguide™ (ID)*
Bantam™	5F	8F (0.087")
	6F	9F (0.101")
	7F	9F
SCA-EX™ or GTO®	5F	9F or 10F
	6F	9F or 10F
SCA-EX™ or GTO®	7F	10F (0.112")
	7FG	10F

Procedure

A detailed description of the procedure and management of patients undergoing DCA can be found in Practical Interventional Cardiology.[48]

Once the AtheroCath® is delivered across the lesion, the housing's window is orientated towards the main bulk of the lesion by manually torquing the AtheroCath® (Fig. 9.5a,b). The balloon is inflated to 10–15 psi (0.5–1.0 atm.) to support the device within the lumen. The cutter is retracted manually and the balloon further inflated to 20 psi (maximum 30 psi), thereby forcing the lesion into the window of the device. The MDU is activated and the spinning cutter advanced over 5–7 seconds using the proximal lever. Cutter advancement should be observed by fluoroscopy. Abnormal tissue protruding into the window is cut and pushed into the nosecone. The balloon is deflated. The window of the device is then directed to a different part of the lesion and the sequence of events repeated (Fig. 9.6). For concentric lesions, systematic cuts in four 90° quadrants (or eight 45° sectors if possible) are usually necessary, but for eccentric lesions cuts are directed at the lesion itself. Once the angiographic appearance of the artery is acceptable (Figs. 9.7 and 9.8), the catheter can be withdrawn and the chamber emptied of its specimens (Fig. 9.9). The specimens retrieved should be counted and weighed in order to provide a quantitative assessment of the degree of debulking.

Optimal endpoints

One should aim at a final residual, angiographic stenosis of $<10\%$, but as close to 0% as possible.[49] The balloon inflation pressure may be increased to 30–40 psi during cutting before upsizing the device. Optimal endpoints also include flow around the device with contrast injection, smooth borders, absence of dissection, no distal complications, large lumen with good flow and good tissue retrieval. The best predictor of a favourable late outcome is the presence of a large lumen diameter immediately following intervention.[50,51] Optimal DCA is best guided by IVUS.

Pre-dilatation

Pre-dilatation of the stenosis should not be done routinely. However, pre-dilatation with a 2.0 mm balloon at low pressure may allow the smooth passage of the atherectomy device through severe, subtotally occluded segments, long lesions, segments of diffuse disease and heavily calcified vessels en route to a stenosis.

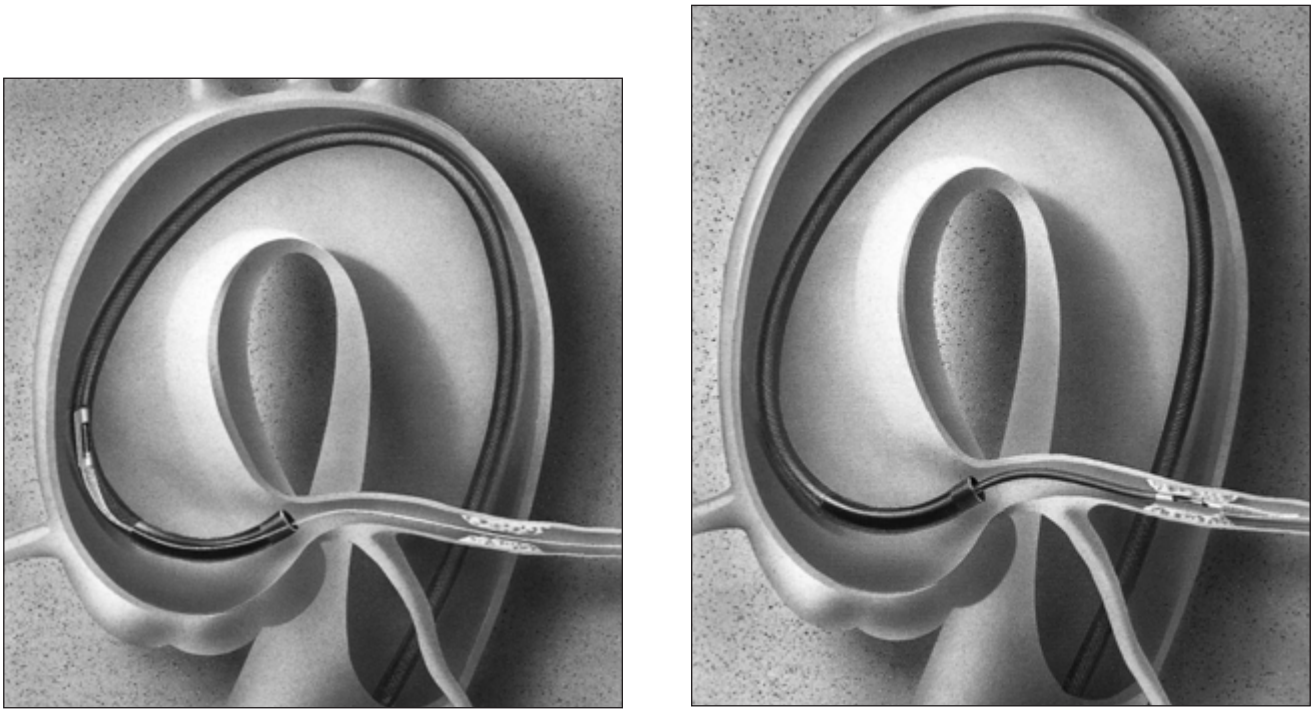

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Figure 9.5
(a) Once the guiding catheter is correctly seated, the SCA device is positioned proximal to guide curve to maintain coaxial alignment during wire placement. (b) The SCA nosecone and housing are then advanced across the lesion aided by rotation of the AtheroCath®. (Courtesy of DVI/Guidant Ltd, Santa Rosa, CA, USA.)

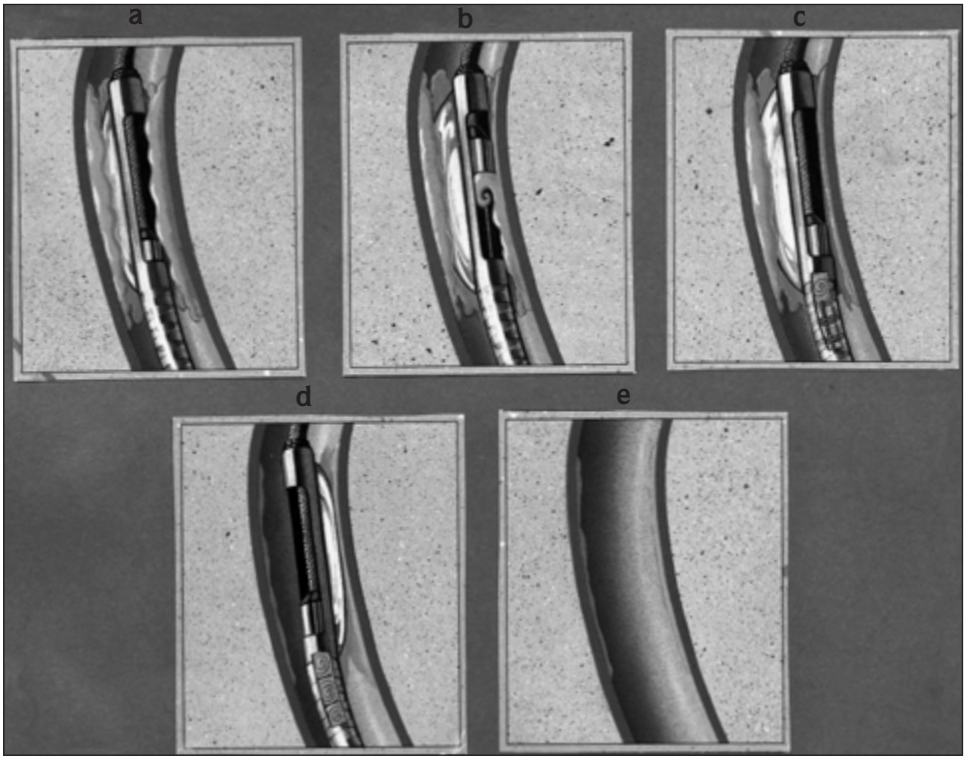

Figure 9.6
DCA cutting sequence.

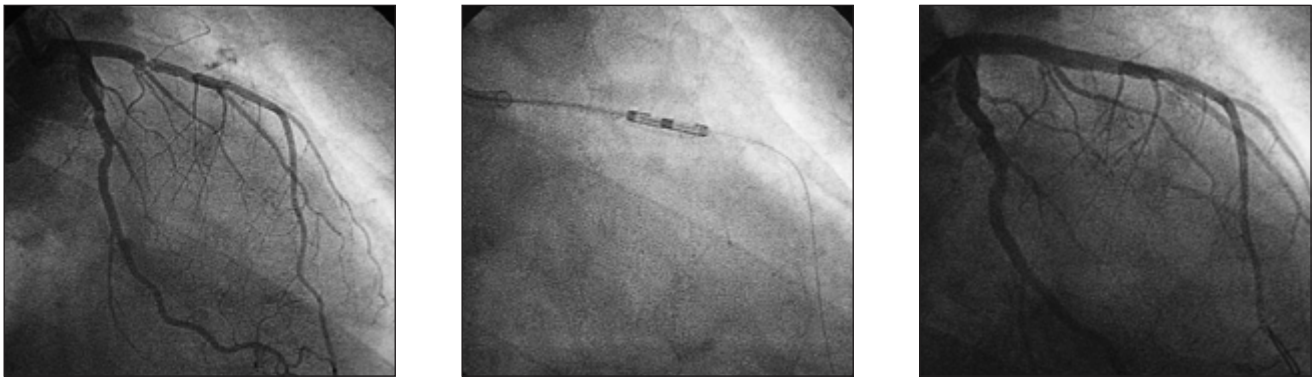

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Figure 9.7
(a) Severe balloon-resistant stenosis in proximal left anterior descending (LAD) coronary artery before DCA. (b) during DCA, with SCA across stenosis and cutter towards distal end of housing. (c) post DCA, showing no residual stenosis.

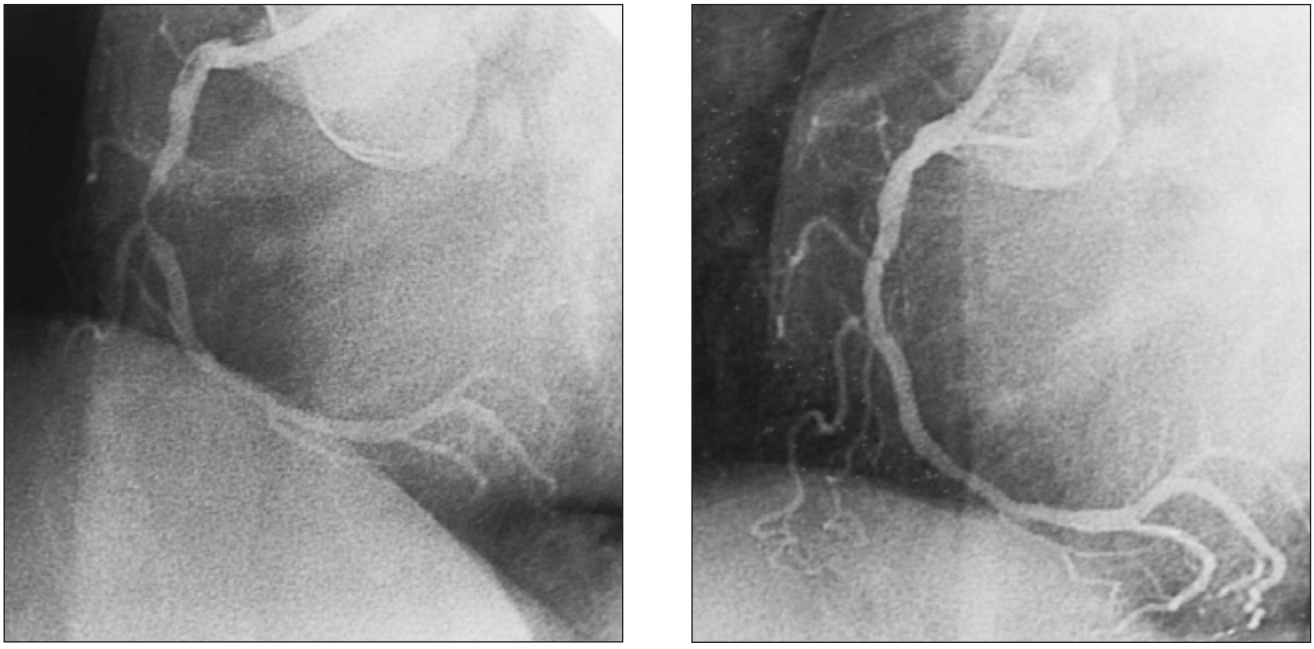

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Figure 9.8
DCA of right coronary artery. (a) Pre DCA. Severe stenosis in mid-third. (b) Post DCA.

Adjunctive balloon dilatation after DCA

Conventional PTCA and stenting is indicated for managing unsuccessful DCA procedures and to rescue DCA induced complications. Most centres who have reported their results claim improved procedural success with DCA plus PTCA over DCA success alone.[52]

Useful technical advice

Exposure to instructional/observational courses, with 'hands-on' experience if possible, is a major advantage for operators commencing a programme of DCA.

The guiding catheter should never be deeply engaged and a 'power position' should be avoided to reduce the likelihood of ostial dissection. Once coaxially aligned, the guiding

Figure 9.9
Coronary atherectomy specimens emptied from the cutting chamber.

catheter should be backed up against the opposite aortic wall for support as the Simpson atherectomy device is advanced down the coronary artery.

Advance the AtheroCath® across the lesion with the cutter locked forwards but this should be unlocked before switching on the MDU to spin the cutter.

Between 2 cm and 5 cm of the distal tip of the guidewire should be in the main vessel and not in a side branch when the cutter is spun.

If the guidewire loses its mobility, further cuts should not be made. The AtheroCath® should be withdrawn and the chamber emptied before proceeding further.

When the AtheroCath® is being withdrawn, the guiding catheter should be held firmly or retracted slightly to avoid deep engagement of the guiding catheter.

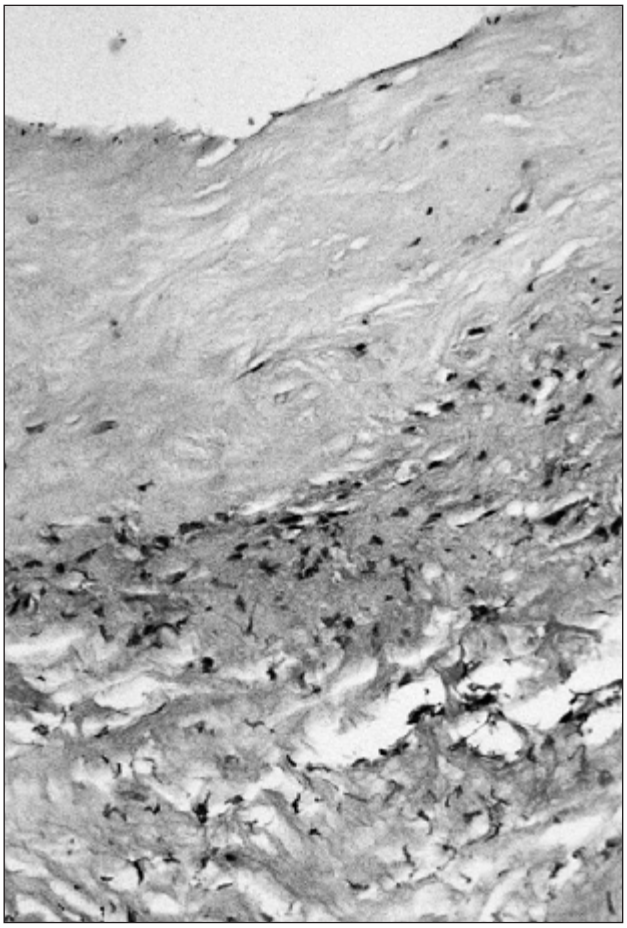
Lesion specific technical tips are worth remembering.[53]

Comparison of DCA with PTCA

Advantages and disadvantages of DCA compared to PTCA are shown in Table 9.5.

Table 9.5 Advantages and disadvantages of DCA.

Advantages	*Disadvantages*
Higher success/lower complication rate for:	Large guiding catheter with limited shapes
– focal, eccentric plaque	AtheroCath® is relatively large
– bulky, ulcerated/complex lesions	Rigid metal housing
– resistant PTCA lesions	Confined to proximal part of non-tortuous, non-calcified, large vessels
– ostial lesions	Need special expertise
More predictable acute result:	More expensive than PTCA
– less frequent dissections	
– less abrupt closure	
– less residual stenosis	
Allows tissue removal:	
– debulking	
– histology, cell culture	
– ? Lower restenosis rates for certain subgroups, eg de novo, discrete, prox LAD lesions in vessels >3.0 mm, after a 7F device with post DCA MLD >3.0 mm	



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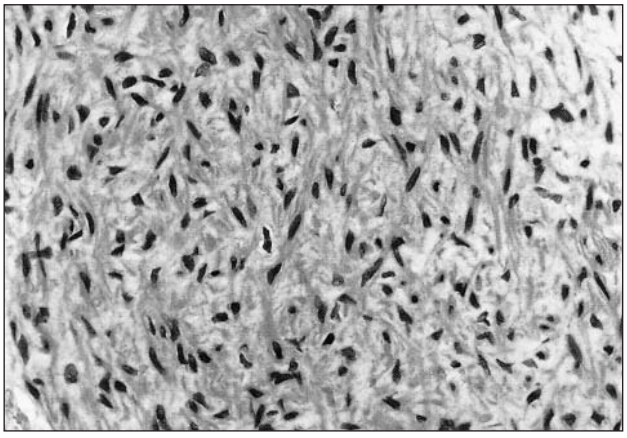

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Figure 9.10
Histopathology of DCA specimens. (a) Fibrous intimal atherosclerotic plaque. (b) Fibrointimal smooth muscle cell hyperplasia from a restenosis lesion.

Histopathology

Analysis of tissue removed during DCA has already helped to provide new insight and understanding of atherosclerosis, restenosis and unstable angina (Fig. 9.10).[54–59] It has provided samples for tissue culture and special immunological and molecular biology studies aimed at developing new strategies and new pharmacological agents for treatment of these conditions.[60–72]

Results

Compared to PTCA, optimal DCA results in significantly improved post procedure angiographic appearances due to less severe residual stenosis and a lower incidence of dissection.

DVI registry

The Investigational Device Exemption (IDE) data were collected from 12 US sites between 1988 and 1990.[9] Data were available on 1032 lesions (838 patients in 923 procedures).

Despite using the original, higher profile and potentially more traumatic SCA–1™ device, the data demonstrated a 85% primary success rate—higher in restenotic and non-calcified lesions. With adjunctive PTCA, the overall success rate was 92%. Major complications occurred in 4.9% of procedures, and included non-fatal myocardial infarction (0.9%), emergency coronary bypass surgery (CABG) (4.0%) and death (0.5%).

Other published results

Individual centres that participated in the IDE investigation have published their own results confirming DCA to be a safe and effective procedure (Table 9.6). For individual operators there is likely to be a learning curve with the results improving beyond the first 50 cases.[81,83] The newer AtheroCaths are more streamlined and less traumatic and this has resulted in low complication rates (OARS, BOAT and ABACAS) (see below).

Sequoia experience

Between 1988 and 1994, 1887 DCA procedures were performed at Sequoia Hospital. 2283 lesions were addressed

with a DCA success rate of 91.9%, a procedural (DCA + PTCA) success of 95.6% and a major complication rate of 3.1%.[75] The AtheroCath® was successfully placed in 95% with pre and post DCA dilatation being performed in 35% and 14%, respectively. On average, 14.8 mg of tissue was excised per case leaving a mean residual stenosis of 14.4%. The 7F device (70% in 1993) resulted in more excised material (18.7 mg), less residual stenosis (10%) and a higher primary DCA success rate (95%).

Concentric and eccentric lesions had high DCA (94%) and DCA + PTCA success (96%) with a low CABG rate (1.2–2.4%). Ulcerated lesions (98%), dissections (91%) and flap

Table 9.6 Results of DCA: success and complication rates.

CENTRE	*PTS* (N)	*LES* (N)	*Proc* (N)	*DCA* (%)	*Proc* (%)	*QMI* (%)	*CABG* (%)	*Death* (%)	*MJR. Comp* (%)	*Perf* (%)	*Out of Lab Closure* (%)	*Leg Compli-cations* (%)	*Reference*
IDE Multicenter 1988–90	838	1,032	923	85	92	0.9	4	0.5	4.9	0.6	0.8	1.1	9
Sequoia Hospital													
1986–88		447		90	94	0.8	3.1	0.3					73
1986–91		1,547		91	95	0.5	3	0.2					74
1988–94		2,283	1,887	91.9	95.6	0.3	3	0.4	3.1				75
Medical College of Virginia 1989–92	300	427	345	95	95	1.7	3.8	0.3	4.6	1.2	1.4	2.3	10
Beth Israel													
1988–91	190	225		91	98	0	0.5	0					76
1993–94		132	120		97	2.5	1.7	0	3.3				Beth Israel Database
NACI Registry (planned DCA)	931	1,026		84	93.2	1.1	1.5	0.6					77
Washington Hospital	306		306		94.8	0.3	1.8	0.6	2.6	0.3	2.3		32
MAHI Kansas City 1989–94	227	264			94	2.6	0.8	0.8	4.4	0.4	2.6		78
Mayo Clinic 1988–90	158	165			92	1	4	3	7				79
Thorax Center and University of Louvain 1989–91	105	113		85.7	95.2	4.7	2.8	0.9	5.7	0.9	0.9	0	80
CTC Liverpool	45	50	45		95.5	0	4.4	0	4.4	0	2.2	0	81
Christian-Albrechts University of Kiel*[a]	325	341	—		92	1	1.8	0.6	—	0	0.6	0.9	82

[a]Details of data from R.Simon – personal communication.

lesions (95%) had similar high procedural success rates to non-complex lesions (96%). Success rates were 96% in lesions <10 mm in length, 95% if 10–20 mm long and 91% if >20 mm long. The corresponding CABG rates were 2.2%, 3.3% and 7.4%. Calcified lesions had a 93% success rate and a 4.8% CABG rate compared to 97% and 3.3% in non-calcified vessels.

Restenosis lesions had a higher success rate than de novo lesions. Aorta-ostial lesions had a procedural success of 95% and a CABG rate of 5.3% (5.9% left main; 8.2% RCA; 2.1% SVG). Non aorta-ostial lesions had a 93% procedural success and a 3.2% CABG rate (2.0% LAD; 13.0% LCX; 0% diagonal). In 85 total occlusions, DCA proved successful in 91% and DCA + PTCA in 94% once the artery was recanalized and predilated. Excised tissue weighed 19.5 mg and the residual stenosis was 10%.

In 312 SVG lesions (20% ostial, 78% body and 2% distal anastomosis) DCA success was 95% and DCA + PTCA success was 97%. Dissection occurred in 8.1%. Major complications occurred in 1.8% (death 0.8%; CABG 1.6%; Q-wave MI 0.4%). In-hospital occlusion occurred in 1%, embolism in 5.7%, CKMB elevation in 12.7% and perforation in 1.0%.

Overall, major complications occurred in 3.2%: Q-wave MI 0.3%, CABG 3.0% and death 0.4%. Other complications include CKMB elevation 12.9%, distal embolization 1.8%, groin repair 1.0%, stroke 0.4% and in-hospital occlusion 1.0%. Twenty four (1.1%) patients had evidence of perforation: 11 (0.5%) perforation, 12 (0.6%) limited pseudo- aneurysm and 1 (0.1%) arteriovenous fistula.

Failure of DCA was due to failure to reach or cross (53%), failure despite tissue retrieval (29%), poor guide support (10%) and no tissue removal (5%).

Clinical trials in DCA

CAVEAT I (Coronary Angioplasty Vs Excisional Atherectomy Trial)[84,85]

In CAVEAT I, 1012 patients (at 35 centres) with a de novo stenosis in any major coronary artery were randomized to DCA or PTCA.

DCA had a greater procedural success than PTCA (82% vs 76%) and a greater angiographic success (89% vs 80%). There was no difference in in-hospital mortality between DCA (0%) and PTCA (0.4%). However, the need for emergency CABG was higher for DCA (3.7% vs 2.2%; ns). Myocardial infarction and abrupt closure rates were both increased in the DCA group although only non-Q wave infarcts were significantly more common after DCA (Q-wave: 2.2% vs 1.0%; non-Q wave: 4.9% vs 2.2%). Abrupt closure occurred in 6.8% and 2.8%, respectively.

Event-free survival rates at 6 months were indistinguishable (60% DCA vs 63% PTCA), but the incidence of myocardial infarction (mainly non-Q wave) was higher among the DCA group (8% vs 4%).

The frequency of angiographic restenosis after 6 months was only marginally lower with DCA (50% vs 57%). One of the limitations of this study was that the vessel size treated was relatively small and the residual stenosis after DCA relatively high (29%), suggesting that optimal debulking was not achieved.

One-year follow-up data suggest that the long-term outcome (death and MI) may be worse in the DCA group, (death 2.2% for DCA vs 0.6% for PTCA), a finding possibly attributable to the doubling of periprocedural non-Q-wave MI in patients treated by DCA.

CCAT (Canadian Coronary Atherectomy Trial)[86]

In CCAT, 274 patients at nine centres with de novo lesions with >60% stenosis in the proximal LAD were randomized to DCA or PTCA.

In this study, the initial angiographic success was greater in the DCA than the PTCA group (98% vs 91%), but in contrast to the CAVEAT data there was no significant difference between the two groups in any of the major complications of death (0%), emergency CABG (1.4% DCA vs 4.4% PTCA), myocardial infarction (Q-wave MI: 0.7% vs 0%; non-Q-wave: 3.6% vs 3.7%) or abrupt closure (4.3% vs 5.1%). Unfortunately residual stenosis after DCA was still 26%.

The restenosis rates were similar 6 months after DCA (46%) as after PTCA (43%). Interestingly, in CAVEAT, proximal LAD lesions had a significantly lower restenosis rate after DCA than after PTCA (51% vs 63%).

CAVEAT II (Coronary Angioplasty Vs Excisional Atherectomy Trial II)[87,88]

CAVEAT II was a randomized trial (involving 52 sites) of PTCA versus DCA in 305 patients with discrete, de novo, SVG lesions. The average age of the SVGs was over 9.5 years. Acute complications were low and similar in DCA and PTCA patients (CABG: 0% vs 1.5%; QMI: 1.6% vs 1.5%; death: 1.6% vs 1.5%) respectively.

At 6 months there was no significant difference in restenosis rates between those undergoing DCA (45.6%) or PTCA (50.5%) and target vessel reintervention (18.6% for DCA vs 26.2% for PTCA; $P = 0.09$) was also similar in the two groups.

Over one year of follow up, similar trends were present with regards to death, MI and CABG, but there was a favourable trend towards fewer repeat procedures after DCA.

OARS (Optimal Atherectomy Restenosis Study)[89,90]

OARS was a four-centre, non-randomized study which aimed to reveal 6-month restenosis rates in patients who achieved the best possible acute DCA result. Two hundred consecutive patients recruited underwent ultrasound-assisted DCA to achieve a residual stenosis of <10% with post dilatation by PTCA being optional if residual stenosis >10% remained despite DCA's best efforts. Enrolment began in January 1994.

Procedural success occurred in 97.5%, with major complications in 2.5% (death 0%; emergency CABG 1.0%; Q-wave MI 1.5%). Salvage stent placement was performed in 3.5% and adjunct PTCA in 87% of patients.

Quantitative coronary angiography (QCA) showed enlargement in MLD from 1.18 mm to 3.16 mm, reducing diameter stenosis from 64% to 7%. IVUS showed that although the luminal cross sectional area was increased from 8.2 mm^2 after DCA to 9.0 mm^2 by adjunctive PTCA, a large amount of residual plaque remained (57%).

At 6 months, the angiographic restenosis rate was 28.9%. At 12 months, the target lesion revascularization was 17.8%.

BOAT (Balloon Angioplasty vs Optimal Atherectomy Trial)[91–93]

BOAT's primary objective was to demonstrate whether it was possible to provide larger acute results safely with DCA (acute residual stenosis <15% via QCA) compared to conventional PTCA, and that such improved acute results translated into reduced angiographic restenosis. Forty individual high volume DCA/PTCA operators randomized 1000 patients to PTCA or DCA using a 7F device. A residual stenosis of <15% (QCA) only would suffice although post DCA PTCA could be used to achieve this if necessary.

The operators were able to apply the 'optimal' DCA strategy, producing a higher lesion (99% vs 97%) and procedural success (93% vs 87%) than after PTCA alone. 79% of patients having DCA also had adjunctive PTCA, leaving a residual stenosis of 15% in comparison to 28% for those undergoing PTCA alone.

There was no increase in major complications after DCA than after PTCA which overall were 2.8% and 3.3% respectively.. Death 0% vs 0.42%; emergency CABG 1.0% vs 2.0% and Q-wave MI 2.0% vs 1.2% occurred with similar frequency although CPK-MB > 3 times normal was more common with DCA (16.0% vs 6.0%; $P < 0.001$). Large non-Q-wave MI (CKMB > 8 times normal) occurred in 6.0% and 2.0% ($P = 0.002$) respectively. The use of emergency bail-out devices was significantly less common (5.0% vs 12.0%) after DCA.

The 6-month angiographic restenosis rates were 31.4% (DCA) and 39.8% (PTCA) ($P = 0.016$), respectively, representing a 20% reduction in restenosis for patients treated with DCA.

At 12 months, the cumulative mortality was 0.6% (DCA) and 1.6% (PTCA) ($P = 0.14$). Moreover there was no association between mortality and post procedural elevation of CK MB. Target vessel revascularization rates were similar (17.1% vs 19.7%).

ABACAS (Adjunctive Balloon Angioplasty following Coronary Atherectomy Study)[94,95]

This study was designed to compare the results of IVUS-guided optimal DCA alone vs IVUS-guided DCA followed by adjunctive PTCA. The study enrolled 214 patients in 12 centres in Japan. Despite aggressive atherectomy (residual stenosis 11–15%), complications were uncommon: death (0%), CABG (0%), Q-wave MI (0.9%) and non-Q-wave MI (1.8%).

The overall restenosis rate at 6 months was 21% (19.6% DCA alone vs 23.6% DCA + PTCA). The target lesion revascularization (TLR) was 17% (15.2% vs 20.6%). This is the lowest restenosis rate for any DCA study and among the lowest for any study comparing restenosis rates for any interventional device.

DCA, excimer laser and Rotablator atherectomy

High speed rotational atherectomy and excimer laser coronary atherectomy can be followed by adjunctive DCA in the treatment of calcific disease in large coronary arteries.[96–98] This combined synergistic technique overcomes

the limitations of each individual procedure and of simple adjunctive PTCA (Figure 9.11). Such procedures require careful planning. Intracoronary ultrasound is effective in assessing vessel morphology and the presence of calcification[99–101] and is helpful in deciding whether a lesion is suitable for DCA alone or whether a combined approach is required.

DCA and coronary artery stenting

Debulking coronary artery plaque burden in a lesion aids more complete and concentric stent deployment and this can be demonstrated by IVUS. Stenting after DCA leads to further increase in lumen diameter, less recoil and a reduction in residual stenosis (Figure 9.12).[102,103] Preliminary data suggests that restenosis occurs in <10% of such cases and is probably less common than after stenting alone.[104,105]

The START trial in Japan[106] was a prospective randomized trial comparing angiographic outcome and chronic vessel response assessed by serial IVUS between primary stenting ($n = 62$) and optimal DCA guided by IVUS ($n = 60$). At 6 months follow-up, aggressive DCA was associated with a larger lumen diameter and less restenosis than stenting (8.5% vs 23.0%; $P = 0.03$). At one year, the restenosis rates were 15.8% and 32.8% respectively, and target-vessel failure was lower in the DCA group (18.3% vs 33.9%).

The SOLD pilot study[107] is a prospective study examining whether DCA prior to stenting increases lumen gain and reduces restenosis. Of the first 90 lesions in 71 patients, clinical success was high (96.0%). Complications were infrequent (CABG, MI and death occurred in one; MI in one; non-Q-wave MI in eight (11.3%)). At 6 months, angiographic restenosis occurred in 11% lesions. TLR was needed in 7% of lesions. The authors further demonstrated that the lowest loss index was found in patients with low residual percent plaque area (<0.6). The basis for this finding might be that

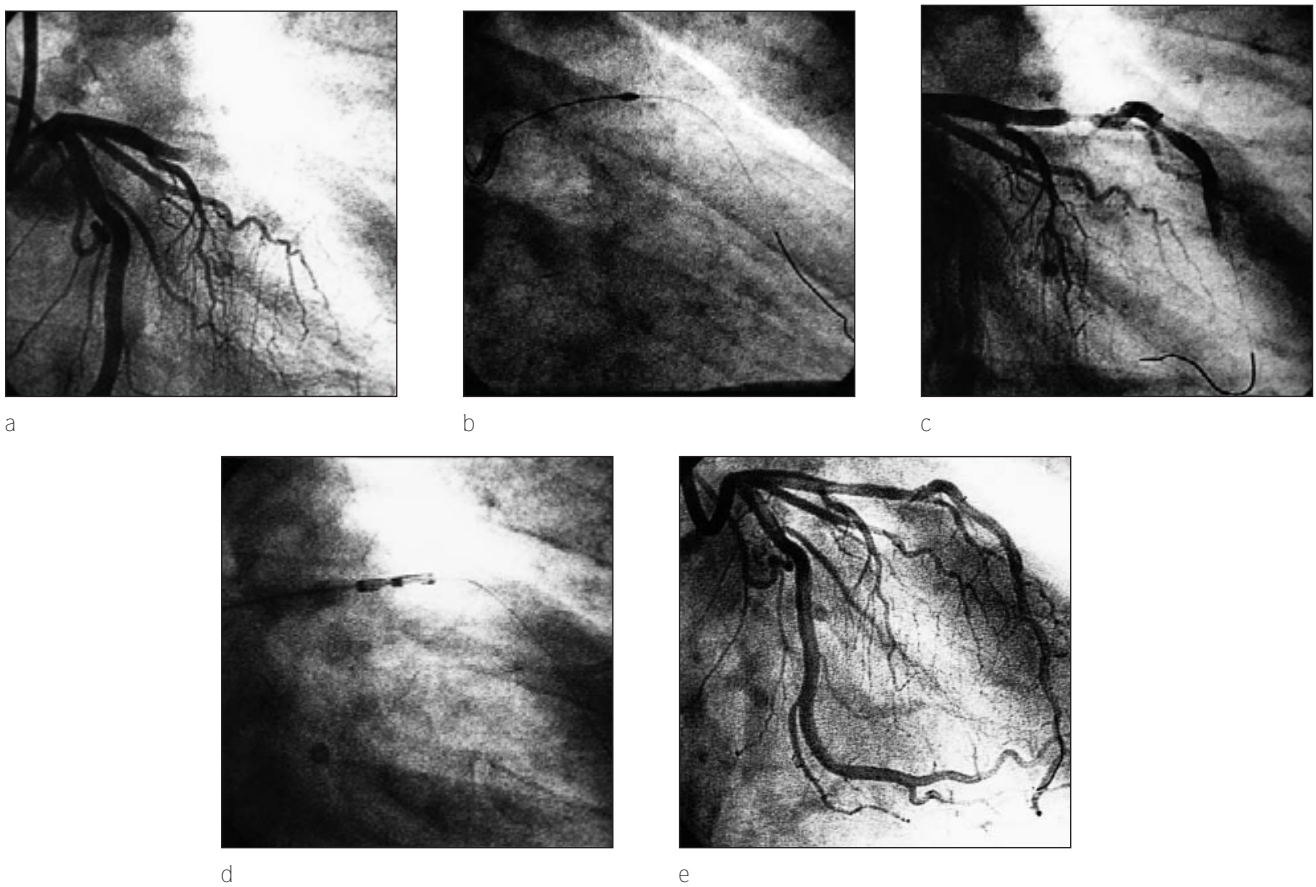


Figure 9.11
Combined DCA and Rotablator atherectomy. (a) Occlusion of proximal left anterior descending (LAD) coronary artery. (b) Rotational atherectomy to reopen LAD. (c) Residual stenosis in proximal LAD. (d) DCA using a 7F SCA device. (e) Final result after removal of 12 specimens.

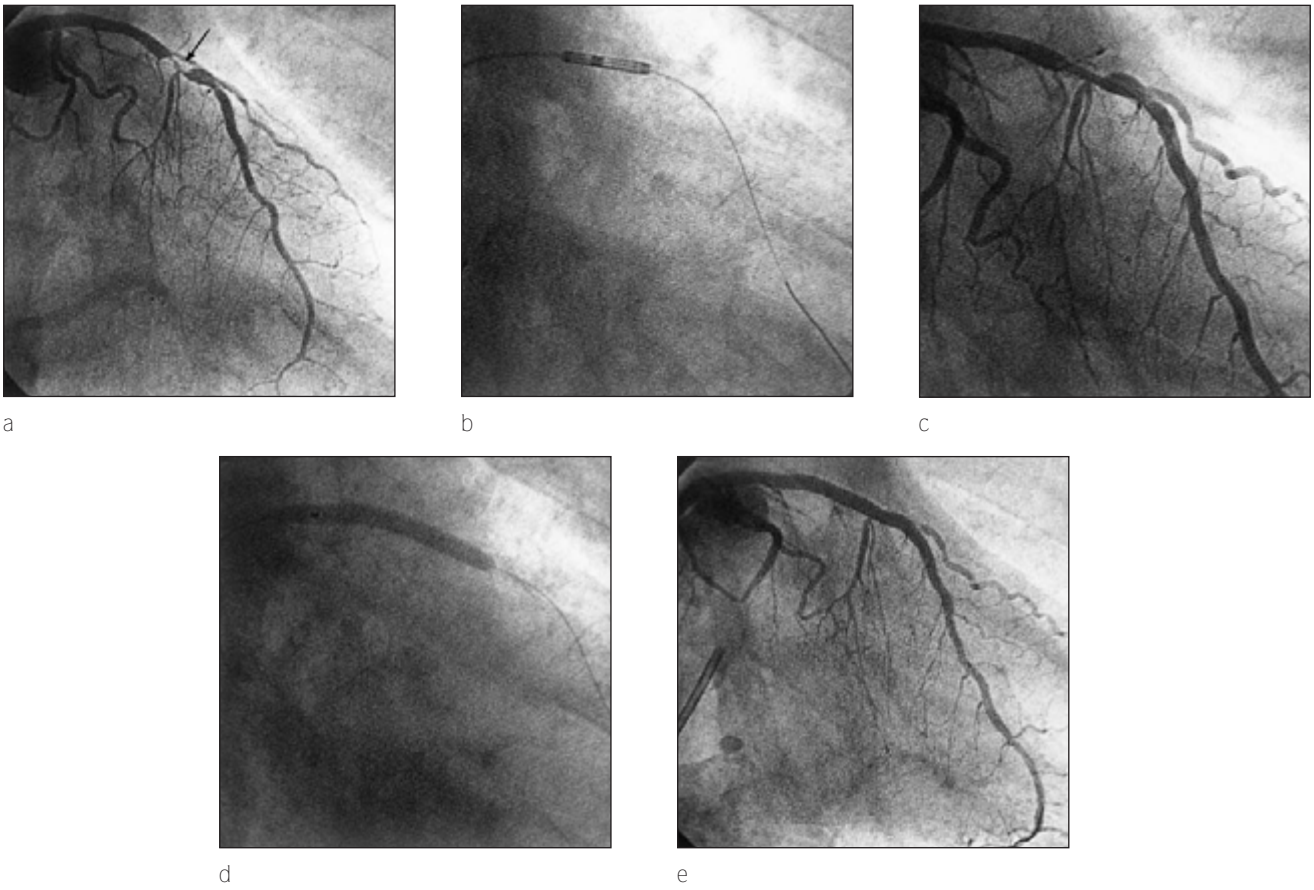


Figure 9.12
Combined DCA and stenting (atherostenting). (a) Severe stenosis in the proximal LAD. (b) 7F SCA device making cut across lesion. (c) Residual lesion after removing 8 specimens. (d) Deployment of a 3.0 mm 25 mm long Multilink® stent. (e) Final result.

less vessel wall stretch and injury occurs if the coronary artery is prepared for stenting by plaque excision. Because intimal hyperplasia is directly related to the degree of vessel wall injury, a lower loss index and greater long-term patency might be expected.

The AMIGO trial will compare the long-term angiographic restenosis rates in 750 patients randomized to undergo Multilink stent implantation either with or without prior adjunctive DCA. The DESIRE study in Japan is also comparing restenosis rates in patients undergoing DCA prior to stenting compared to those undergoing stenting alone.

Complications of DCA and their management

Although DCA is safe and effective in selected cases, as with PTCA complications can occur.[74,108] They are generally more common in the RCA than in the LAD or SVGs. The data below were obtained in the pre stent era.

Death

Major complications resulting in death are infrequent, with most series showing <1%.

Emergency CABG surgery

Emergency CABG surgery may be required—the majority for acute or threatened occlusion and a small number for perforation. Most of these complications can now be treated by stent implantation. In the pre-stent DVI Registry, obstructive complications at the lesion site accounted for 57% of

cases referred for CABG, perforation (9%), guiding catheter injury (13%), device-related complications (8%) and PTCA-related complications (11%).

Acute coronary occlusion

In the DVI Registry, acute occlusion was observed in 4.2% (out-of-lab 0.9%) ie 75% occurring in the catheter lab. PTCA or intracoronary stent implantation can be used to treat acute occlusion after DCA but a proportion (1.5%) will need CABG. The causes of acute occlusion are summarized in Table 9.7 and differ according to the site of occlusion.

Myocardial infarction

Acute coronary occlusion often gives rise to myocardial infarction (MI) unless it is rectified promptly. Q-wave MI occurs infrequently (0.3–2.5%) in experienced centres. However, CKMB elevation has been observed in 10% of patients undergoing DCA without any other evidence of significant myocardial ischaemia and late mortality at 3 years has been found to be worryingly increased in patients who experienced significant enzyme rises. Distal embolization of debris without angiographic evidence, prolonged ischaemia during the procedure due to device placement or small branch occlusions have been offered as possible explanations. Non-Q-wave MI occurred in 3.4% of patients in the DVI Registry.

Table 9.7 Causes of acute coronary artery occlusion after DCA.

Occlusion proximal to lesion
Guide-catheter-induced dissection (RCA>LCA)
Aggressive device manipulation (existing mild disease)
Occlusion at lesion
Failure to cross
Salvage PTCA for failure to cross—dissection
Device-induced dissection
Thrombus
Inadequate tissue removal
Occlusion distal to lesion
Nosecone trauma—dissection, thrombus
Nosecone trauma—spasm

Coronary perforation, pseudoaneurysm and ectasia

These consequences of deep arterial resection are uncommon.[109–114] Perforation occurs infrequently (0.5–1.3%). The causes are listed in Table 9.8. Although a small localized perforation can be sealed off by prolonged inflations with a perfusion balloon or by 'covered-stent' implantation and reversal of heparin, persisting significant perforations require emergency CABG without hesitation. Pseudoaneurysm formation occurs in 0.5% of cases and coronary ectasia in 13%.

Distal embolus

This complication is unusual for native coronary arteries (<1%), but may occur in 8% of SVGs when slow flow or angiographic cutoff may be evident.[115] Most emboli occur in diffusely diseased, old vein grafts.[74] The treatment includes PTCA of vessel cutoff together with intracoronary nitrates/calcium channel blocker to increase flow and reduce spasm.

Side branch occlusion

This can occur in up to 4% of cases due to a 'snow plough' effect.[9,76,116] Side branches proximal or distal to the lesion have a low risk of occlusion (1.5%).[117,118] The incidence is higher for those branches exiting the diseased segment (36%) and especially those with significant ostial stenoses (45%).[116] If the branch is of moderate size, it may be pre dilated before DCA is performed in the main artery. Occluded side branches can usually be reopened by PTCA.

Table 9.8 Causes of coronary artery perforation after DCA.

Case selection
Severe angulation
Extensive or spiral dissection
Small vessel (<2.0 mm)
Procedure
Oversized device
Too high balloon inflation pressure
Incorrect device positioning
Incorrect window orientation (very eccentric lesion)
Cutting on spasm

Arrhythmias and hypotension

In the DVI Registry,[119] ventricular tachycardia or fibrillation complicated 0.5–1.7% of cases and hypotension occurred in 1.8%. Both complications should be treated aggressively to avoid a fall in coronary blood flow and treatment-site thrombosis.

Femoral artery complications

Because large arterial sheaths are often used, groin complications requiring blood transfusion (2.6%) or surgical repair (3.7%) may be higher than after PTCA.[76,120]

Haematoma or bleeding may occur in 1.6% of cases.[121] Patients with hypertension, obesity or agitation have a higher incidence of haematoma because of inadequate initial haemostasis.

Pseudoaneurysms of the femoral artery and arteriovenous fistulae occasionally result and may require surgical repair.[121] Complications can be minimized by careful and prolonged haemostasis after sheath removal when the ACT is normal.

Retroperitoneal haematoma is unusual (0.3%),[121] should be treated conservatively (bed rest, intravenous fluids and blood transfusion) and anticoagulation reversed.

Femoral artery thrombosis and femoral neuropathy are rare and should be treated surgically and conservatively, respectively.[121]

Device-specific complications

These are rare but may include guidewire fracture and entrapment, entrapment of the AtheroCath® within the coronary artery and even fracture of the drive cable.[122]

Contrast volume overload

Because of the large size of the guiding catheter employed during DCA, it is important (especially in complex cases such as multivessel DCA or bifurcation DCA) to avoid excessive contrast loading.

Late outcome and restenosis after DCA

Restenosis remains a significant late complication.

Although data from Sequoia suggest that 74% of patients were asymptomatic or clinically improved at 6 months, 32% subsequently required treatment by CABG (14%), PTCA (4%) or repeat DCA (13%).[36] Angiographic evidence of restenosis was observed in 42%, usually occurs within 3 months and in >90% of cases it occurs within 8 months. Few events relate to the DCA site after the first year of follow-up. The restenosis rate in native coronary arteries was 31% for primary lesions and 28% and 49% respectively for lesions treated with one or two previous PTCAs. The restenosis rates for SVGs were 53% for primary lesions and 58% and 82%, respectively, for lesions treated with one or two previous PTCAs.[123]

Risk factors for increased restenosis included SVG lesions, lesion length (>10 mm), use of smaller device (6F), smaller vessel (<3 mm), non-calcified lesions, small MLD post-DCA, unstable angina, hypercholesterolaemia, hypertension, male gender, previous restenoses and short time interval after previous PTCA.[124]

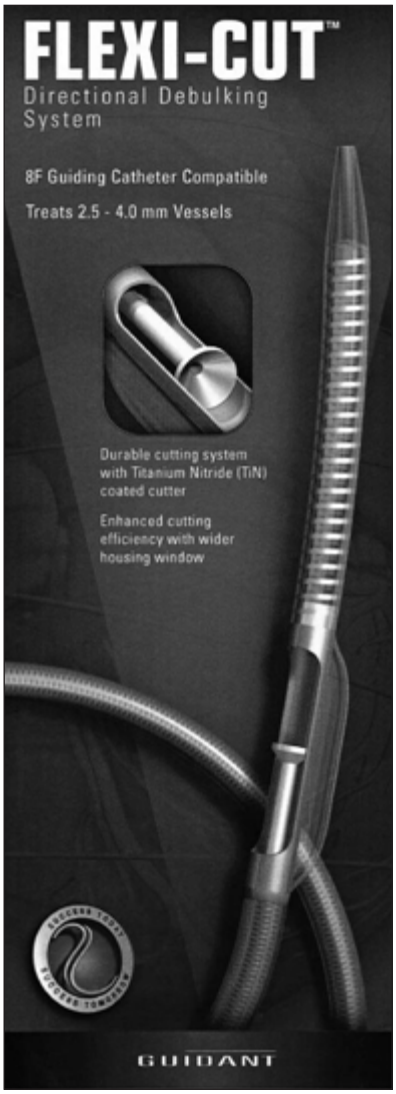
In the Netherlands, one group prospectively followed up 150 DCA procedures performed for stable and unstable angina.[125] One and two year survival rates were 100% and 97% and 98% and 96%, respectively. Event-free survival at one and two years was significantly lower in the unstable angina group (57% and 54%) than in the stable group (78% and 69%). Restenosis rates were 39% and 32% in the respective groups.

IVUS-guided, aggressive debulking by DCA to produce an optimal acute result is likely to result in low restenosis rates, but whether adjunctive stenting will reduce this further remains to be seen (see above).

DCA for restenosis after PTCA or previous DCA has a high success rate but a higher restenosis rate than de novo lesions. In addition, DCA can be used for restenosis after other interventional procedures such as coronary stenting and can provide insight and understanding of the ongoing pathobiology.[126]

Recent technical developments

Recently, Guidant™ have introduced FLEXI-CUT™, a low-profile (0.076" maximum diameter of housing and shaft), more flexible atherectomy device suitable for use in 2.5 mm–4.0 mm vessels (Fig. 9.13a). The 134 cm catheter is compatible with a 8F guiding catheter and the custom-moulded PEBAX® baloon has a flat-bottom design to enhance stability of the housing within the vessel. The housing length is 17% less than the GTO® device and the shaft diameter has been reduced by 11% (Fig. 9.13b). The nosecone has a lower profile and a cylindrical shape and a 'dam' design at the top prevents material being extruded out of the nosecone's distal end (Fig. 9.13c). Its capacity is at least equal to that of a 7F GTO® device. The 9 mm long cutter window has an expanded arc of 127°—improving tissue yield per cut. The ultra-hard titanium nitride-coated cutter (see Fig. 9.13a) makes cutting plaque easier and more efficient and is held in place by a bushing/cutter stem design.



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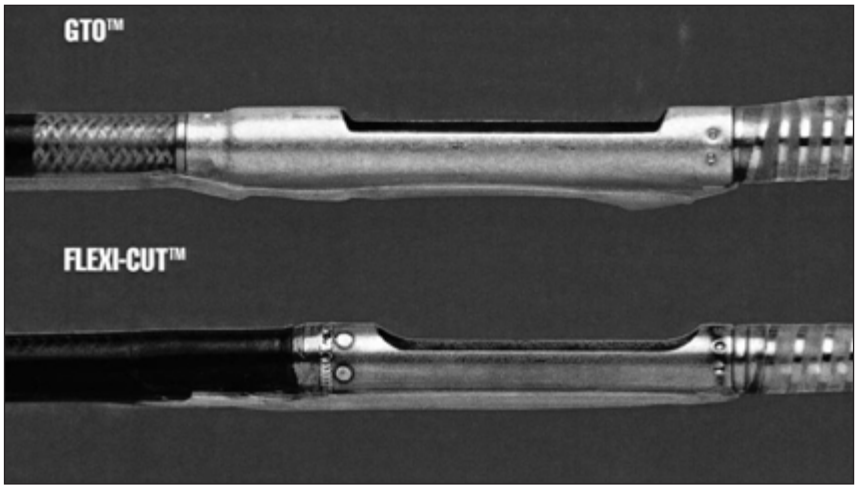

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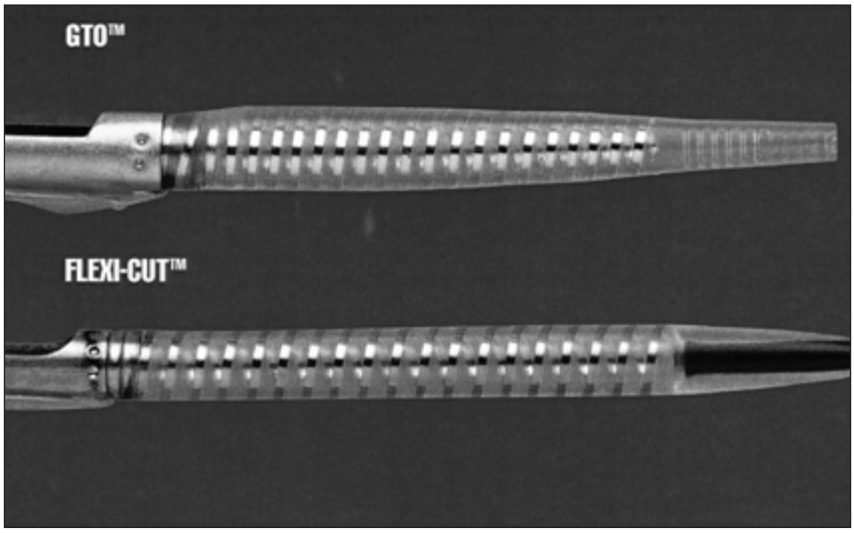

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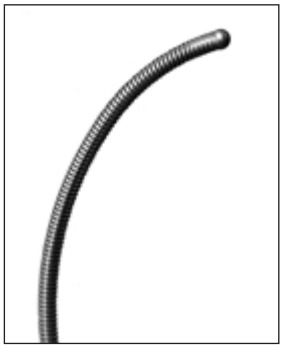

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Figure 9.13
(a) FLEXI-CUT™ is the newer, low-profile, more flexible atherectomy device from Guidant™, compatible with an 8F guiding catheter. (b) The housing length is 17% less than the GTO® device and the custom-moulded PEBAX® balloon has a flat-bottom design. (c) The nosecone has a lower profile and a cylindrical shape. (d) The new 0.014" Hi-Torque EXTRA S'PORT™ guidewire has a supportive PTFE-coated distal core and a MICROGLIDE® coating for reduced friction and smooth tracking. (e) The 8F Viking XT™ guiding catheter has an internal diameter of 0.087", provides exceptional support, flexibility and torque and is available in a range of shapes including the JC.

A new 0.014" guidewire, Hi-Torque EXTRA S'PORT™ has a supportive PTFE-coated distal core for smooth device delivery, a MICROGLIDE® coating for reduced friction and smooth tracking (Fig. 9.13d). It provides excellent support and steerability. The 8F Viking XT™ guiding catheter has an internal diameter of 0.087" and provides exceptional support, flexibility and torque (Fig. 9.13e).

Summary

Directional coronary atherectomy can be used in 10–15% of current interventional cases, providing excellent acute results with a low complication rate especially for morphologically complex lesions which are unfavourable for PTCA. Case selection and careful technique have the major influence on the results achieved. Low restenosis rates are somewhat dependent on achieving a large post-DCA minimal luminal diameter (MLD) and removal of a significant tissue mass. This can probably only be achieved in large (>3 mm) vessels. Post-DCA PTCA should be used to help achieve the largest MLD safely and the least residual stenosis. Combination of DCA with other techniques such as Rotablator atherectomy and excimer laser atherectomy for calcific and bulky disease and as a preliminary debulking procedure prior to intracoronary stenting may improve overall early and late results.

Its use is limited by the rigid housing of the device. Currently only proximal or mid lesions in large (>2.5 mm), non-tortuous, non-calcified vessels are approachable. Intracoronary ultrasound studies suggest that substantial plaque burden remains even after much tissue removal and a good angiographic result. The low profile, more flexible FLEXICUT™ atherectomy device may make cutting plaque easier and more efficient although a combined IVUS/AtheroCath® might help in the removal of optimal amounts of plaque safely by improving the catheter's ability to direct the cuts more appropriately.

A major bonus of DCA is retrieval of tissue and this has already allowed study of the pathological process of atherosclerosis, unstable angina and restenosis by light and electron microscopy, cell culture experiments, cellular and molecular biology. In particular, the study of smooth muscle cell proliferation and their migratory and secretory activity has helped in the understanding of the response to arterial wall injury and the potential for locally applied agents and gene therapy to limit the phenomenon of fibrointimal hyperplasia.

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10

Rotational coronary atherectomy

Peter J Casterella and Paul S Teirstein

Introduction

Rotational coronary atherectomy was developed by Auth in the early 1980s as an alternative to percutaneous transluminal coronary angioplasty (PTCA).[1] The Rotablator™ device was approved for the treatment of obstructive coronary artery disease in Europe and the United States in the early 1990s. The mechanism of the Rotablator is uniquely different from other percutaneous revascularization devices. The device uses sized burrs coated with 10 μm diamond chips. The burr rotates at high speed over a guidewire and abrades atherosclerotic plaque into micro-particles that are delivered to the distal coronary circulation. The abrasive surface of the burr allows selective cutting of hard, calcified plaque, while the softer, elastic components of the normal vessel wall are deflected away from the burr, preventing damage. Early clinical trials with the Rotablator showed that it was a safe and effective treatment modality with particular efficacy in the treatment of calcified lesions.[2,3]

Advancements in rotational atherectomy (RA) over the past 5 years include refinement of equipment, changes in technique, and developments in adjunctive pharmacology. Continuing experience with rotational atherectomy has defined ideal lesion subsets for treatment and synergy between the Rotablator and other devices. This chapter will focus on the major developments and changes in rotational atherectomy since the last publication of this text.

Device description

The Rotablator device is an elliptically shaped burr, coated on the leading half with diamond microchips (Fig. 10.1). The burr is welded to a helical flexible drive shaft housed in a 4 French teflon sheath which is connected to a compressed-air-powered turbine. Air pressures of 4–5 atmospheres rotate the burr at speeds of up to 200 000 revolutions per minute (rpm) when activated by a foot pedal. Rotation speeds are recorded with a fiberoptic light probe and are digitally displayed on the device console (Fig. 10.2). Rotation speed is controlled by manual adjustment of a control knob located on the console. The proximal end of the Rotablator catheter is attached to a housing unit. The housing unit has connections to the air turbine, device console, and an infusion line for the teflon sheath. The housing unit also contains a central lumen for the guidewire, a control knob for advancement and retraction of the burr, and a brake to prevent spinning of the guidewire during burr activation. The original Rotablator unit consisted of a burr, drive shaft, and housing unit for each available burr size. Recently, the Rota-

Figure 10.1
Close-up view of the Rotablator burr. The elliptically shaped burr is impregnated on the leading half with 10 μm diamond chips to create an abrasive surface. The burr is welded to a helical drive shaft, which is encased in a 4 Fr teflon sheath. The burr rotates co-axially over a 0.009-inch stainless steel guidewire.

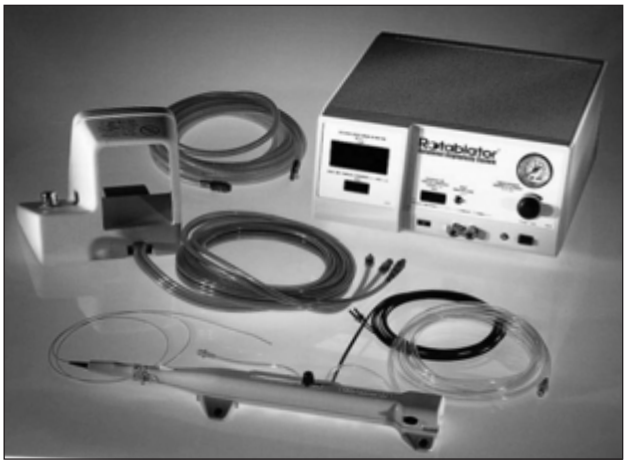

Figure 10.2
The Rotablator system is shown here with the foot pedal used to activate the burr, and connecting tubes for the compressed air system, foot pedal, and housing unit. The control knob on the housing unit is used to advance and retract the burr. A control knob on the device console is used to adjust the rotational speed, and burr revolutions per minute (rpm) are displayed digitally on the console.

Link system (Fig. 10.3) was developed as a means of reducing the cost of performing procedures in which multiple burrs are used. The proximal end of the Rota-Link housing unit connects to the distal end of the Rotablator catheter. Thus, while multiple burrs may be used during an atherectomy procedure, a single housing unit is used with a resultant decrease in equipment costs. Additionally, procedure time is reduced with the Rota-Link system because the connections between the housing unit, console, infusion line, and the air turbine do not have to be repeated with each burr used. Rotablator burrs are available in sizes ranging from 1.25 mm to 2.5 mm.

Rotablator guidewires are steerable, 325 cm long, uncoated, stainless steel wires. At the time of release of the Rotablator device, guidewires were available in two varieties, a stiffer tip (type A) and floppier tip (type C). Several recent developments in Rotablator wire technology have expanded the choice of wires available to operators (Fig. 10.4). The type C wire has been modified significantly to create the RotaWire extra support wire. The tip diameter has been reduced from 0.017 to 0.014 inches, and the radio-opaque tip length has been reduced from 40 mm to 28 mm. The transition zone of the wire increases from a diameter of 0.005 inches at the weld point to 0.009 inches, over a 50 mm segment. The extra support wire provides support in steering the burr into lesions and has a tendency to straighten vessels. The straightening tendency can be used to create 'favourable' guidewire bias during rotablation. However, the extra support wire may create excessive and 'unfavourable' guidewire bias in tortuous vessels. The

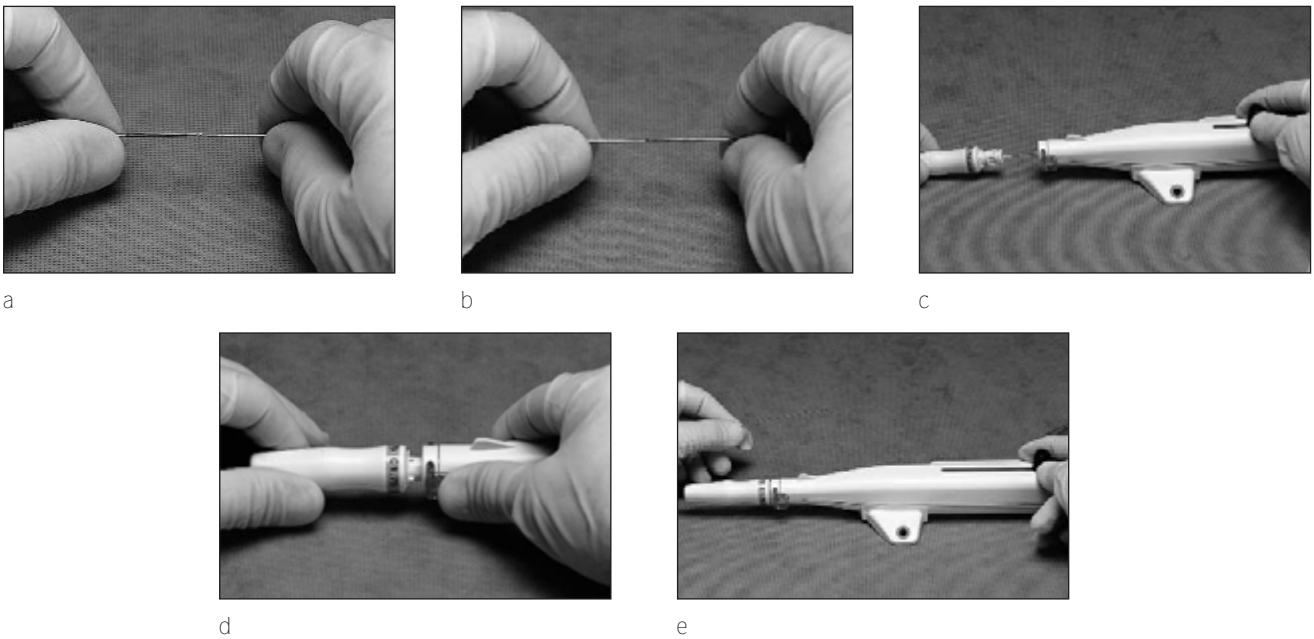

Figure 10.3
The Rota-Link system, shown here, allows multiple burr sizes to be used with a single housing unit and connections to the device console. (a) Close-up view of the connections for the Rota-Link system. On the left is the catheter link, on the right is the housing unit link. (b) Close-up view showing the Rota-Link system with the two links connected. (c) After connecting the links, the control knob on the housing unit is retracted to allow connection of the catheter to the housing unit. (d) Close-up view of the Rota-Link catheter being connected to the housing unit. (e) The Rota-Link system is shown here, fully connected and ready to use.

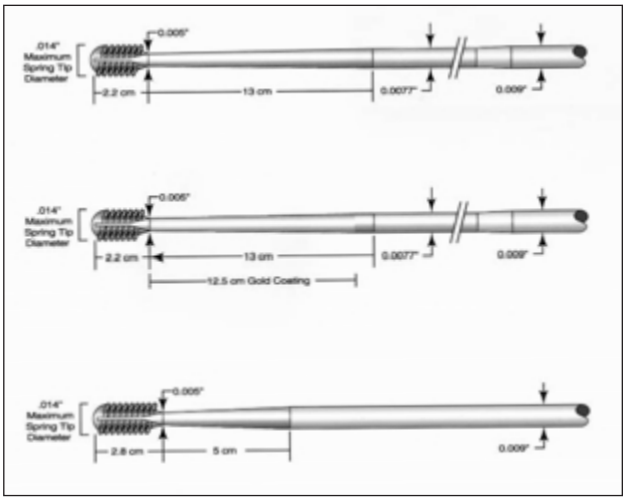

Figure 10.4
The varieties of Rotablator guidewires available to operators are shown here. Top: Rotawire floppy wire, middle: Rotawire floppy gold wire, and bottom: Rotawire extra support wire.

recently developed RotaWire floppy wires are available in two varieties: the regular floppy wire, and a gold-coated wire. The floppy wires have a shorter length tip of 22 mm compared to the 28 mm tip of the extra support wire. The transition zone is longer, spanning 130 mm, and increasing from 0.005 inches at the weld point to 0.0077 inches at the end of the transition segment. The transition zone of the gold wire is coated with gold to provide radio-opacity and facilitate identification of guidewire bias. The floppy wires have greater flexibility and a lower tendency to straighten vessels, making them ideal for use in tortuous vessels.

Rotational atherectomy procedure

Guide catheter selection

Guide catheters ranging from 6 to 9 French are currently used to perform RA, representing a significant change since the previous publication of this text when a minimum guide size of 8 French was required (Table 10.1). The development of larger lumen guide catheters in 6 and 7 French sizes obviates the need for a large guide catheter size in the majority of patients. Most operators prefer the use of side-hole catheters when the guide size is ≥ 8 French. Excellent guide support is not mandatory when performing rotational atherectomy; however, it is important to choose a guide catheter that directs the burr in a co-axial manner relative to the lesion to maximize the cutting effect of the burr, and to minimize the risk of dissection or vessel perforation.

Table 10.1 Guiding catheter selection for rotational atherectomy.

Burr size (mm)	*Burr diameter (inches)*	*Minimum guide size (French)*
1.25	0.049	6
1.50	0.059	6
1.75	0.069	7
2.00	0.079	7[a]
2.15	0.085	8
2.25	0.089	8[b]
2.50	0.098	9

[a] Internal diameter must be at least 0.081 inch.
[b] Internal diameter must be at least 0.091 inch.

Guidewire passage

The 'bare-wire' technique remains the preferred technique for guidewire passage during RA. The recent advancements in Rotablator wire technology have facilitated wire passage such that many lesions can be crossed primarily with a Rotablator guidewire. However, in special circumstances, such as complex, tortuous lesions, or total occlusions, the recommended technique is to cross the lesion with a flexible exchange length wire, and use an exchange catheter or low-profile balloon catheter to exchange for a Rotablator wire.

Burr selection

The most common practice of RA at present is the 'stepped burr' approach. With this technique, the maximum burr size is 70–80% of the reference vessel diameter. The procedure is initiated with a smaller burr size, with sequential increments in burr size until the maximum burr size is reached. Using this strategy, two or three burrs will be used in most cases. In cases involving long lesions or diameter stenosis >90%, starting with smaller burr sizes (1.25–1.50 mm) has been advocated to reduce the incidence of complications.

Burr activation

Once the lesion has been crossed with the guidewire, the Rotablator catheter is back-loaded onto the wire, the wire clip is attached, and a test rotation is performed prior to passing the burr into the guide catheter. Depression of the foot pedal activates the turbine, causing rotation of the burr, and the speed of rotation is adjusted using a knob on the console. The current recommended rotation speed for testing the burr is 160 000

rpm, representing a significant decrease from the previously recommended speed of 180 000–200 000 rpm. After confirming optimal rotation speed outside the body, the burr is advanced through the guide catheter and positioned just proximal to the target lesion. Substantial back-tension on the guidewire may be required during burr advancement because there can be significant resistance to burr advancement through the bends in the guide catheter or the target vessel. The resistance to burr advancement can create significant stored tension between the guide catheter, guidewire, and burr and can lead to the development of guidewire bias. Excessive guidewire bias causes malalignment of the burr relative to the lesion, and increases the risk of dissection or vessel perforation during burr passage. Excessive tension between the guide catheter, burr and wire can cause the burr to leap forward when activated, increasing the potential for dissection, perforation or other complications. Manoeuvers that assist in relieving wire bias and tension within the Rotablator system include: re-alignment of the guide catheter and burr, gentle retraction of the distal tip of the guidewire, insuring that the burr is free and mobile within the vessel and positioned proximal to the lesion, gentle adjustment of the burr advancement knob on the housing unit, and 'milking' the proximal shaft of the Rotablator catheter between the thumb and forefinger to relieve built-up tension in the system. It is vitally important that the operator confirm optimal positioning of the burr relative to the lesion prior to activating the burr. Careful attention to detail in positioning the burr is essential to prevent complications.

Once appropriate burr position is confirmed, the burr is activated by depressing the foot pedal. The burr is advanced slowly using the control knob on the housing unit. At present, the recommended burring speed is 160 000–170 000 rpm for up to 30 seconds per run. Avoidance of burr decelerations of >5000 rpm is of paramount importance in the prevention of complications. An audible decrement in burr speed typically denotes an excessive degree of deceleration. One of the great challenges facing the operator performing RA is the conflicting goals of avoidance of rapid burr advancement, and avoidance of long (>30 s) burr runs. In the case of long lesions, it may be preferable to approach the lesion in segments with multiple short burr passes, rather than attempting to treat the entire lesion with one pass of the burr. When resistance to burr advancement is encountered, a technique of slow advancement and retraction ('pecking') or gentle, steady pressure is recommended. It is important not to use excessive force or rapid movements of the burr, especially when resistance is encountered, as such manoeuvers can result in dissection, vessel perforation, distal embolization, vessel spasm, or no-reflow phenomenon. After an initial slow passage of the burr is accomplished, if there is no resistance to burr advancement, more rapid back-and-forth passes of the burr may be performed to 'polish' the treatment area. The spinning burr should then be retracted to a position proximal to the treatment site prior to release of the foot pedal and deactivation of the burr. In general, it is undesirable to deactivate the burr distal to, or within the treatment site in the vessel. To remove the burr and exchange for the next larger size, the 'dynaglide' switch on the foot pedal is activated, reducing the rpm to 75 000. Low-speed rotation of the burr during removal reduces resistance and tension, and decreases the likelihood of inadvertent loss of guidewire access. Subsequent atherectomy is performed with increasing burr sizes until the target burr size is reached. Further atherectomy passes should be aborted if significant complications occur, such as sustained chest pain, dissection, no-reflow, or abrupt vessel closure.

Advancements in procedural technique

In recent years, several modifications in technique have been developed to improve outcome and reduce the incidence of complications with rotational atherectomy. Early experience identified vessel spasm and the no-reflow phenomenon as significant complications limiting the efficacy of RA in treating coronary artery disease. The most significant modifications in technique include a reduction in burring speeds to 160 000–170 000 rpm, a reduction in burring times (15–30 seconds/run) and avoidance of decelerations of >5000 rpm. It has been theorized that the higher burring speeds (180 000–200 000 rpm) used in the early experience with the Rotablator cause excessive heat generation, platelet activation, and micro-cavitation, leading to impaired distal coronary perfusion. Stertzer et al reported a significant decrease in the incidence of spasm and no-reflow with the adoption of slower burring speeds and shorter burr runs.[4] The recent introduction of a new lubricant for the Rotablator system is the latest technical advancement in rotational atherectomy. 'Rotaglide' lubricant is an emulsion of olive oil, glycerin, egg yolk phospholipids, sodium deoxycholate, L-histidine, disodium EDTA, sodium hydroxide and water in a 20 ml vial. One vial is added to each litre bag of flush used during a procedure. The lubricant is designed to reduce friction between the burr and the guidewire to facilitate burr advancement through catheters and vessels. It is theorized that reducing friction will result in less heat generation during the procedure and will reduce the force required to advance the burr through lesions in coronary arteries.

Rotational atherectomy strategies

The two major strategies currently employed with RA are lesion modification and optimal debulking. Lesion modification is the most common application of RA and involves limited atherectomy with one or two burrs to change lesion morphology and characteristics such that other devices

(primarily PTCA and stents) can be optimally applied. Recent statistics indicate that 75–80% of percutaneous coronary interventions (PCI) involve coronary stent placement. If coronary stent placement is planned, RA can be an effective adjunctive therapy to debulk calcified or fibrotic lesions to allow optimal stent expansion. The optimal burr-to-artery ratio in such cases is 0.6–0.7.

Optimal debulking involves maximal safe debulking of the lesion usually followed by adjunctive PTCA, or rarely as stand-alone therapy. The derived burr-to-artery ratio for the optimal debulking strategy is 0.75–0.85. Optimal debulking is sometimes not possible due to the inability to deliver large burrs to the lesion because of proximal vessel tortuosity, or clinical or procedural factors (poor LV function, or ischaemia) that preclude the use of larger burrs. There has been significant debate regarding the optimal approach to adjunctive PTCA after rotational atherectomy. Some have advocated low-pressure inflations (1–2 atm) with a slightly oversized balloon (balloon–artery ratio 1.1), while others support the use of a balloon–artery ratio of 1.0 and typical inflation pressures (6–12 atm) to achieve an optimal angiographic result. This controversy in technique was addressed in the STRATAS trial, investigating the optimal debulking plus low pressure PTCA technique vs optimal debulking plus standard PTCA technique.[5] No significant difference in outcomes was seen between the two strategies. To some degree, the debate over optimal adjunctive PTCA with rotational atherectomy has become a moot issue with the growing popularity of Rota-stenting.

Adjunctive therapies

Advancements in adjunctive therapies are an area of significant recent progress in rotational atherectomy. Early trials with the Rotablator reported a low incidence of no reflow (1.2%) and vessel spasm (1.6%).[2] However, initial clinical experience with the Rotablator demonstrated that the incidence of vessel spasm and slow flow, or the no-reflow phenomenon, appeared to be greater than that observed with PTCA and other PCI devices.[6] In addition to technique modifications, changes in adjunctive therapy have assisted in reducing the incidence of impaired distal coronary perfusion during rotational atherectomy.

Vasodilators

Liberal use of coronary vasodilators improves coronary flow and reduces the incidence of vasospasm and no reflow. Intracoronary nitroglycerin (100–300 μg), verapamil (100–300 μg), diltiazem (100–300 μg), and adenosine (18–30 μg) are used prophylactically or therapeutically to improve coronary perfusion during RA. In cases of severe spasm or no reflow, selective administration of these agents by an infusion catheter may be more effective in improving distal blood flow. An additional benefit of selective administration is the ability to give larger doses of vasoactive agents without compromising systemic blood pressure and haemodynamics. In one study, the prophylactic use of intracoronary adenosine prior to RA of complex lesions was associated with a significant reduction in the incidence of no-reflow.[7] Another significant change in technique is the addition of vasodilators and anticoagulants to the flush system that is attached to the sheath of the Rotablator system. The current additives to the flush system include verapamil 10 μg/ml, nitroglycerin 4 μg/ml, and heparin 3 U/ml. A small clinical study evaluating this drug cocktail in the Rotablator flush system showed good procedural success rates with low complication rates.[8] Recently, a number of operators have advocated the intracoronary injection of nitroprusside (50–100 μg) to treat vasospasm or no reflow. No formal evaluation of this intervention is available at present. A note of caution is warranted; in our experience significant hypotension can occur with the use of intracoronary nitroprusside. If one chooses to use nitroprusside, small escalating doses starting at 50 μg with concurrent fluid boluses are advised.

Glycoprotein IIb/IIIa inhibitors

Recently, it has been recognized that platelets may contribute to the development of impaired coronary perfusion during RA. Sharma et al reported that rest angina on presentation was associated with a significantly higher incidence of slow flow during RA.[9] Reisman demonstrated increased platelet aggregability in an in vitro rotational atherectomy model.[10] Williams et al, using an in-vitro model, reported that activation of platelets during rotational atherectomy is dependent upon burring speed and can be inhibited by abciximab.[11] Finally, Koch et al evaluated 75 patients undergoing rotational atherectomy with or without abciximab.[12] All patients underwent Tc-99m Sestamibi scintigraphy before, during, and after treatment. The patients treated with abciximab had a significantly lower incidence of transient hypoperfusion during RA, resulting in a significantly lower incidence of peri-procedural myocardial infarction. Given the encouraging results of early evaluations of GP IIb/IIIa inhibitors with rotational atherectomy, and the consistently positive results with GP IIb/IIIa inhibitors in multiple PCI trials, many operators use a GP IIb/IIIa inhibitor in the great majority of rotational atherectomy cases.

Temporary pacing

Transient bradycardia and high-grade AV block are seen in a substantial number of patients undergoing rotational atherectomy, particularly if a dominant right or circumflex coronary

artery is treated. In such cases, prophylactic pacemaker placement is warranted. Another scenario where pacing should be considered is the treatment of proximal LAD lesions, particularly in patients with a history of conduction system disease (fascicular blocks, or left bundle branch block). Recently, several operators have advocated the use of temporary infusions of aminophylline as an alternative to temporary pacing. If bradycardia develops during RA, bolus doses of atropine (0.6–1.0 mg) and aminophylline infusions may function as temporizing measures while a temporary pacemaker is being placed.

Intra-aortic balloon counterpulsation

The use of intra-aortic balloon pump (IABP) counterpulsation is very beneficial in high-risk patients undergoing rotational atherectomy. Risk factors for complications during RA include advanced age, multivessel disease, and reduced left ventricular systolic function. Performance of RA in these patients is associated with a greater incidence of hypotension, impaired coronary perfusion, arrhythmias, and myocardial ischaemia and/or infarction. The use of prophylactic IABP in such high-risk patients has been associated with improved outcomes.[13]

Post-procedure management

Post-procedure management after rotational atherectomy is similar to the approach used after all PCI. Temporary pacemakers can usually be removed at the conclusion of the procedure unless the patient demonstrates persistent bradycardia or heart block. Arterial sheaths can be removed using vascular closure devices or manual compression; the latter approach should be guided by measuring activated clotting times (ACT). Recent studies have demonstrated no significant benefit to continuation of IV heparin therapy after successful PCI procedures, and an increased incidence of bleeding complications in the patients treated with heparin after the procedure.[14] Thus, the current standard of practice is to stop heparin at the completion of the procedure. Investigators have reported an association between impaired coronary perfusion during RA and preprocedural treatment with beta blockers.[9] Thus beta blockers should be withheld or tapered if possible before RA, and should not be re-instituted for 24 hours after the procedure. At the operator's discretion, topical or IV nitrates or calcium channel antagonists may be used after the procedure to promote coronary vasodilation. These agents may be particularly useful in managing patients who demonstrate spasm, or impaired coronary perfusion during rotational atherectomy. All patients should receive indefinite aspirin therapy after RA, and all patients receiving stents should be treated with a thienopyridine (ticlopidine or clopidogrel) for a minimum of 2 weeks after the procedure.

Results

Early registry trials (Table 10.2)

Two multicentre registry trials, one in the US and one in Europe, evaluated success and complication rates during the early experience with the Rotablator.[2,3] In these trials, success rates of 86–95% were reported, and the incidence of major complications was 3–4%. The incidence of angiographic restenosis, using the binary definition of >50% diameter stenosis at follow-up, was 38% in both trials.

Comparative trials of Rotablator versus other devices

Three major randomized trials (DART, ERBAC, and SPORT) have been completed comparing RA to other PCI techniques. The Dilatation vs Ablation Revascularization Trial (DART, Table 10.3) randomized 442 patients with target vessel diameters <3 mm and significant lesions to optimal debulking with RA vs PTCA.[15] Procedural success rates were high (99% RA, 100% PTCA) and not significantly different between the two techniques. Major complication rates were low in both groups (1.3% RA, 0% PTCA) and not significantly different. The incidence of slow flow was higher in the RA group, while major dissection and bail-out stenting was higher in the PTCA group.

Table 10.2 Results of the US and European multicentre rotational atherectomy registries.

Trial	*No of patients*	*No of procedures*	*Success (%)*	*Major complications (%)*	*Death (%)*	*Q-wave MI (%)*	*CABG (%)*	*Non-Q-wave MI (%)*	*Abrupt closure (%)*	*Restenosis (%)*
US	709	743	95	3.0	0.8	0.9	1.7	5.2	3.1	38
European	129	129	86	3.9	0.0	2.3	1.6	5.4	7.8	38

Table 10.3 Results of the DART trial.

Variable	*PTCA*	*Rotational atherectomy*	*P value*
No of patients	220	222	NS
Males (%)	70	61	<0.04
Post-MI angina (%)	29	18	0.02
Mild calcification (%)	79	83	NS
B2+C lesions (%)	79	56	NS
Reference vessel diameter (mm)	2.43 ± 0.39	2.45 ± 0.4	NS
Residual diameter stenosis (%)	31 ± 12	30 ± 11	NS
Procedural success (%)	100	99	NS
Major complications(%)	0	1.3	NS
CK-MB 1–3 x Normal (%)	6	11	<0.07
CK-MB 3–8 x Normal (%)	4	2	NS
CK>8 x NI (%)	1	3	NS
Slow flow (%)	0.5	8	<0.01
Perforation (%)	0.45	1.8	NS
Restenosis rate (%)	48	52	NS

NS: not significant

There was a trend towards a greater incidence of low-level CK-MB elevations (1–3 × normal) in the RA group (11%) vs the PTCA group (6%), $P < 0.07$. There was no significant difference in the incidence of angiographic restenosis between the two groups at 6-month follow-up (52% RA, 48% PTCA).

The Excimer Laser, Rotational Atherectomy and Balloon Angioplasty Comparison (ERBAC, Table 10.4) trial was a single-centre, randomized comparison of the three treatment modalities in 685 patients with CAD and type B or C de novo coronary lesions.[16] The procedural success rate was the highest with RA (89%) vs excimer laser coronary angioplasty (ELCA) (77%) or conventional PTCA (80%), $P = 0.0019$. Major complication rates ranged from 3.1 to 4.3% and were not significantly different between the three groups. Restenosis rates were high in all three groups, ranging from 47% with PTCA, to 57% for RA, and 59% for ELCA. Interestingly, the target lesion revascularization (TLR) rate was significantly greater for RA (42%) and ELCA (46%) vs PTCA (32%), $P = 0.013$.

The SPORT (Stent Implantation Post Rotational Atherectomy Trial) evaluated RA plus stenting vs PTCA plus stenting in 725 patients with moderately long calcified

Table 10.4 Results of the ERBAC trial.

Variable	*PTCA (n = 222)*	*ELCA (n = 232)*	*RA (n = 231)*	*P value*
Age (years)	62.5 ± 9.5	61.7 ± 8.8	61.6 ± 10	NS
Males (%)	81	78	80	NS
Unstable angina (%)	12	16	18	NS
Stable angina (%)	72	67	65	NS
Reference vessel diameter (mm)	2.93 ± 0.62	2.96 ± 0.56	2.93 ± 0.57	NS
Diameter stenosis (%)	75 ± 11	75 ± 11	76 ± 12	NS
Post procedure residual diameter stenosis (%)	35 ± 16	33 ± 15	33 ± 15	NS
Procedural success (%)	80	77	89	0.0019
Major events (%)	3.1	4.3	3.2	NS
Restenosis (%)	47	59	57	NS
6-month TLR (%)	32	46	42	0.013

PTCA = Percutaneous Transluminal Coronary Angioplasty
ELCA = Excimer Laser Coronary Angioplasty
RA = Rotational Atherectomy
TLR=Target Lesion Revascularization

lesions.[17] Angiographic success rates were 100% in both groups with 18 (5%) of the PTCA + stent patients crossing over to the RA + stent arm. There was no significant difference in major adverse cardiac events (MACE) during hospitalization, or 6-month target vessel revascularization (TVR) rates (15% PTCA + stent vs 18% RA + stent). Thus, the SPORT trial showed that RA + stent is feasible, but not superior to PTCA + stent in the treatment of calcified lesions.

Clinical applications of rotational atherectomy

During the development and early application of RA, it was theorized that its unique mechanism of action would result in higher success rates, lower complication rates, and lower restenosis rates compared to PTCA. Results from subsequent clinical trials have shown that lower complication rates and restenosis rates have not been demonstrated with the Rotablator compared to other devices. However, procedural success rates with rotational atherectomy *are* superior to PTCA in subsets of patients in whom PTCA yields suboptimal results. Accordingly, the Rotablator has evolved to become a 'niche' device that is useful in lesion subsets that are not optimally treated with PTCA. Additionally, the Rotablator functions synergistically with other devices because of its ability to modify lesions, permitting the effective use of other devices. Perhaps the best example of device synergy with the Rotablator is the combination of RA and stenting in the treatment of calcified lesions (Rotastent).

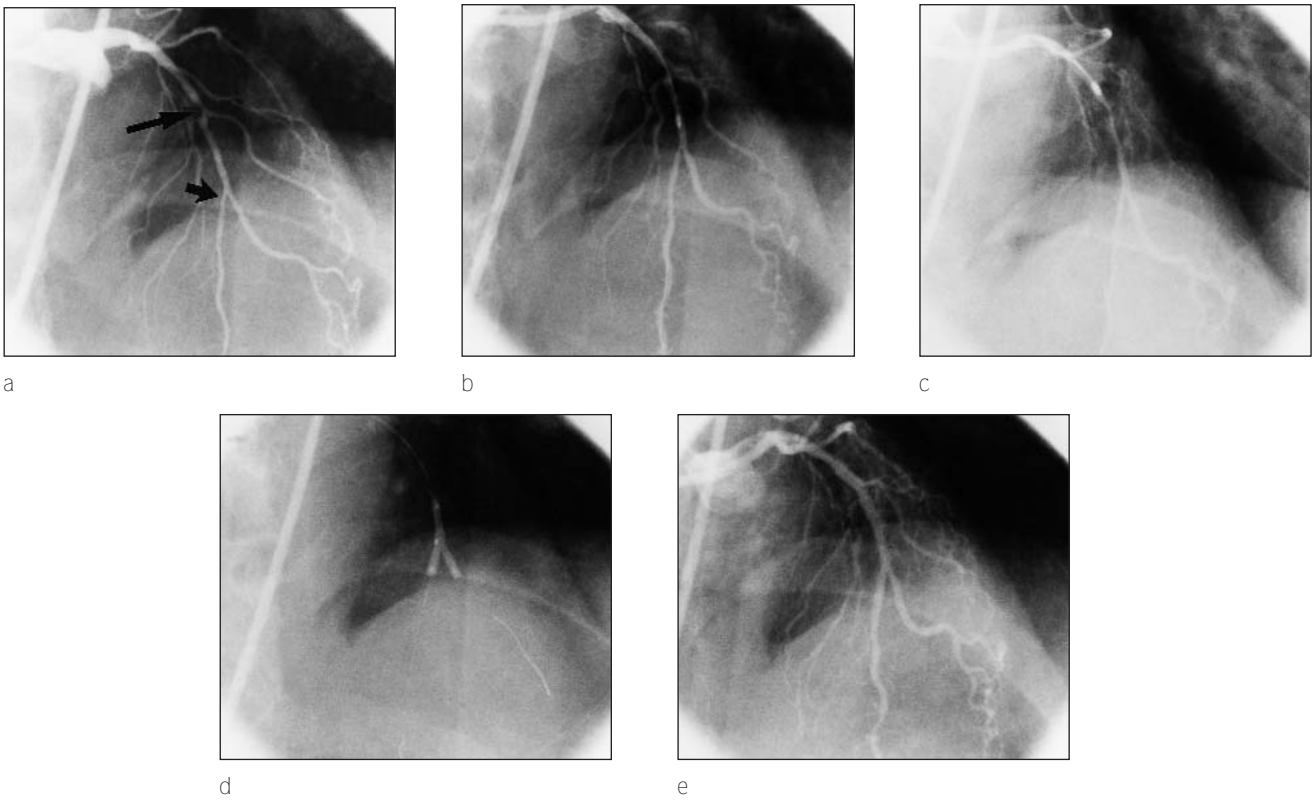

Figure 10.5
(a) AP cranial view of the left coronary artery. A calcified 75% stenosis is present at the bifurcation of the distal LAD with the third diagonal branch (short arrow). A calcified 80% stenosis is also present at the bifurcation of the mid-LAD with the second diagonal branch (long arrow). Both lesions had been treated by PTCA with sub-optimal results 5 weeks prior to this angiogram. The patient presented with recurrent angina and an abnormal exercise stress test. (b) A 1.5 mm burr has been used to treat the more proximal lesion, and is shown here entering the more distal lesion. Note that the extra support wire has created 'favourable' wire bias, directing the burr preferentially towards the lesion in the LAD. (c) A 2.0 mm burr is shown entering the more proximal lesion in the LAD. Optimal positioning of the burr prior to activation is demonstrated here. (d) A 'kissing' balloon inflation is demonstrated here. A 2.5 mm stent was placed in the LAD, across the origin of the diagonal branch, resulting in 'pinching' of the diagonal branch. The simultaneous dilatation of both branches allows recovery of the side branch, while preserving the angiographic result in the stented portion of the main vessel. (e) AP cranial view of the LAD showing the final result after RA and stenting of both lesions. There is no significant residual stenosis at either treatment site. The large third diagonal branch is also widely patent with normal flow.

Calcified lesions (Fig. 10.5)

Target lesion calcification is the most frequent indication for RA in current interventional cardiology practice. Several studies have demonstrated that the presence of target lesion calcium is a significant predictor of decreased procedural success rates and increased complication rates with conventional PTCA.[18–21] Hard, calcified lesions are often eccentric and resistant to balloon expansion. The higher pressures required to 'crack' such lesions can lead to extensive vessel dissection, and possibly abrupt vessel closure. The differential cutting mechanism of the Rotablator makes it ideal for the treatment of hard and calcified lesions. A review of calcified vs non-calcified lesions from the US Rotablator multicentre registry showed no significant difference in procedural success (94% vs 95%), or major complications (4% vs 3%).[22] Interestingly, target lesion calcification co-existed with other factors that have been associated with decreased procedural outcomes with conventional PTCA, such as angulation, eccentricity, and lesion length. Despite the preponderance of factors predisposing to a less favourable outcome, RA for these complex lesions was associated with high success and low complication rates.

Non-dilatable lesions (Fig. 10.6)

Inability to cross a lesion with a balloon catheter, or inability to fully dilate a lesion, are causes for PTCA failure that can be effectively treated with RA. Several authors have reported successful RA results after failed PTCA.[23–25] The operator should confirm absence of dissection prior to performing RA after failed PTCA.

Total occlusions (Fig. 10.7)

Total occlusion lesions are a significant challenge for the interventional cardiologist. The greatest limitation to treating total occlusions is crossing the lesion with a guidewire, and insuring that the wire remains in the true lumen of the vessel. In some cases, wire access is achieved, but balloon catheters will not cross or dilate the lesion. In such cases, the Rotablator is ideally suited to treat a total occlusion. It is often necessary to cross the lesion first with a hydrophilic guidewire, and then use a small balloon or exchange catheter to exchange for a

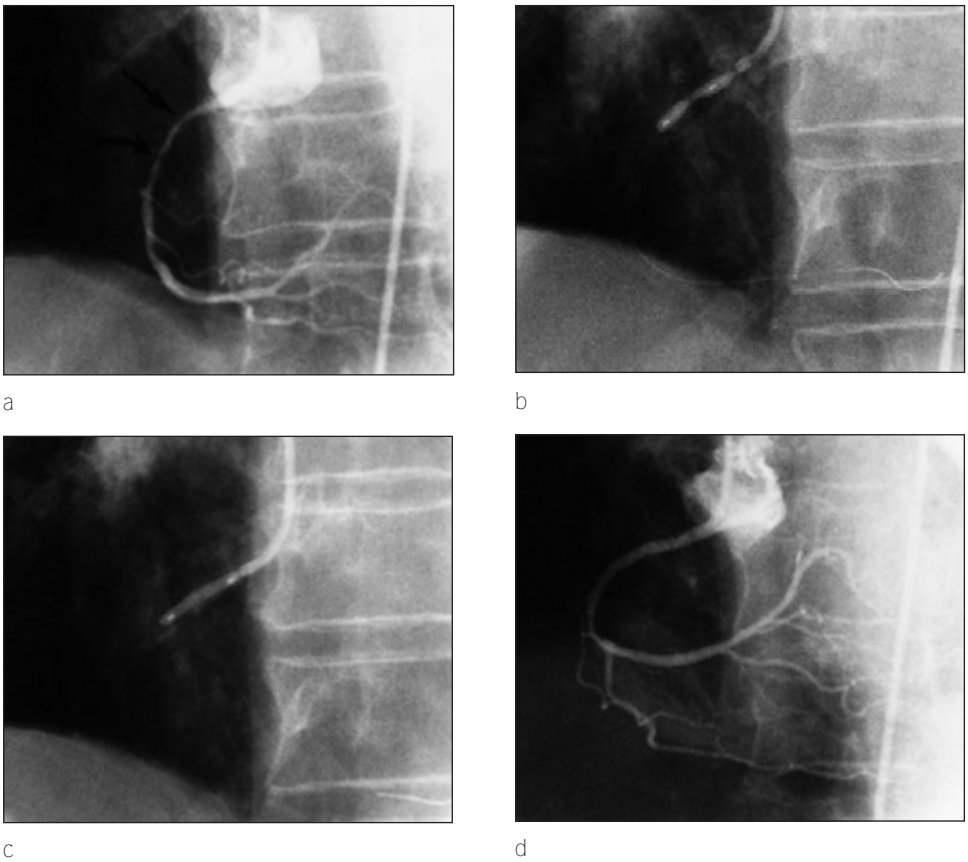

Figure 10.6
(a) LAO view of the RCA of a patient with a recent inferior myocardial infarction treated with thrombolysis. Moderate calcification is noted, with two high-grade proximal lesions (straight and curved arrows). (b) The more proximal of the two lesions could not be fully dilated with a 2.75 mm non-compliant balloon inflated to 16 atmospheres of pressure. (c) Following rotational atherectomy, the same balloon is now fully expanded at 10 atmospheres of pressure. (d) Final LAO view after coronary stent placement shows an excellent angiographic result with no residual stenosis.

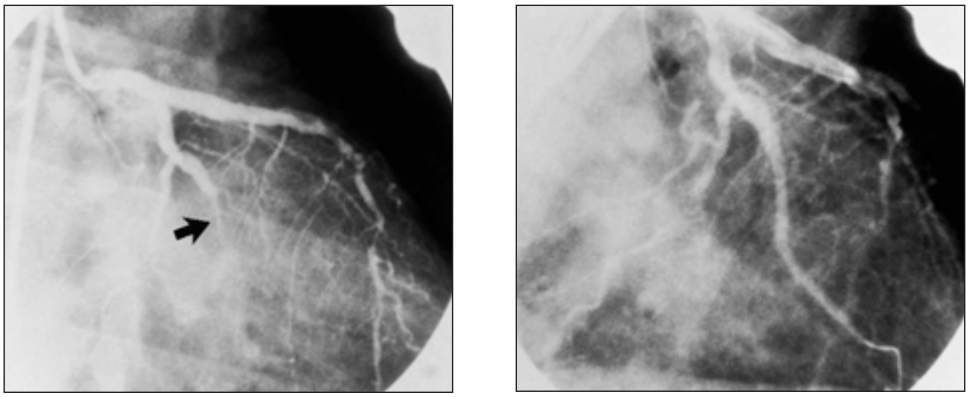

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Figure 10.7
(a) RAO view of the left coronary artery shows a total occlusion of the left circumflex coronary artery (arrow). (b) Final RAO view after rotational atherectomy and adjunctive PTCA.

Rotablator guidewire. Consideration should be given to contrast injection through the distal port of the balloon or exchange catheter to document that the distal guidewire position is in the vessel lumen. Levin et al reported success in a small series of patients with total occlusions treated with RA.[26] Based upon the results of the SICCO trial,[27] which showed lower restenosis rates in total occlusion lesions after stent placement, it would be advisable to combine RA with stent placement when treating total occlusions.

Ostial lesions (Fig. 10.8)

Aorta-ostial and branch vessel ostial lesions are frequently calcified and/or fibrotic and are thus suboptimally treated with conventional PTCA. RA is ideal to debulk ostial lesions, but can be a technically challenging procedure. Co-axial alignment of the guide catheter to the vessel is essential to optimally align the burr with the ostium of the vessel to avoid preferential ablation, and potential complications. Because aorta-ostial vessel segments are typically large in diameter, the ideal use of RA is to accomplish lesion modification, followed by adjunctive PTCA and stenting. Several studies have demonstrated that RA with adjunctive PTCA or stenting is safe and effective in the treatment of aorta-ostial lesions.[28–31]

Bifurcation lesions (Fig. 10.5)

Bifurcation disease is currently one of the greatest challenges for interventional cardiologists. Treatment of bifurcation lesions with conventional PTCA is frequently associated with plaque shifting and potential closure of the parent or branch vessel. Dauermann et al reported higher success rates and lower late target vessel revascularization in the treatment of bifurcation lesions using atherectomy (RA or directional atherectomy) compared to conventional PTCA.[32] Several considerations are important in the approach to bifurcation lesions using the Rotablator. Guidewire access in both branches during RA is not possible. Compromise of the unprotected branch is more likely to occur due to vasospasm than plaque shifting. The preferred technique of RA in bifurcation lesions is to treat the largest branch first, followed by the smaller branch second. In the case of equal calibre branches, the vessel with the highest degree of difficulty of wire placement, or greatest angulation, is treated first, followed by the second branch.

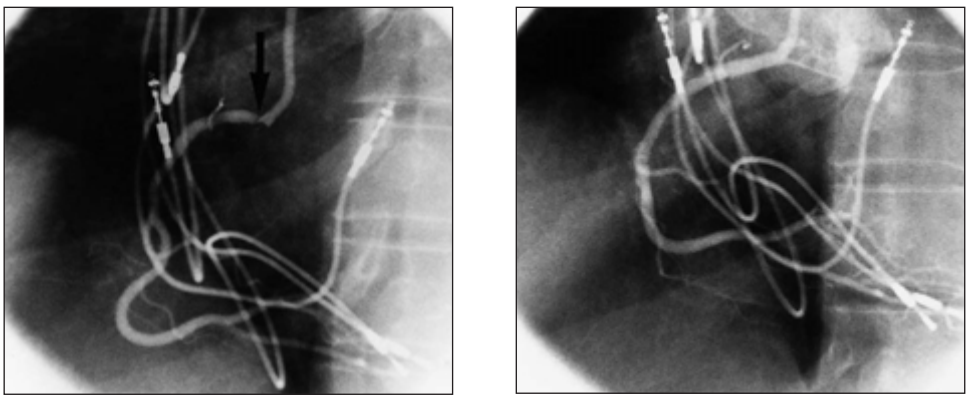

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Figure 10.8
(a) LAO view of the right coronary artery shows a high-grade focal ostial stenosis of 90% (arrow). (b) Final LAO view after rotational atherectomy and coronary stent placement shows an excellent angiographic result with no residual stenosis.

Table 10.5 ARTIST Trial results.

Variable	*PTCA (n = 146)*	*RA (n = 152)*	*P value*
Age (years)	60 ± 10	62 ± 11	NS
Male (%)	82	79	NS
Reference vessel diameter (mm)	2.65 ± 0.40	2.63 ± 0.45	NS
Preprocedure diameter stenosis (%)	80.5 ±11.9	80.2 ± 11.4	NS
Postprocedure residual stenosis (%)	29 ± 10	29 ± 12	NS
Procedural success (%)	88	89	NS
Spasm (%)	0	7.9	0.0004
Slow flow (%)	0	5.3	0.007
6-Month event-free survival	91.1	79.6	0.005
Restenosis (%)	51.2	64.8	0.04
Target vessel revascularization (%)	36.2	47.8	0.06

NS: not significant
RA = Rotational atherectomy

In-stent restenosis

Rotational atherectomy has been advocated to treat in-stent restenosis (ISR), particularly diffuse cases where the entire stent demonstrates aggressive neo-intimal tissue proliferation. It has been theorized that debulking of such diffuse lesions might result in a lower subsequent restenosis incidence. Several small non-randomized trials showed promising results with RA for in-stent restenosis.[33–38] However, the recently completed Angioplasty vs Rotablation for the Treatment of Diffuse In-Stent Restenosis (ARTIST)[39] trial found no benefit with RA vs PTCA in the treatment of ISR (Table 10.5). In this trial, 298 patients with ISR were randomized to treatment with RA or PTCA. Procedural success rates were similar between the two groups, although procedural complications including spasm, slow flow, and arrhythmia were more frequent with RA vs PTCA. At 6-month follow-up, the angiographic restenosis rate (>50% diameter stenosis) was significantly higher with RA (65%) than with PTCA (51%), $P = 0.04$. Importantly, event-free survival from death, MI, or TLR was significantly higher in the PTCA group (91%) compared to the RA group (80%), $P = 0.005$.

Rotational atherectomy may have a role as an adjunct to intracoronary radiation therapy in the treatment of ISR. Recent studies have shown that late stent thrombosis rates are significantly higher when new stents are placed during intracoronary radiation therapy procedures.[40] In the treatment of ISR, RA may work synergistically with radiation by optimizing angiographic results and reducing the need for repeat stenting (Fig. 10.9).

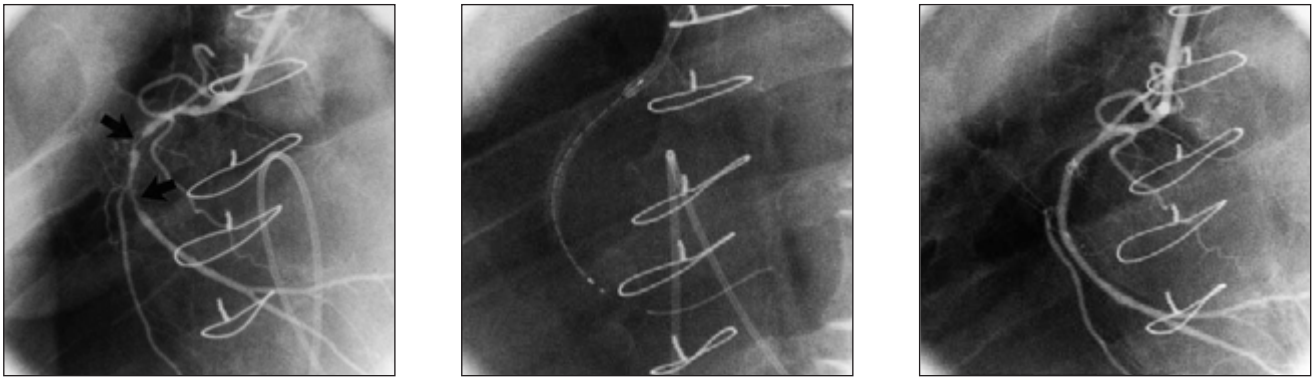

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Figure 10.9
(a) LAO view of the right coronary artery (RCA) shows diffuse in-stent restenosis in the mid-portion of the vessel (arrows). (b) Iridium^{192} sources in place after rotational atherectomy and PTCA. (c) Final LAO view after RA, PTCA and radiation.

Complications of rotational atherectomy

The potential complications associated with RA are similar to those seen with all PCI devices. However, because the Rotablator ablates plaque material, and delivers micro-particulate debris to the distal coronary bed, the possibility of impaired coronary perfusion during RA is greater than with other PCI devices. Major complications that may be associated with RA include death, need for emergent coronary artery bypass graft (CABG) surgery, or myocardial infarction. The incidence of major complications in studies evaluating RA has ranged from 3 to 6%.[2,3,41]

Vasospasm

The reported incidence of vasospasm during RA varies widely from as low as 1.6% in the multicenter registry[2] to >20% in other series.[42] The wide variation in incidence is likely attributable to differing definitions of spasm, and differences in the patient populations studied. More recently, the New Approaches to Coronary Intervention (NACI) registry reported procedural success and complication rates of 525 patients undergoing treatment of 670 lesions with RA. In this series, the incidence of transient vasospasm was 5%.[40] Vasospasm usually responds promptly to intracoronary boluses of 100–300 μg of nitroglycerin or verapamil. Subselective coronary injection of these agents using an infusion catheter may be useful in cases of refractory spasm. Additionally, low-pressure balloon inflations at the site of persistent narrowing may assist in relieving vasospasm.

Impaired coronary perfusion

Impaired coronary perfusion is also known as 'no-reflow' or 'slow-flow' (depending on severity) and has been observed with all PCI devices. It is characterized by a reduction in coronary blood flow in the absence of angiographically evident dissection, vessel spasm, thrombus formation, or distal embolization. The aetiology of this phenomenon is unclear, but may involve microvascular spasm, microscopic embolization, procedurally-induced endothelial dysfunction, micro-cavitation, or platelet activation.

Early reports suggested a low incidence of no-reflow with RA (1.2%);[2] however, more recent studies have demonstrated a 6–9% incidence of impaired coronary perfusion during RA.[6] The clinical sequelae of no-reflow can be severe in refractory cases and include ischaemia and infarction, hypotension, cardiogenic shock, arrhythmias, and death. The treatment of choice for no-reflow is intracoronary injection of a calcium channel blocker using an end-hole infusion catheter. Direct delivery of the drug to the target vessel is important to avoid loss of the agent from side-hole guide catheters, and to avoid systemic circulation of vasoactive agents in patients with tenuous haemodynamics. Other agents that may be useful in treating no-reflow include nitroglycerin (100–300 μg), adenosine (18–30 μg), and nitroprusside (50–100 μg). Glycoprotein IIb/IIIa receptor antagonists have been advocated anecdotally to treat no-reflow. However, one must be mindful that patients with complications may require emergency CABG surgery, and the bleeding risks should be weighed against the potential benefits. Mechanical adjuncts are often useful in treating cases of severe or sustained no-reflow. An intra-aortic balloon pump (IABP) counterpulsation device provides haemodynamic support for the patient and augments coronary perfusion, which may assist in reversing no-reflow. Temporary pacemaker placement may be required for patients who develop significant bradycardia or heart block as a consequence of no-reflow. It has been theorized that several of the technique modifications and adjunctive pharmacological therapies outlined in this chapter may assist in preventing no-reflow. The results of ongoing clinical trials with the Rotablator will determine whether these advances in technique and adjunctive therapy result in a decreased incidence of impaired coronary perfusion.

Myocardial ischaemia and non-Q-wave myocardial infarction

Development of myocardial ischaemia is a significant concern during RA because the abrading mechanism of the burr results in delivery of atherosclerotic debris to the distal circulation. Additional concerns specific to rotational ablation and development of ischaemia include activation of platelets and micro-cavitation during activation of the burr. Patients may develop significant symptoms of ischaemia during RA, and these symptoms may persist after completion of burr runs, and in the face of normal angiographic coronary perfusion. Williams et al performed an echocardiographic analysis of patients undergoing RA and compared them to patients undergoing conventional PTCA.[43] The mean ischaemic times related to device use were similar in the two groups, 10.3 minutes for RA vs 9.6 minutes for PTCA. However, the RA group showed a significantly higher incidence of prolonged wall motion abnormalities compared to the PTCA group. The mean time to recovery of baseline wall motion was 153 minutes for the RA group, compared to 2.6 minutes for the PTCA group, $P = 0.0001$. If a patient develops prolonged chest pain or signs of ischaemia during RA, further ablation runs should not be attempted.

The definition of non-Q-wave MI after coronary interventions varies widely and has changed in recent years. It has recently

been recognized that elevations of CK-MB as low as 1–3 times normal identify a subgroup of patients with a significantly higher long term morbidity and mortality after PCI procedures. It has been theorized that periprocedural CK-MB elevations may be related to platelet activation during PCI procedures. In several recent trials, glycoprotein IIb/IIIa antagonists have shown a benefit in reducing the incidence of CK-MB elevations after PCI procedures. A recent study of 1675 patients published by Kini et al evaluated the incidence of CK-MB elevations after PCI with various devices.[44] The incidence of any CK-MB elevation was 18.7% for the total group, and 19.5% for non-balloon devices vs 11.5% for PTCA, $p<0.01$. The observed incidence of CK-MB elevation was 11.5% for PTCA, 16% for RA, 21% for stent, 21% for RA-stent, 23% for DCA ± stent, and 22.5% for TEC ± stent. To fully assess the incidence of non-Q-wave MI after RA, a randomized comparison of RA with and without GP IIb/IIIa inhibition would be very useful.

Perforation

Coronary perforation is perhaps the most dreaded and life-threatening complication of all percutaneous coronary interventions. Fortunately, the incidence of perforation during RA is low, 0.7–1.8% in various series.[2,6,15,45] Perforation is more common in the right coronary artery and left circumflex coronary artery than the left anterior descending or left main coronary artery, presumably because of angulation of the right and circumflex vessels. Cohen et al have identified lesion eccentricity, vessel tortuosity, and lesion length >10 mm as predictors of a greater risk of perforation.[45] Extreme caution is advised in attempting to perform RA on highly angulated lesions (≥ 45%) or in tortuous vessels. The stiffness of the Rotablator guidewires may create significant straightening of these types of vessels with resultant unfavourable wire bias, increasing the risk of intramural ablation and perforation. It is also important to recognize that increasing use of hydrophilic-coated guidewires, GP IIb/IIIa antagonists, and thienopyridines (stent patients) may result in an increased incidence of clinically important micro-perforations. Micro-perforations may not be evident during the PCI procedure, but can present clinically as unexplained and unremitting hypotension several hours after completion of the procedure.

Successful management of a perforation requires prompt recognition and immediate action. Heparin, GP IIb/IIIa antagonists and all other anti-thrombotics should be stopped immediately upon recognition of a perforation. Consideration should be given to reversing heparin effect with administration of 15–30 mg of protamine, and platelet transfusion may be required to reverse the effects of GPIIb/IIIa antagonists. Prolonged inflation (15–30 minutes) of a perfusion balloon at low pressure across the perforation may permit sealing of the hole. Alternatively implantation of a covered stent or coil placement may obviate the need to perform emergency surgery. Severe perforations with extensive contrast extravasation are often associated with cardiac tamponade requiring emergency pericardiocentesis. In this scenario, emergency surgery to oversew the perforation, and perform coronary bypass to the distal circulation, is often required. If a perforation is successfully sealed in the catheterization laboratory, patients should be monitored closely in the intensive care unit after completion of the procedure. Right heart pressures should be monitored continuously, and frequent bedside echocardiography performed to evaluate the possibility of pericardial fluid accumulation and evolving tamponade.

Predictors of complications

Predictors of complications with RA vary depending on the type of complication being analysed. However, in reviewing available data on RA, several important trends emerge.

Lesion length >10 mm has consistently been a significant predictor of several RA complications including myocardial infarction, no-reflow, dissection, and perforation.[2,9,41,42] Presence of unstable angina and preprocedure use of beta blockers have also been identified as predictors of impaired coronary perfusion during RA.[9] Interestingly, Reisman et al reported that the presence of ≥70% stenosis of the RCA in patients undergoing left coronary vessel RA was associated with a 5-fold increase in death, a 2.6-fold increase in emergency CABG, and a 1.8-fold increase in non-Q-wave MI compared to patients without significant RCA disease.[46] Left ventricular dysfunction has been identified as an independent predictor of complications with all PCI procedures. Operators contemplating performance of RA on such patients should have a low threshold for utilization of mechanical adjunctive therapies such as intra-aortic balloon pumps and temporary pacemakers.

Contraindications to rotational atherectomy

Contraindications to performance of RA include the presence of dissection, angiographically visible thrombus, or severe angulation, or tortuosity of the target lesion or vessel.

Relative contraindications to performance of RA include long lesions, particularly >20 mm, unprotected left main disease and performance of RA to the sole remaining viable circulation in a patient with severely impaired left ventricular function. In general, RA is contraindicated in de novo saphenous vein graft (SVG) lesions because of the friable nature of these lesions. However, RA has been used safely and successfully to treat fibrotic lesions at the proximal or distal anastomosis of SVGs, or to treat in-stent restenosis in SVGs.[47, 48]

Conclusion

The Rotablator has become a valuable tool in the armamentarium of devices available to interventional cardiologists. Over the past 5 years, technique modifications and advances in adjunctive therapies have permitted safe performance of RA in patients with complex, high-risk obstructive coronary lesions. The unique mechanism of action of the Rotablator makes it ideally suited to treat lesions that respond suboptimally to PTCA such as hard, calcified lesions, ostial lesions, total occlusions and bifurcation lesions. The Rotablator has demonstrated synergy with other devices, particularly intracoronary stents. In larger vessels (≥ 3.0 mm), it appears that the primary role of RA will be lesion modification followed by stent implantation. In smaller vessels, RA as stand-alone therapy, or with adjunctive low-pressure PTCA will continue to offer a viable treatment option for lesions that are not well served by PTCA alone. Accordingly, the Rotablator has found a niche in most catheterization laboratories, and is used in 5–10% of PCI cases. The unique ability of the Rotablator to treat lesions that are not effectively treated by other PCI devices makes it a valuable tool for interventional cardiologists.

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11

Excimer laser coronary angioplasty

Saibal Kar and Frank Litvack

Introduction

Although laser coronary angioplasty was initially met with enthusiasm by the interventional cardiology community,[1] this was mitigated by a variety of factors, in particular the widespread use of stents. Further concerns arising from a paucity of clinical data with respect to randomized trials and unequivocal demonstration of marginal benefit have also limited enthusiasm.

Recently, interest has increased as a consequence of improved technique, equipment, and newer indications. Current cardiovascular applications include coronary and peripheral angioplasty, pacemaker lead extraction and transmyocardial revascularization.[2] This chapter will provide a review of the scientific background, experimental data, practical procedural techniques, and clinical applications of excimer laser coronary angioplasty (ELCA) in the treatment of coronary artery disease.

Historical aspects

The first attempt at laser angioplasty in an ischemic limb was performed in 1983, using continuous wave laser angioplasty.[3] Early clinical investigation focused on the use of argon or Nd:YAG laser technology which converted laser light to thermal energy in a continuous wave form to vaporize tissue. Unfortunately this early technology, referred to as laser thermal angioplasty, was met with unsatisfactory results as a result of excessive thermal injury and vessel damage. To avoid this problem produced by continuous wave lasers, pulsed energy using an excimer laser was developed.[4] This technology, termed ELCA, produced nanosecond pulses of short wavelength ultraviolet energy, which (theoretically) could precisely ablate a localized area of an atherosclerotic plaque without significant thermal injury. After initial laboratory testing the first successful human ELCA was performed at Cedars-Sinai Medical Center in Los Angeles in the summer of 1988. Since then, ongoing research has led to an improvement in catheter design and operator technique, improving the function and safety of ELCA. Recently, a laser wire has been developed for the treatment of chronic total occlusions. This wire is available internationally for clinical use, but has not been introduced in the US.

Laser fundamentals

The word laser is an acronym for Light Amplification by Stimulated Emission of Radiation. The laser beam consists of a highly directional beam of monochromatic light that can produce intense power densities. The term excimer is an acronym for excited dimer. The excimer lasers release energy in the ultraviolet range (193 to 351 nm) in very short pulses rather than in a continuous wave form.[4,5] The precise wavelength of emission depends on the exact nature of the gas mixture from which the photons are generated. Experience in the cardiovascular field has involved the xenon chloride (XeCl) 308 nm laser, which became available in 1983 for research and was approved by the FDA for its first clinical indications in 1992. The laser beam is formed as a result of high voltage electrical discharge across a mixture of the xenon gas and a highly diluted (0.1%) hydrogen chloride solution, leading to the production of an excited state molecule of XeCl (the excited dimer), which subsequently drops to its ground state of XeCl, a weakly covalent molecule which liberates a photon with a wavelength of 308 nm.[5]

The mechanism by which the excimer laser ablates vascular tissue is always debated. In vitro studies on segments of vascular tissue exposed to air or saline have demonstrated that

excimer lasers ablate tissue with a minimal thermal effect, in comparison to continuous wave lasers.[1,5,6] In recognition of this the excimer laser was dubbed the 'cool laser'. At least part of the process results from relatively high-energy, ultraviolet photons disrupting chemical bonds and destroying tissue on a molecular level.[7] An alternative view is that the unique precision of excimer ablation is a consequence of intense localized heating from the nanosecond duration pulse.[8] It is important to note that the precise tissue ablation during tissue irradiation in air is not necessarily identical to what occurs in vivo during laser angioplasty in a blood medium. The 308 nm wavelength photon beam is avidly absorbed by blood and contrast media, leading to the production of insoluble gas and rapidly expanding cavitation bubbles, which has been dubbed the 'Moses Effect'.[9] These bubbles generate intense pressure wave pulses, which are in part responsible for complications such as dissections and perforations[10] (Fig. 11.1). Knowledge of this deleterious interaction led to the development of the saline flushing technique, which has substantially reduced the severity of coronary dissections, and is now a routine part of the procedure.[11,12]

Regardless of the mechanism(s), the excimer laser theoretically possesses three unique characteristics: it ablates tissue without thermal effect; it ablates on a pulse-by-pulse basis leaving smooth incision margins, at least during in vitro study; and it is the only laser capable of ablating calcified material.[1] While the laser is capable of ablating densely calcified material, the current catheters, which are multi-fiber in design and have a certain amount of peripheral dead space, are not designed for calcium ablation. Research continues on catheters for the ablation of highly calcified lesions.

Laser equipment

At its inception there were two major manufacturers of ELCA, namely Advanced Inteventional Systems (AIS) (Irvine, CA) and Spectranetics Corp. (Colorado Springs, CO). Later these companies merged and the modern ELCA equipment is manufactured by Spectranetics (Colorado, CO). The system consists of a laser unit which generates the laser beam, and a series of catheters of various sizes which transmit this energy by fiber optics to the tip of the catheter, delivering the energy to the intended lesions.

The new version of the Spectranetics laser unit, the CVX-300 system, is a portable unit, which is 35 inches high, 49 inches long and 24 inches wide, and weighs about 650 pounds (Fig. 11.2). It emits laser energy with a catheter output flow range between 30 and 60 mJ/mm^2, a repetition rate of 25–40 pulses/s and a pulse width of 125 to 200 ns (nominal 135 ns). This unit is the energy source for ELCA pacemaker lead extraction using the Spectranetics laser sheath (SLS), peripheral excimer laser angioplasty (PELA)

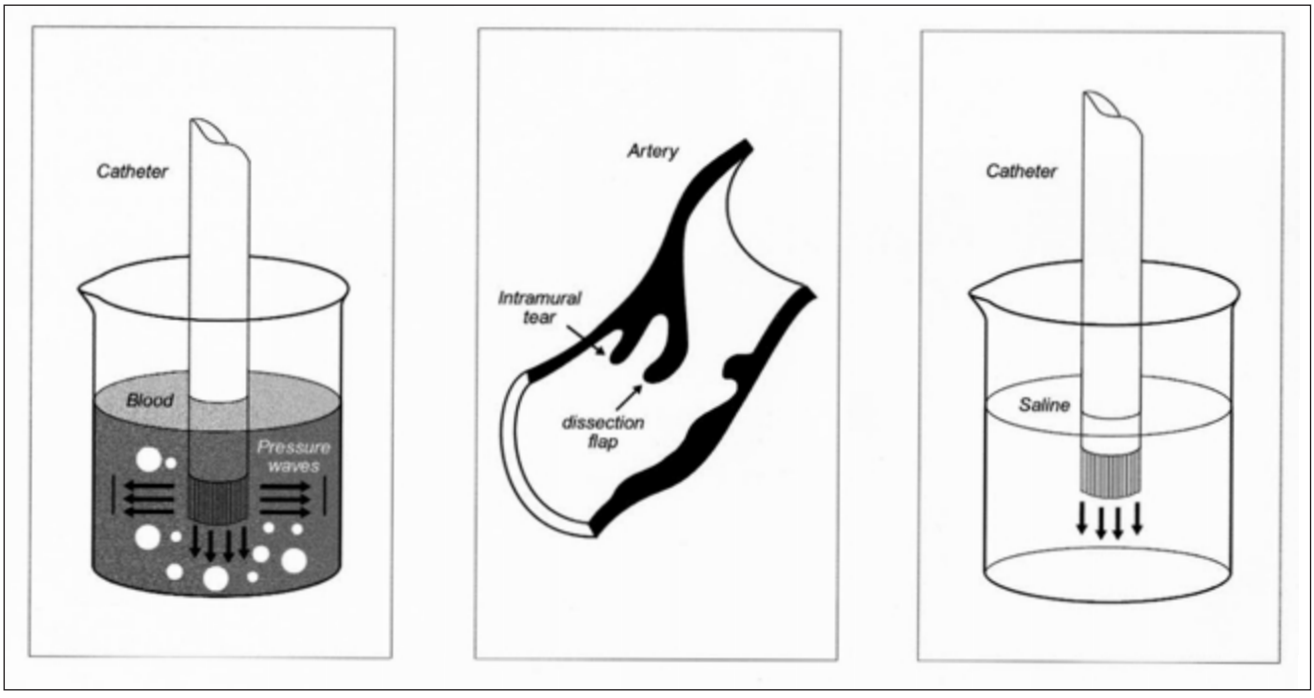

Figure 11.1
Laser energy absorbed by blood/contrast (left), causing rapidly expanding bubbles that disrupt the arterial wall, leading to coronary dissections (middle). Such dissections can be avoided by replacing blood in the artery with saline, and by flushing saline through the guiding catheter during lasing which allows the beam to transmit through the saline without absorption (right). (Adapted with permission from Scientific American.)

Figure 11.2
The new version of the Spectranetics laser unit, the CVX 300. This portable system generates cool ultraviolet light with a 308 nm wavelength in controlled energy pulses. The excimer laser energy is delivered by means of laser catheters from this unit to the target tissue. (Reproduced by courtesy of Spectranetics.)

and the laser guidewire for treatment of difficult total occlusions.

The currently available laser catheters include conventional over-the wire laser catheters as well as the rapid exchange or monorail catheters. The rapid exchange version of the co-axial catheter (Vitesse C® and Vitesse Cos®) (Spectranetics Corp, Colorado, CO) produces a more axial force transmission and tip control than the earlier over the wire systems. Each co-axial catheter (Vitesse C® and Vitesse Cos®) consists of 110 to 240 individual 61 μm fibers concentrically arranged around the guidewire lumen (Fig. 11.3). A radio-opaque marker is located at the distal end of the catheter to aid localization of the laser tip within the coronary vasculature. The guidewire lumen begins at the tip of the catheter and exits the laser catheter 9 cm from the distal tip. The new Vitesse Cos system is an improved version of the Vitesse C. It consists of a redesigned outer marker band, a smaller guidewire lumen, and optimal spacing of fibers, thereby helping to increase the ablative area as well have more trackability. The concentric catheters were limited primarily to treat concentric lesions and are not suitable for treating highly eccentric plaques. In particular, treatment of lesions on the inner curve of an angulated segment of an artery results in less tissue ablation, and may cause disruption of the normal arterial wall opposite the plaque at the angulated segment of the artery (Fig. 11.4a).

To overcome this limitation, the Vitesse E® series (Spectranetics Corp, Colorado, CO) of eccentric excimer laser catheters were developed (Figs. 11.4 and 11.5). The catheter shaft consists of an eccentric fiber optic bundle opposite the guidewire lumen, which runs through a tip with an eccentrically placed guidewire lumen. A radio-opaque marker with a radiolucent window is situated at the tip of the catheter. The window aids in directing the tip properly. There is a torque knob which enables the catheter to be rotated so that the fiber optic bundle is in contact with the plaque.

A laser guidewire (Prima FX® and SX®, Spectranetics Corp) has been developed for crossing total occlusions which cannot be crossed by a conventional guidewire (Fig. 11.6). The wire has a diameter of 0.018 inches and is 300 cm long. The wire

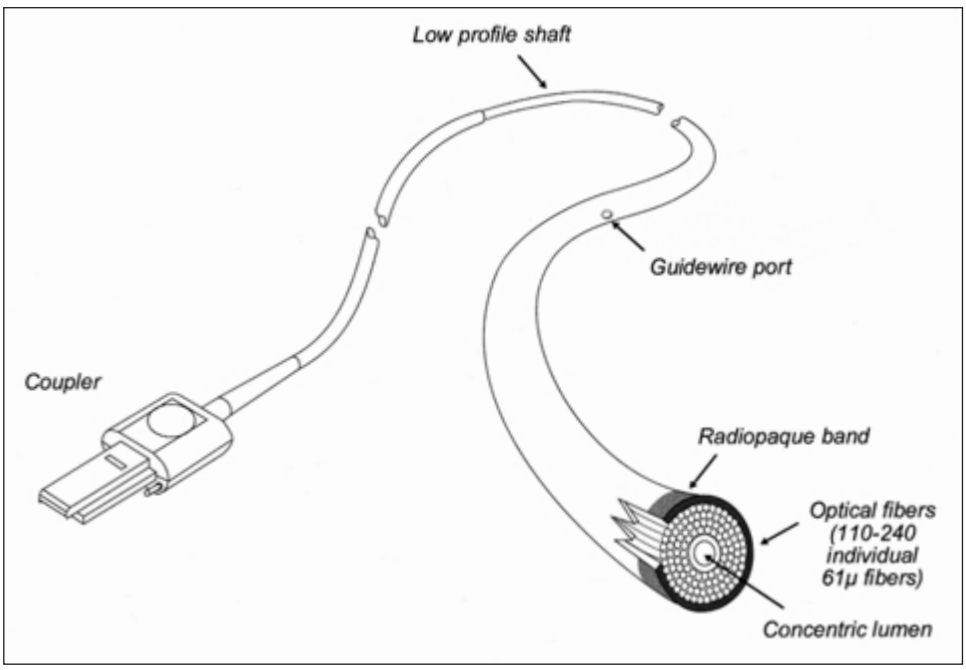

Figure 11.3
Schematic diagram of a concentric laser catheter (Vitesse C® and Vitesse C_{OS}®) (Spectranetics, Colorado, CO, USA). The catheter consists of multiple concentrically arranged fibers around a guidewire lumen. This catheter is ideally suitable for concentric lesions.

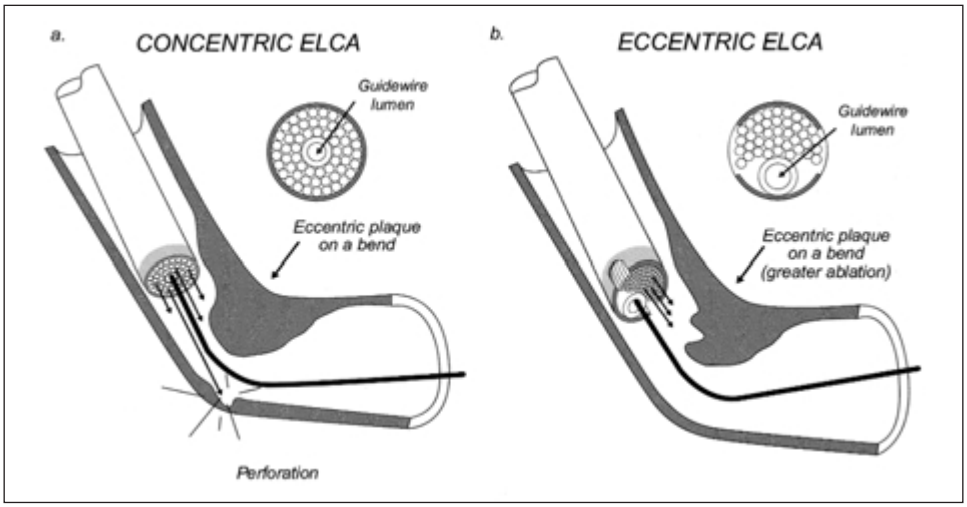

Figure 11.4
The potential hazards of ELCA of eccentric lesions on angulated segments. (a) The concentric ELCA may cause disruption of the normal arterial segment opposite the plaque. (b) The fiber optic bundle of the eccentric laser catheter (Vitesse E®) can be directed by means of an external torque knob towards the plaque, leading to greater tissue ablation, with a lower risk of disruption to the normal arterial wall.

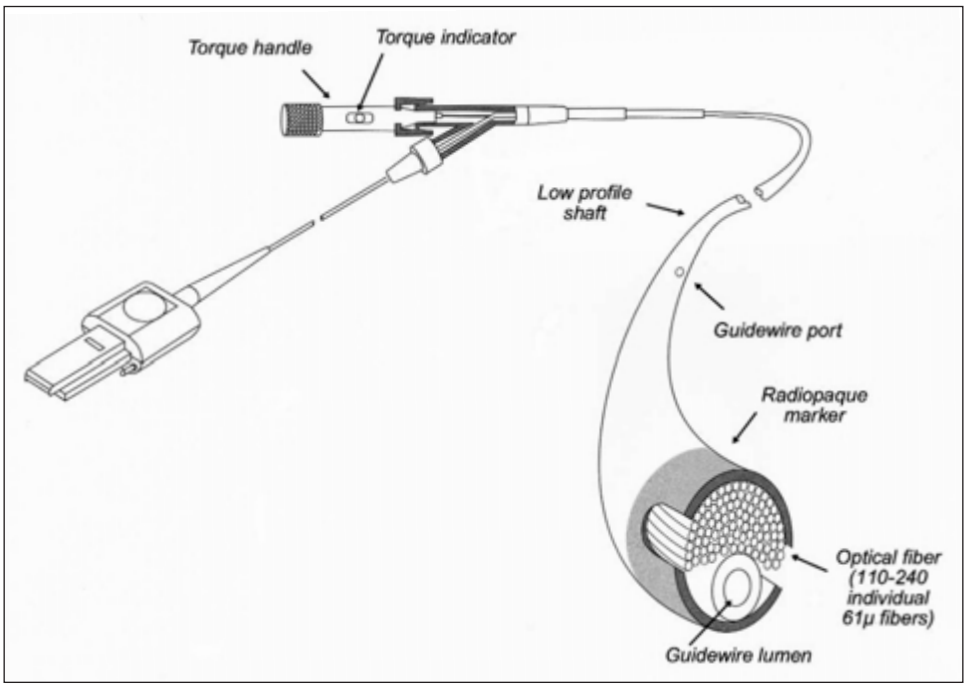

Figure 11.5
Schematic diagram of an eccentric laser catheter (Vitesse E®). It consists of an eccentric fiber optic bundle opposite the guidewire lumen. The tip of the catheter has a radio-opaque marker with a radiolucent window which aids in directing the tip properly. The torque knob helps to rotate the tip of the catheter so that the fiber optic bundle is in contact with the eccentric lesion.

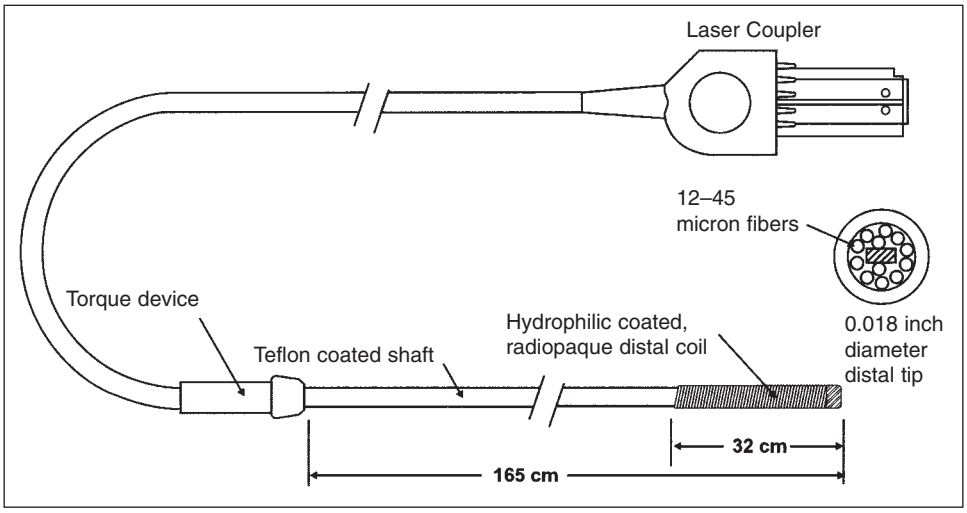

Figure 11.6
Schematic diagram of the Prima FX® or SX® laser guidewire used for refractory total occlusions. The laser wire has a shapeable 0.018 inch diameter tip. It helps to provide a pilot channel as an adjunct to conventional PTCA or ELCA (reproduced by courtesy of Spectranetics).

Table 11.1 Coronary laser devices and recommendations of sizing and guide catheter selection.

Catheter type	*Tip diameter*	*Recommended guidewire (inch)*	*Guide catheter (French) (mm)*	*Minimal vessel diameter (mm)*
Over the wire				
Extreme™	2.0	0.014/0.018	9	3.0
Rapid exchange concentric laser catheters				
Vitesse C™	1.4	0.014	7	2.0
Vitesse C™	1.7	0.014/0.018	8	2.5
Vitesse C™	2.0	0.014/0.018	9	3.0
Vitesse C_{os}™	1.4	0.014	7	2.0
Vitesse C_{os}™	1.7	0.014	8	2.5
Vitesse C_{os}™	2.0	0.014	9	3.0
Rapid exchange eccentric laser catheters				
Vitesse E™	1.7	0.014	8	2.5
Vitesse E™	2.0	0.014/0.018	9	3.0
Laser wire for chronic total occlusion				
*Prima FX™ 0.018 guidewire				>2.0
* Available for clinical use only in Europe				

has a shapeable tip and consists of 12 individual 45 μm laser fibers. The proximal end of the wire has a laser coupler which can be attached to the CVX 300 Spectranetics laser unit. The device is available for clinical use outside the US.

The above mentioned catheters available for clinical use are tabulated in Table 11.1, as are suggested guiding catheters for the various laser catheters and recommended laser catheter sizes for various vessel sizes.

Case selection

Case selection significantly affects the outcome of this procedure. Table 11.2 lists the current recommended indications and contraindications for the use of ELCA. Over the last few years there have been more indications. Recently, one of the important has been the treatment of diffuse in-stent restenosis, which in some studies has been shown to be superior to angioplasty.[13] Furthermore, the concept of optimal debulking followed by stent deployment is evolving as a new modality for catheter based treatment for coronary artery disease.

Procedure

Once a decision is made to consider ELCA, the involved coronary artery is cannulated with a 7F or 8F guiding catheter without side holes. It is preferable to use a well supported large bore guiding catheter such as an 8F catheter. An adequate lumen is needed to help flush saline using the 'saline flush protocol' and guide catheters without side holes improve saline infusion. As with any percutaneous coronary intervention (PCI), the selection of a proper guide catheter can be critical to the success of the procedure.

The lesion is crossed with a suitable guidewire, and the tip of the guidewire is placed as distal as possible in order to help

Table 11.2 Indications and contraindications for excimer laser angioplasty (ELCA).

Current indications for the use of ELCA

Long lesions and diffuse disease (>20 mm length)
Aorta-ostial lesions
Chronic total occlusions crossable by a guidewire
Less than 3.0 mm diameter vein graft lesions where primary stenting is not an option
Diffuse instent restenosis, as a 'debulking' technique prior to definitive redilatation
Non-dilatable rigid lesions
Eccentric lesions not on an acute bend
Chronic total occlusions not crossable by a guidewire (using the laser wire)

Contraindications for the use of ELCA

Unprotected left main coronary artery disease
Acute angulation (< 45°)
Coronary dissection
Lesions in vessels with smaller diameter than the catheter size
Moderate to severe calcified lesions

tracking of the laser catheter along the stiffer part of the wire.

The choice of the size and type (concentric versus eccentric) of laser catheter should be decided on the basis of the size of the native vessel, eccentricity of plaque, severity of the lesion, tortuosity and calcification of lesions. A laser catheter with a diameter of about two-thirds of the diameter of the artery is usually appropriate. In cases of very tortuous, calcified, or severely narrowed vessels, a smaller catheter would be more appropriate in order to minimize the occurrence of complications. Eccentric rather than concentric laser catheters are preferable in cases of highly eccentric plaques, especially when they are situated at the bend of a vessel (Fig. 11.4).

Prior to the introduction of the laser catheter, this should be calibrated by pointing the tip of the catheter towards the energy detector on the CVX 300 unit and activating the laser, by pressing on the foot pedal for 5 seconds. The laser will calibrate automatically and enter into a standby mode.

The laser catheter is advanced so that the tip is in direct contact with the proximal end of the lesion to minimize the blood interface between the laser tip and the lesion. An energy density of between 45 and 60 mJ/mm^2 at frequencies of 25 Hz is usually chosen.

Saline flush protocol

A warm bag containing 0.9% normal saline is attached by means of a sterile intravenous line to one of the ports of a triple manifold. Residual contrast is injected back into the contrast bottle. A fresh 20 ml Luerlock control syringe is attached to another manifold port and is used to flush with normal saline all traces of blood and contrast from the entire system including the manifold, Y-connector, guiding catheter, and the target coronary artery. Just prior to activation of the laser, the assistant operator injects a 10 ml bolus of normal saline through the guiding catheter, and then continues to inject saline at rate of 1–3 ml/s during the lasing procedure. Lasing is commenced immediately after the 10 ml bolus of saline for 2–4 seconds (maximum 5 seconds). The saline injection is terminated at the end of a lasing sequence. The laser catheter is advanced at a rate of no greater than approximately 1 mm/s. The system will allow lasing for a maximum of 5 seconds at a time, then automatically enters a 10 second standby mode. The end of the standby period is marked by an audible signal indicating that the operator can continue.

In the early ELCA experience only one pass would generally be performed through the entire lesion. With the improvement in catheter design and the proper use of saline infusion, operators have been able to optimize results, making additional laser passes when lesion contact can still be made.

While using the eccentric laser catheters, there are two methods employed to ablate tissue. The first method involves simply advancing the catheter through the target tissue, withdrawing the catheter and then repositioning the catheter tip using the torque knob, and then re-advancing the catheter again. The second method, which has not been used as commonly, involves actively torquing the catheter at the proximal part of the target lesion, in an attempt to ablate as much tissue as possible. The operator only advances the catheter when tissue has been removed in a 360° pattern. This method may limit the catheter from slipping into the lumen, which sometimes occurs when using the more commonly applied first method. In order to achieve a maximum diameter to ensure good short and long term results, adjunctive balloon angioplasty with or without stent placement is usually performed after the lasing procedure.

Use of the laser wire for chronic total occlusions

In certain cases of chronic total occlusion which cannot be crossed by a wire the PRIMA FX^{TM} or SX^{TM} (Spectranetics Corp) laser guidewire can be used. A well supporting guiding catheter must be used, and the tip of the catheter should be coaxial within the lumen of the vessel. With the help of simultaneous right and left coronary angiography, the proximal and distal ends of a chronic occlusion can be identified. This form of angiography can mean the difference between success and failure. The wire is gently advanced applying a laser energy of 40–60 mJ mm^2 at 30–60 Hz. This procedure has the potential for perforation, and therefore guidewire position should always be checked in two orthogonal views. Once the lesion is crossed and perforation is ruled out by contrast injection, the small channel thus formed may be further dilated by ELCA, or balloon angioplasty and stent deployment.

Avoiding and managing complications

ELCA is a procedure that requires careful attention to case selection and technical detail. The major complications which plagued this procedure during the early experience have been almost resolved. The incidence of coronary perforations and major flow limiting dissections has decreased significantly due to improved catheter design and better operator techniques, including the routine use of saline infusion. If resistance is encountered in spite of optimized guide catheter and guidewire position and selection, increased laser energy, or the catheter fails to negotiate around an acute bend in the vessel, ELCA should be abandoned.

The incidence of ELCA-induced major coronary dissections, once considered the Achilles' heel of this procedure,

has been considerably reduced with the advent of the saline infusion technique in 1995.[12] The saline infusion technique eliminates blood and contrast from the laser field, resulting in a significant decrease in dissections from 24% to 7%.[12] Other measures used to prevent dissections include avoiding excessive force or oversizing the laser catheter. If a flow limiting dissection develops, the laser part of the procedure should be discontinued, and the dissection should be treated by balloon angioplasty and stent placement. The intra-procedural use of platelet glycoprotein IIb/IIIa receptor antagonists in such situations could be very helpful.

Perforation is a serious but not catastrophic complication. It has been reported to occur in 0.3 to 2% of cases.[14,15] Perforations are more likely to occur in the following situations: (a) use of a catheter that is equal to or greater than the vessel diameter, (b) use of a concentric catheter on a very eccentric lesion, particularly if on a tight bend, and (c) applying laser energy in a previously dissected vascular segment. Perforation may result in cardiac tamponade if there is significant bleeding in patients with intact pericardium. Once a perforation is diagnosed, the laser catheter is removed without altering the guidewire position. The guidewire position should be assessed prior to advancing other devices, to ensure that the guidewire has not inadvertently been placed outside the true lumen. The effect of heparin may be reversed with intravenous protamine. A balloon is slipped over the guidewire and inflated across the perforation for a few minutes in an attempt to seal the perforation. A covered stent, if available, can be deployed at the site of perforation. If there is any evidence of hemodynamic compromise due to cardiac tamponade, pericardiocentesis should be performed immediately. Most perforations can be treated successfully, by the above conservative means, and urgent cardiac surgery is required in only a minority of cases.

Clinical experience

Since the first successful human ELCA procedure in 1988, over 50 000 laser angioplasties have been performed worldwide. Most of the experience has been obtained using devices made by two manufacturers: Advanced Interventional Systems (AIS) and Spectranetics. Since the companies have merged, most of the recent experience has been with the system developed and modified by Spectranetics. The results of the first 3000 patients treated at 33 sites with the AIS system were reported in 1994.[15] A total of 3592 lesions in 3000 patients underwent ELCA. There was a wide variety of lesions, including 20% long lesions (>20 mm) and 8% aorta-ostial lesions. Significant dissections occurred in 13.0%, and perforation occurred in 1.0% of lesions. Procedural success was achieved in 90% of patients, and the incidence of major complications was 0.5% in-hospital death, 2.1% Q-wave myocardial infarction, and 3.8% in-hospital bypass surgery. This early experience highlighted the importance of adjunctive balloon angioplasty to attain better angiographic results. One subgroup of this registry was specifically studied to assess the role of ELCA in aorta-ostial lesions.[16] In this study 209 aorta-ostial lesions in 200 patients were treated with ELCA. Procedural success was 90%, and major complications were uncommon (0% death, 0.5% Q-wave MI, 3.4% bypass surgery). The overall restenosis rate was 39%, with the highest restenosis rate being in the left main lesions. This study demonstrated the safety and efficacy of ELCA in aorta-ostial lesions with an acceptable 6 month restenosis rate.

The New Approaches to Coronary Intervention (NACI) registry reported a series of 1000 lesions in 887 patients, treated by either the AIS or Spectranetics excimer laser systems.[17] The procedural success rate was 84%. However, there were significant dissections in up to 23.4% of lesions and perforation occurred in 2.6%. The in-hospital mortality was 1.2% while at 1-year follow-up the incidence of death, Q-wave MI or target vessel revascularization was 42.3%.

A smaller number of poorly designed randomized trials comparing ELCA versus other catheter based interventions have been tested. In the ERBAC trial (excimer laser vs rotational atherectomy vs balloon angioplasty comparison), a single-center study conducted in Germany, 620 patients undergoing catheter based revascularization for native type B or C lesions were randomized to receive treatment with conventional balloon angioplasty (210 patients), ELCA (195 patients), or rotational atherectomy (215 patients).[18] Total occlusions, saphenous vein grafts, and long lesions (three groups which do well with ELCA) were excluded from the study. This study showed a higher procedural success by rotational atherectomy than ELCA and balloon angioplasty. There were no differences in in-hospital complications and a higher 6-month target lesion revascularization rate in the two atheroablative groups was observed (42.4% for rotablation, 46.0% for ELCA, and 31.9% for balloon angioplasty, $P = 0.013$).[18] Once again, there was a statistically significant increase in the number of flow limiting dissections within the ELCA group compared to the Rotablator group (6.9% versus 0.9%, $P < 0.001$). Of note, the saline infusion technique which is known to reduce dissections was not used at this time. Furthermore, the lesions best suited for ELCA—diffuse and saphenous vein graft lesions, and total occlusions—were excluded. Densely calcified lesions, known to favour rotablation, were included.

Another small randomized trial, the AMRO (Amsterdam-Rotterdam) trial, compared ELCA (with or without adjunctive balloon angioplasty) with balloon angioplasty in 308 patients with lesion greater than 10 mm in length and stable angina.[19] Although ELCA appeared safe in this study, there was no reduction in the long-term clinical adverse event rate compared to balloon angioplasty, and angiographic follow-up suggested a tendency to a higher restenosis rate (52% for ELCA versus 41% for PTCA, $P = 0.13$).[19] Subsequent subgroup analysis did not suggest any advantage of ELCA over

balloon angioplasty in patients, with long lesions (20 mm), small vessels (<2.5 mm), calcified lesions or total coronary occlusions—some of the categories that were believed to be potential niches for ELCA.[20] Of note, this trial was conducted very early in the history of ELCA. There was no saline-flush used, nor were vein graft lesions included. Furthermore, there was no attempt to optimize minimal luminal diameter.

The recent widespread use of stents has led to an emergence of an important clinical problem of in-stent restenosis (ISR). ISR is usually secondary to localized or diffuse neointimal hyperplasia (NIH).[21] Intravascular ultrasound studies have shown that PTCA alone for the treatment of ISR leads to a modest lumen enlargement as a result of additional stent expansion and tissue extrusion out of the stent, leaving behind a significant residual stenosis due to the remaining in-stent neointimal tissue.[21] Not surprisingly, the restenosis rate after PTCA alone for diffuse ISR has been reported to be as high as 80%.[22] The use of ELCA or other atheroablative procedures followed by adjunct PTCA has therefore been proposed as an alternative approach to the treatment of ISR in an effort to reduce the residual in-stent neointimal tissue, improve lumen dimensions, and decrease subsequent clinical recurrence (Fig. 11.7).

In a study reported by Mehran and colleagues, the clinical safety, mechanisms and 6-month results of ELCA + adjunct balloon angioplasty (PTCA) were compared with results of PTCA alone for the treatment of in-stent restenosis in 98 patients with 107 restenotic stents.[13] ELCA +PTCA resulted in greater lumen gain, more NIH ablation/extrusion, larger final lumen diameter, and a tendency for less frequent need for subsequent target vessel revascularization (21% versus 38%, $P = 0.0823$) in patients treated with ELCA and adjunctive PTCA. The procedural success rate was 91%, and there was a low adverse event rate, which included death (1.6%), Q-wave MI (0.5%), and tamponade (0.5%). Perforations occurred in 0.9%, and dissections occurred in 4.8% of patients with ELCA.

The Laser Angioplasty of Restenosed Coronary Stents (LARS) trial was a multicenter or surveillance trial which evaluated the safety and efficacy of ELCA for treatment of restenosed stents.[23] A total of 440 patients with restenosis in 527 stents were enrolled for treatment with ELCA and adjunctive PTCA. Procedural success was achieved in 91% of patients. The authors concluded that ELCA with adjunctive PTCA is a safe and efficient technology to treat in-stent restenosis, and that the data justify a randomized comparison with PTCA alone.

A recent single-center, non-randomized study compared the mechanisms and clinical results of ELCA versus rotational atherectomy (RA), both followed by adjunct PTCA for the treatment of ISR.[24] In this study, even though RA led to a greater reduction in intimal hyperplasia volume in comparison to ELCA (43 ± 14 versus 19 ± 10 mm^3, $P < 0.001$), both these interventional strategies had similar long-term clinical outcomes: the 1-year target lesion revascularization rate was 26% with ELCA + PTCA versus 28% with RA + PTCA (P = NS).

Another recently published prospective study reported the 6-month clinical and angiographic outcome after successful excimer laser angioplasty for in-stent restenosis.[25] In this study all 96 consecutive patients with in-stent restenosis were treated successfully with ELCA and adjunctive PTCA. At 6 months there was a >50% diameter stenosis present in 54% of the patients. Reinterventions were necessary in 31% of patients. This prospective non-randomized trial demonstrated a highly successful initial result with ELCA, but a significant restenosis at follow-up. The important drawbacks of this study are a lack of comparison with other treatment strategies, as well as less aggressive debulking in a cohort of patients who had a higher restenosis rate. The authors

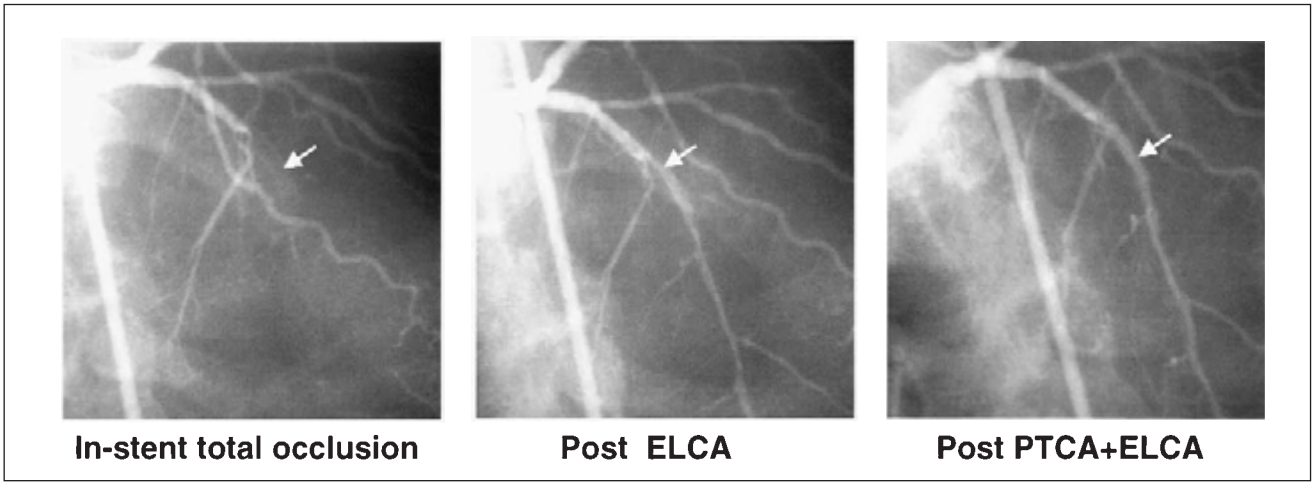

Figure 11.7
Angiographic studies of in-stent total occlusion in a left anterior descending artery, before intervention (left), after ELCA (middle), and after adjunct PTCA (right) (single arrow).

concluded that in view of the high restenosis rate, ELCA + adjunctive PTCA for in-stent restenosis would have to be combined with some other strategies such as brachytherapy in order to reduce the restenosis rate.

The above clinical data have supported the resurrection of ELCA as an important tool in our interventional armamentarium. The concept of optimal debulking followed by PTCA or stenting is being entertained with rejuvenated interest in the treatment of certain complex coronary lesions.

Application of the laser in specific lesions

Saphenous vein grafts

Lesions in these vessels are often multi-focal, diffuse and degenerative, and are prone to distal embolization. These lesions are potential targets for ELCA. In the heparin registry study, a success rate of 94% with ELCA for graft lesions <3.0 mm was reported in comparison to 77% with balloon angioplasty alone.[26] In a study comparing transcatheter extraction (TEC)/stent versus ELCA/stent, the initial procedural success was similar, although the rate of complications was higher in the TEC group (Non-Q-wave MI 15.6% vs 8.7%, acute closure 2.9% vs 0%, no-reflow 2.2% vs 0%).[27]

Aorta-ostial lesions (Fig. 11.8)

These challenging lesions are usually focal and often calcified. The success rate of laser use in two series of patients was reported to be as high as 94%[16] in comparison to a 74% to 80% success rate with standard angioplasty.[26] The routine use of stents along with other atheroablative procedures can achieve similar successful results. This challenging lesion can be treated with rotablation, or directional atherectomy (DCA). However, ELCA can be done with routine guide catheters and guidewires with much less complexity. In diffuse mildly calcified ostial lesions, ELCA along with stenting is possibly superior to rotablation or DCA.

Undilatable or uncrossable (balloon) lesions

Not infrequently, a balloon is unable to cross or dilate a lesion which has been crossed by a guidewire. In a small series using ELCA, it was found that ELCA was successful in 76% of calcified lesions and in 96% of non-calcified lesions ($P < 0.05$).[28] Therefore ELCA is a reasonable option for lesions which are uncrossable or undilatable with a balloon, especially if the lesion appears non-calcified.

Total occlusions (Fig. 11.9)

Occasionally a chronic total occlusion is not crossable by a guidewire. In such situations the Prima FX/SX 0.018-inch laser wire (Spectranetics Corp, Colorado) can be used to cross the lesion. In the European multicenter surveillance study, there was a 56% success rate in crossing a lesion, which failed to be crossed by a conventional guidewire.[29] Adjunctive balloon angioplasty or ELCA increased the

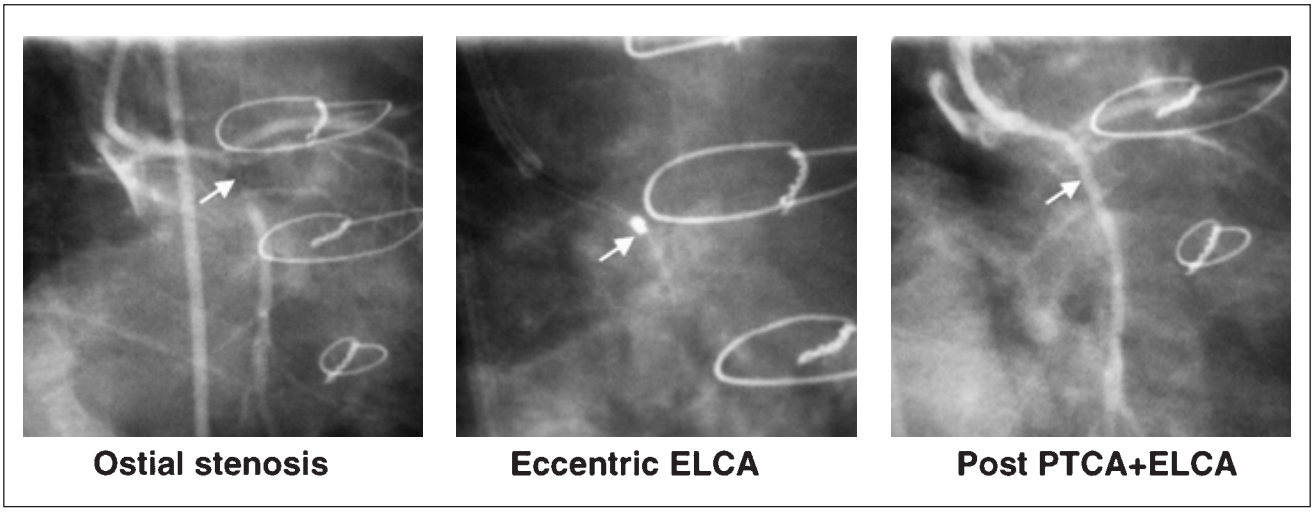

Figure 11.8
Angiographic studies of a high grade ostial left circumflex artery stenosis, before intervention (left), after eccentric ELCA (middle), and after adjunct PTCA (right) (single arrow).

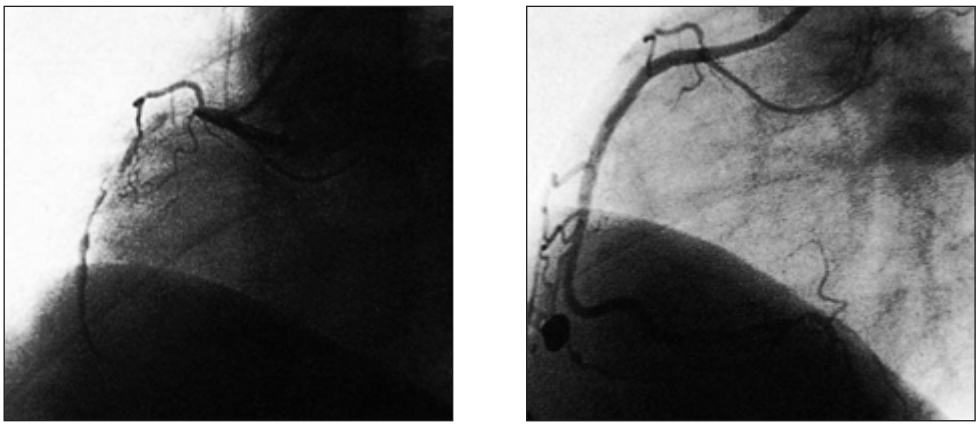

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Figure 11.9
Angiographic studies of chronic total occlusion of the right coronary artery which could not be crossed by conventional guidewire (left), and after treatment with a laser wire, and adjunctive angioplasty (right).

overall success rate even further. This new technological breakthrough is not without complications. A wire exit was noted in 24% cases, although cardiac tamponade was noted in only 0.5% cases. The merits of opening a chronic stable occlusion should be weighed against the markedly prolonged fluoroscopic time, the large volume of contrast medium, and the small but definite risk of cardiac tamponade.

In-stent restenosis (Fig. 11.7)

As discussed earlier, this entity has become one of the most important indications of ELCA in the modern stenting era. In-stent restenosis is a new and very challenging problem. Studies using ELCA with adjunctive PTCA have demonstrated both superior short and moderate long term results compared to PTCA alone.[13,24,25] Recently, intracoronary brachytherapy has been shown to be very effective in the treatment of this condition.[30] Studies using ELCA + PTCA along with other modalities such as brachytherapy are needed to assess the potential improvement in the long term outcome of the treatment of in-stent restenosis.

ELCA induced complications

Although ELCA is a reasonably user-friendly procedure, it is a much less forgiving technique in comparison to balloon angioplasty and stent deployment. Complications of Percutaneous Coronary Interventions notably perforations, dissections and acute closure, can occur with this procedure. The frequency of perforation has declined to less than 1% with increased operator experience.[31] Attempts at maintaining co-axiality, as well as using eccentric laser catheters for eccentric plaques, may reduce this complication. Dissections, as previously mentioned, have dramatically decreased from a rate as high as 22% to around 1%, with the routine use of safe lasing techniques described earlier. Acute closure and distal embolization have also rarely been encountered. The routine use of powerful antiplatelet agents such as the intravenous glycogen IIb/IIIa receptor blockers during these interventions has led to a reduction in the incidence of acute ischemic complications following PCI.[32]

Future directions

The development of safer techniques and refinements of catheter design will make ELCA a safer procedure with wider applications. One important potential advance in laser technology which has been studied, is to homogenize the laser beam. It is thought that homogenization of the laser beam can be used to reduce the overall amount of energy needed to ablate tissue. So far, bench results are promising, although clinical results have not yet been reported.[33] Another promising technology is 'multiplexing'. With this system, rapid sequential firing of different sections of the multifiber catheter facilitates a decrease in the pulse energy.[34] Experimental studies have shown reduced photoacoustic effects on tissues, thus preventing dissections. Further work in this area needs to be done. Additional study into the development of laser catheters which can be used to ablate through highly calcific plaques is being carried out.

The role of debulking prior to stent deployment in order to achieve maximal luminal gain is a new concept which is gaining popularity. Studies using optimal debulking with other devices followed by stenting have shown superior short and long term results in comparison to stents alone.[35] Debulking by ELCA followed by stenting is therefore an attractive option, which needs to be explored and systematically studied. Finally the application of lasers for photoacoustic thrombolysis in patients with acute coronary syndromes has generated significant interest. In the future, intracoronary thrombus, once a contraindication, may become an indication for the use of laser angioplasty.[36]

Summary

The excimer laser produces pulses of laser energy that debulk and evaporate tissue without causing significant thermal injury. Since its invention, ELCA has generated major expectations, disappointments, and finally renewed interest. The potential risks of dissections and perforation associated with this procedure, as well as the development of safer and effective techniques such as stenting, waned away the initial enthusiasm in ELCA. However, with the development of modern laser catheters, safer techniques, and the renewed interest in the concept of lesion debulking, there has been a resurrection of ELCA. This procedure is useful in complex coronary artery stenoses which are not successfully treated by conventional balloon angioplasty. ELCA along with balloon angioplasty is especially effective in the treatment of in-stent restenosis. Most second generation devices such as stents, atherectomy devices, radiation, and laser angioplasty continue to undergo extensive research. ELCA will continue to evolve as a useful adjunct to the interventional armamentarium for selected coronary lesions. Hopefully this multi-device approach to coronary revascularization, coupled with effective restenosis prevention, will allow most patients with symptomatic coronary artery disease to be treated non-surgically.

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12

Transluminal extraction catheter atherectomy

Sameer Mehta, James Margolis and Andres Hidalgo

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) has proven to be an extremely effective treatment for coronary artery revascularization. Balloon dilatation of an atherosclerotic plaque increases the cross-sectional area of the arterial lumen by barotrauma injury to the plaque and the arterial wall. Although some plaque compression occurs, the major change in lumen geometry is caused by fracturing and fissuring of the atherosclerotic plaque[1] extending for variable lengths and depths from the lumen into the arterial wall. Not only is the endothelial surface of the artery and the plaque disrupted but the collagen matrix of the media is exposed to blood and jagged plaque edges are created. In addition, dissection planes are often produced within and sometimes through the media of the artery.[1] Plaque disruption probably accounts for the two most difficult problems associated with PTCA, namely abrupt occlusion and lesion restenosis. Abrupt coronary occlusion is caused by complicated intimal and medial dissection together with a large intimal flap and associated thrombosis. Restenosis appears to be due to a combination of elastic recoil and smooth muscle cell proliferation causing fibrointimal hyperplasia as a result of extensive disruption of intima and media.

Mechanical atherectomy may have the potential to ameliorate and modify these inherent limitations of PTCA by its ability to debulk the atherosclerotic plaque.[2] An endarterectomy catheter has been developed by Interventional Technologies Inc (San Diego, CA, USA) that simultaneously cuts and removes atherosclerotic plaque from within the coronary artery. This unique device is referred to as the Transluminal Endarterectomy (or Extraction) Catheter (TEC).[3] Mechanical excision and removal of atherosclerotic plaque from within the lumen of the coronary artery should be as effective as PTCA, but cause less trauma to the arterial wall and thus fewer acute complications with perhaps a decreased likelihood of restenosis.

History

Initial experiments with the TEC device were focused on evaluating its safety and efficacy in normal and diseased atherosclerotic arteries.[4] TEC atherectomy was first performed on explanted human cadaver arterial segments (femoral, popliteal and coronary) grafted into the exposed femoral arteries of intact anesthetized dogs.[5] In vivo testing thereafter was performed percutaneously in canine femoral and coronary arteries using a 10.5 Fr guiding catheter to deliver and support the TEC device. The results demonstrated that the TEC device could be easily advanced into canine peripheral and coronary arteries and rotate smoothly around a central guide wire without causing dissection.

Beginning in December 1987 at Duke University Medical Center, extensive further clinical data were then accumulated with the peripheral TEC device prior to its use in coronary arteries.[5,6] Indications for peripheral TEC atherectomy included symptomatic claudication of the lower extremities and arteriographic evidence of significant stenosis involving the external iliac, superficial femoral, popliteal, tibial or peroneal arteries. Stack et al[7] reported the first results of a multicentre trial using the TEC device to treat peripheral vascular disease. A primary angiographic success rate of 98% was achieved without evidence of significant distal embolization or vessel perforation.

Based on the convincing clinical data regarding the use of the TEC device in experimental and human peripheral arteries[4–6] the Food and Drug Administration granted approval to test the TEC device in human coronary arteries in 1988. The objectives of the studies undertaken with the TEC device have been to evaluate the acute and long-term effects of mechanical rotational and extraction atherectomy in native coronary arteries and saphenous vein grafts. In particular, because the TEC device has been demonstrated to remove thrombus effectively,[8] clinical trials have also focused on its

ability to safely and effectively extract coronary artery thombi during myocardial infarction.[9] In June 1992, the FDA approved the use of TEC for both saphenous vein grafts and native coronary arteries.

Equipment

TEC device

The coronary TEC equipment is composed of an atherectomy catheter, a special guidewire and a catheter drive unit that incorporates a vacuum aspiration system (Fig. 12.1). The endarterectomy catheter, which is a wire-reinforced epoxy torque tube with a distally placed conical-shaped cutting head, is available in 5.5 Fr, 6.0 Fr, 7.0 Fr, and 7.5 Fr diameters (Fig. 12.2). The catheters are 153 cm long with a working length of 113 cm and possess a central lumen that extends the length of the torque tube, allowing vacuum aspiration of the excised plaque. The catheter and its cutting head, which contains two stainless steel, microtome-sharp blades, rotate at approximately 750 revolutions per min. The proximal end of the catheter inserts into a hand-held catheter drive unit, which possesses sites for attachment of a removable battery power switch and a 30 ml vacuum bottle for aspiration of excised atheroma and thombus through the central lumen of the catheter. A trigger switch located at the bottom of the hand-held unit activates both the rotating cutting blades and the vacuum system, while the lever or slider at the top of the unit allows advancement or retraction of the cutter for up to 3.5 cm over the guidewire and along the coronary artery or saphenous vein graft. A large-bore rotating haemostatic valve that contains a side-arm for contrast injections and infusion of pressurized flush solution also accompanies the TEC hardware. Figure 12.3a shows the TEC equipment schematically, and Fig. 12.3b a close-up view of the distal end of the catheter and guidewire.

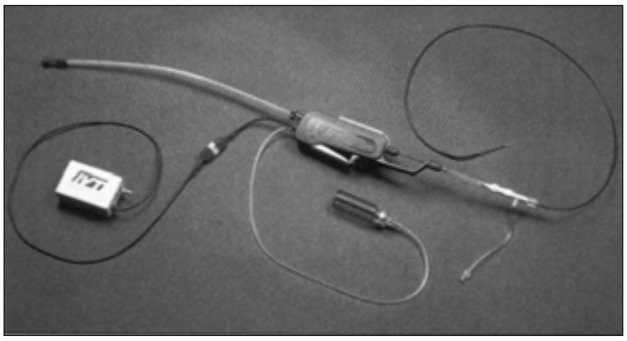


Figure 12.1
Coronary TEC device.

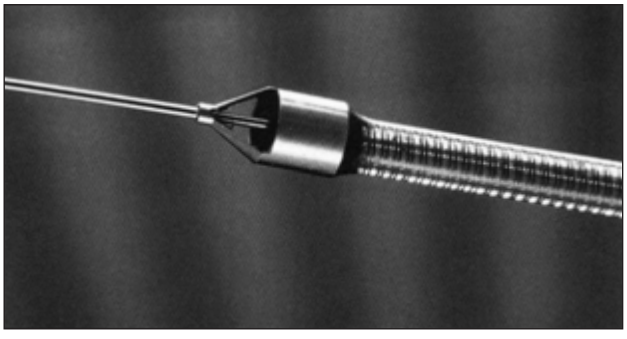


Figure 12.2
Cutting head of TEC device.

TEC guidewire

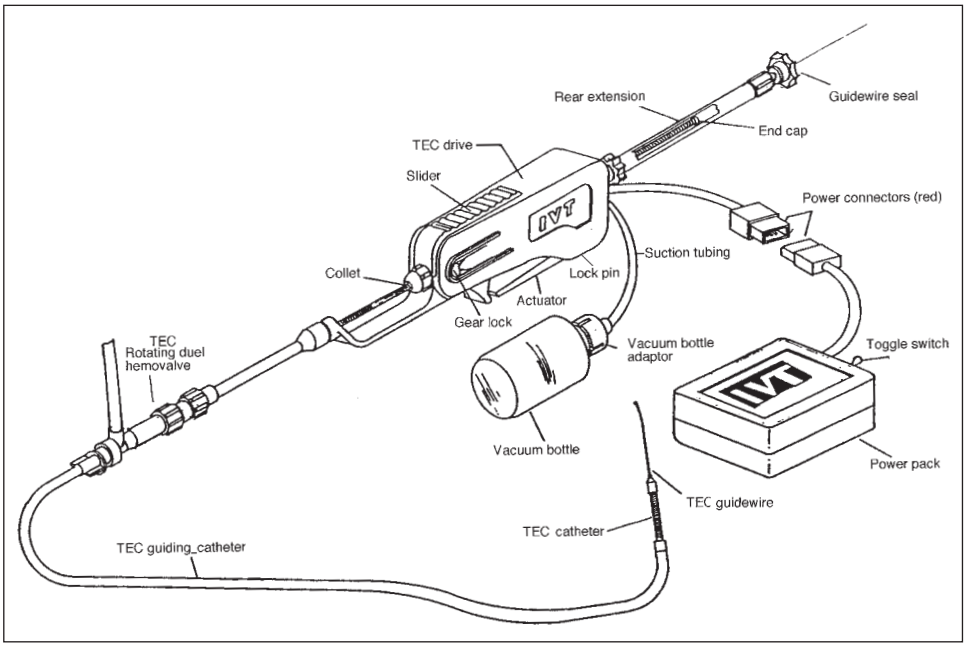
The 0.014-inch TEC Lubrithene-coated guidewire possesses more tensile strength than a standard PTCA guidewire. The more proximal portion of the wire is stiff and acts like a rail to permit smooth delivery of the TEC into the coronary artery. It provides a platform for catheter tracking and prevents wobbling of the catheter during cutting. The distal 2.5 cm is floppy and the last 2.0 cm is radio-opaque, ending in a small ball 0.020 inch in diameter, that is a safety feature. Should the torque tube fracture or the cutting head separate from it, the distal ball prevents loss of the cutting head or torque tube from the guidewire.

Two high-torque guidewires are available with lengths of 274 cm and 300 cm. Occasionally, it may be necessary to cross the lesion with a 0.014-inch high-torque floppy guidewire and then exchange it for the TEC wire to allow introduction of the TEC catheter.

TEC guide catheter

The 10 Fr TEC guide catheters (IVT) have an internal lumen 0.104 inch in diameter. They are available as: FL 3.5, 4.0, and 5.0; FR 3.5, 4.0 and 5.0; and in multipurpose graft, modified and left Amplatz, right coronary bypass and hockey-stick shapes. These large-lumen epoxy and wire-reinforced guide catheters have soft distal tips. They are designed to provide strong support, although excessive back-up should be avoided because this may force the device across the lesion before cutting is complete. Coaxial alignment of the guide catheter is extremely important, especially for saphenous vein grafts.

Generally, left Judkins guide catheters are used for left anterior descending lesions; Amplatz guide catheters for left circumflex lesions; hockey-stick, left Amplatz or right Judkins catheters for right coronary artery lesions; and hockey-stick, multipurpose graft or right Amplatz guide catheters for saphenous vein grafts.



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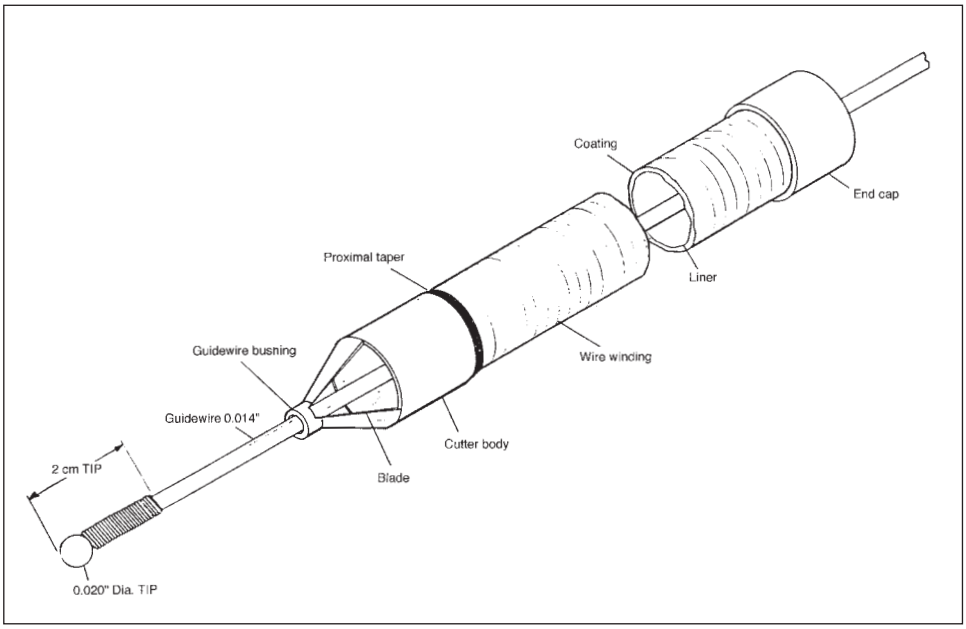


b

Figure 12.3
(a) Schematic diagram of TEC equipment. (b) Schematic close-up view of the distal end of the TEC catheter and guidewire.

Indications and contraindications

Emphasis is placed on proper case selection.

Clinical inclusions include symptomatic patients without contraindications to PTCA who do not have severe peripheral vascular disease that precludes femoral access (Table 12.1). Initial criteria include those with proximal, discrete concentric lesions in non-tortuous vessels, although complex lesions unfavourable for PTCA are now being addressed.

Table 12.1 Indications for TEC atherectomy.

Lesions favourable for PTCA
Morphologically unfavourable lesions for PTCA
Ostial lesions
Long (10–20 mm) lesions
Thrombus-associated lesions, e.g. acute myocardial infarction
Saphenous vein grafts

Patients with ostial or long (10–20 mm) lesions and those with coronary artery thrombi, perhaps due to acute myocardial infarction, may be particularly suitable.[9] Diseased saphenous vein grafts with much intraluminal material are also well suited to TEC atherectomy.

Contraindications include extreme coronary tortuosity, severe eccentricity or angulation (>45°) of the target lesion, lesions >20 mm in length and bifurcation lesions where the origin of the major side branch contains a severe stenosis. Heavily calcified lesions, coronary ectasia, major dissections and internal mammary arteries are unsuitable. Severe peripheral vascular disease also precludes TEC atherectomy (Table 12.2).

Table 12.2 Contraindications to TEC atherectomy.

Severe coronary tortuosity
Marked angulation of target lesion
Very long lesions (>20 mm)
Severe lesion eccentricity
Heavily calcified lesions
Bifurcation lesions requiring wire protection of side branch
Small vessels (<2.5 mm diameter)
Coronary ectasia
Major coronary dissections
Internal mammary arteries
Severe peripheral vascular disease

Procedure

Patients undergoing TEC atherectomy are treated according to a protocol identical to that for standard PTCA. Table 12.3 outlines pre and post procedural protocols that are commonly employed. Aspirin, heparin and calcium channel blockers are used for pretreatment. Activated clotting times are used to monitor heparin dosage and are maintained between 300 s and 400 s.

A 10.5 Fr arterial sheath is inserted into the femoral artery under local anaesthetic. Once an appropriate guide catheter has engaged the coronary ostium, lesions are usually crossed using a bare wire technique which allows easy steering and excellent visualization from guiding catheter injections. After the 0.014-inch TEC guidewire is placed across the coronary stenosis and as distal as possible, the TEC catheter is introduced over the guidewire and is positioned proximal to the lesion. The TEC drive unit is then connected and activated, simultaneously initiating vacuum extraction and rotation of the cutter-catheter at approximately 750 rev/min. The cutter-catheter is advanced slowly by the operator through the plaque material. During this advancement, the atheromatous material is excised and extracted into the small vacuum bottle attached to the rear end of the drive unit, aided by a pressure infusion of heparinized Ringer's lactate solution through the guiding catheter in order to create a slurry of aspirated blood and tissue (Fig. 12.4).

Table 12.3 Pre- and post-procedural protocols for TEC atherectomy.

Pretreatment
Aspirin
Heparin
Calcium channel blocker
Surgical standby indications similar to those of PTCA
Informed consent
Post procedure
Intensive-care monitoring as for PTCA, with heparinization, intravenous nitroglycerine, aspirin
Discontinue sheaths on the following morning
Ambulate 6–8 h after sheath removal
Discharge home that evening
Follow-up treadmill testing at 1 week, 3 months and 6 months postangioplasty

Caveats for successful extraction atherectomy include careful case selection, strong guiding catheter support and continuous vacuum suction during cutting. A step-up approach in device size selection seems reasonable, with the largest device being 1 mm less than the target vessel's diameter. Multiple passes may be required, particularly when treating saphenous vein grafts containing abundant grumous material[9,10] where it is often best to use the larger TEC catheters. Following TEC atherectomy, the cutter is removed and contrast injections are made to assess the need for making additional catheter cutting passes or performing

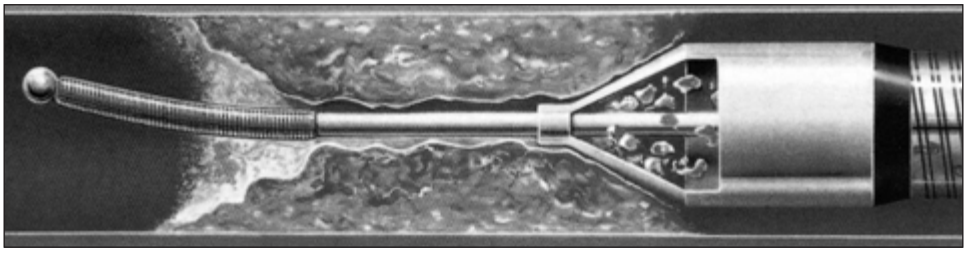


Figure 12.4
The coronary TEC system in action. The rotating cutting tip is advanced through the plaque material while the excised debris is removed by continuous vacuum suction.

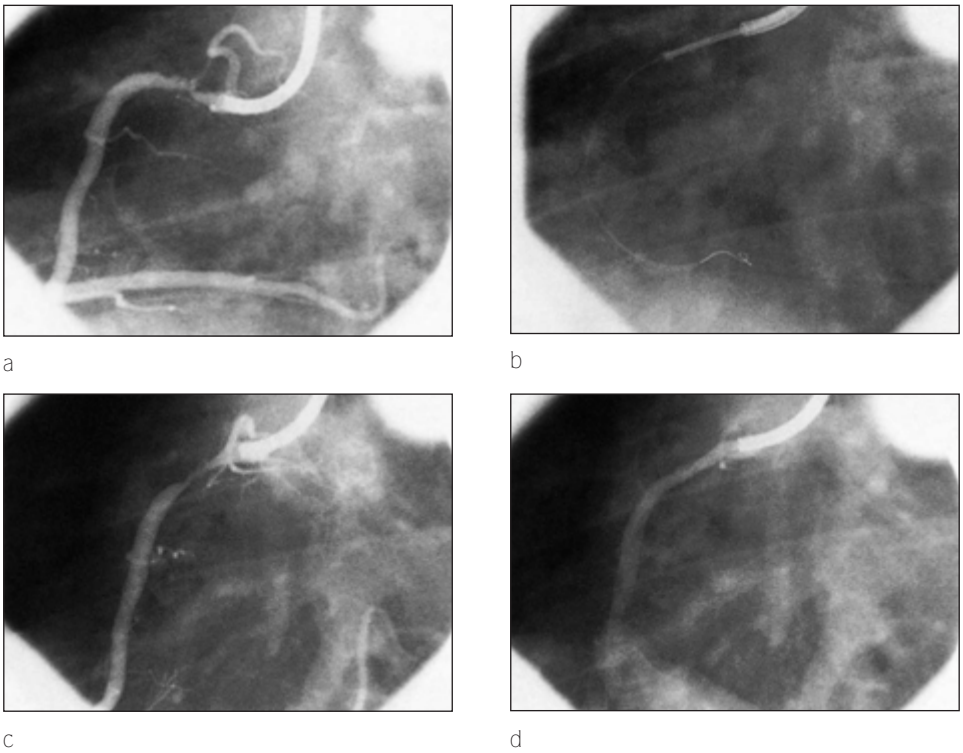


Figure 12.5
(a) Severe proximal RCA lesion. (b) 2.5 mm TEC device tracking over 0.014-inch TEC guidewire. (c) Immediately after 2.5-mm TEC atherectomy. (d) After adjunctive PTCA.

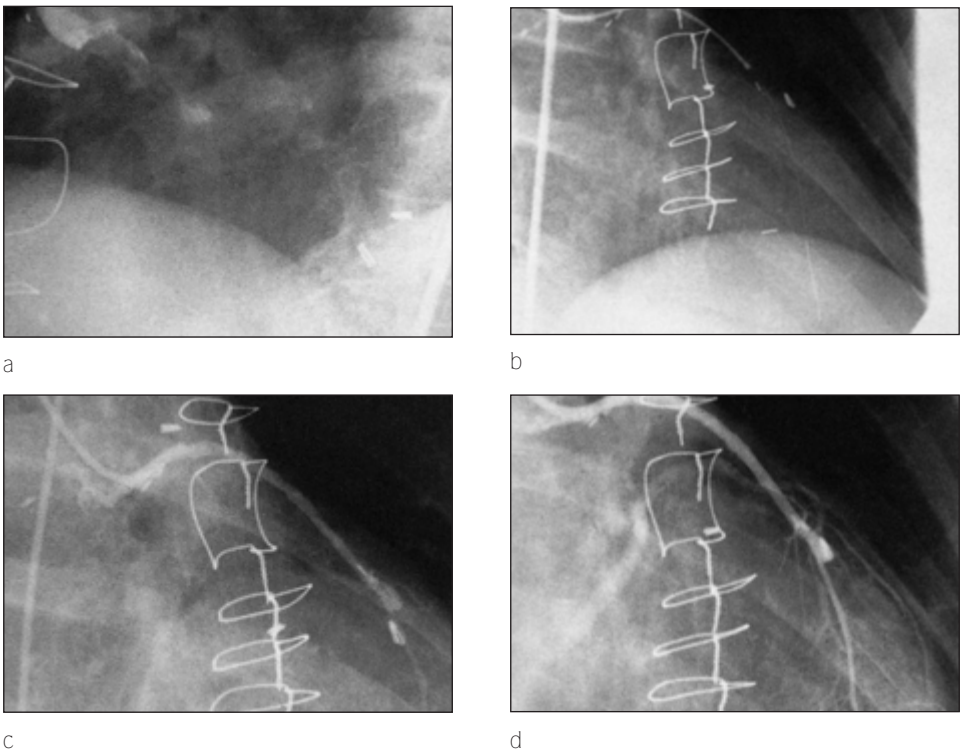
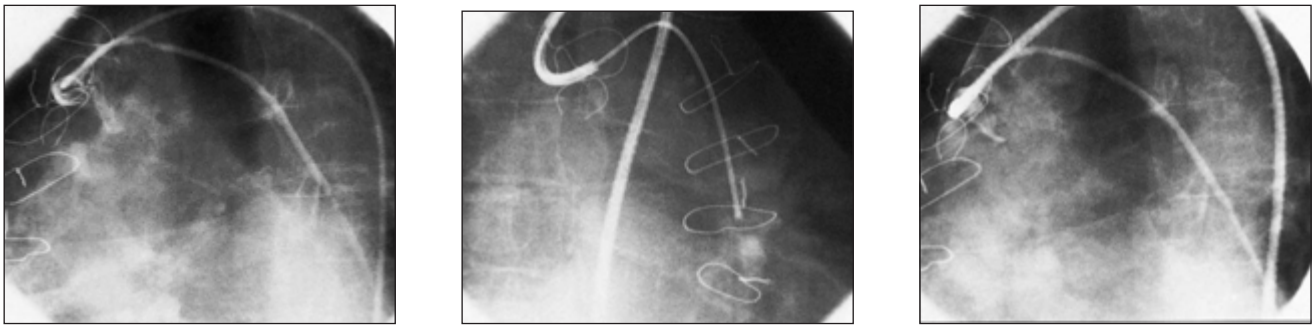


Figure 12.6
(a) Totally occluded diagonal saphenous vein graft (LAO projection). (b) 2.5-mm TEC catheter in situ (RAO projection). (c) After TEC atherectomy. (d) After adjunctive PTCA.

adjunctive PTCA. On average one to three passes across the lesion (10–15 s each) are made. The present philosophy revolves around obtaining the best result with the least residual stenosis, as opposed to only performing stand-alone atherectomy. When performing multiple passes, it may be helpful to adjust the guiding catheter position during subsequent passes, which helps to redirect the atherectomy cutter.

The presence of transluminal haziness, significant dissection or a large residual stenosis warrant the use of adjunctive PTCA. Catheter exchanges are facilitated by use of a rapid



a b c

Figure 12.7
(a) Thrombotic lesion in saphenous vein graft to left circumflex artery (LAO projection). (b) 2.5-mm TEC catheter in situ. (c) After stand-alone TEC atherectomy.

exchange system but conventional over-the-wire balloons are satisfactory too. Balloon profile is generally not a problem because the post-extraction atherectomy lumen easily admits even high-profile catheters.

Post-TEC atherectomy care is identical to that after conventional PTCA.

Figure 12.5 shows the results of TEC atherectomy in a native right coronary artery, and Figs. 12.6 and 12.7 show the results in occluded saphenous vein grafts.

Results of TEC atherectomy

TEC registry

Although TEC atherectomy is presently being used worldwide, the TEC registry still serves as the major source of results with this technique. This registry was started at Duke University following the initial clinical investigation of the first 50 cases beginning in July 1988. It was formed to determine the feasibility of the procedure as an alternative or adjunct to PTCA, although initial efforts were directed toward testing the safety and efficacy of early-generation equipment, developing and perfecting clinical technique and improving catheter and delivery systems. Long-term goals of the registry were to study the effect of TEC atherectomy on restenosis and to modify equipment and techniques to obtain optimal late results.

The TEC Registry collected data from all 19 American institutions investigating extraction atherectomy. The final results of enrolled patients have recently become available. Up to April 1994, 1614 patients were enrolled into the coronary TEC database. Most patients were severely symptomatic. Patients' angina grades were: Class I, 7%; Class II, 10%; Class III, 36%; Class IV, 46% (Fig. 12.8). Seventy-six percent were men with a mean age (±SD) of 65 (±10) years. Sixteen percent of these patients presented with acute myocardial infarction. Fifty-nine percent had undergone prior CABG, and 44% prior myocardial infarction. Sixty-three per

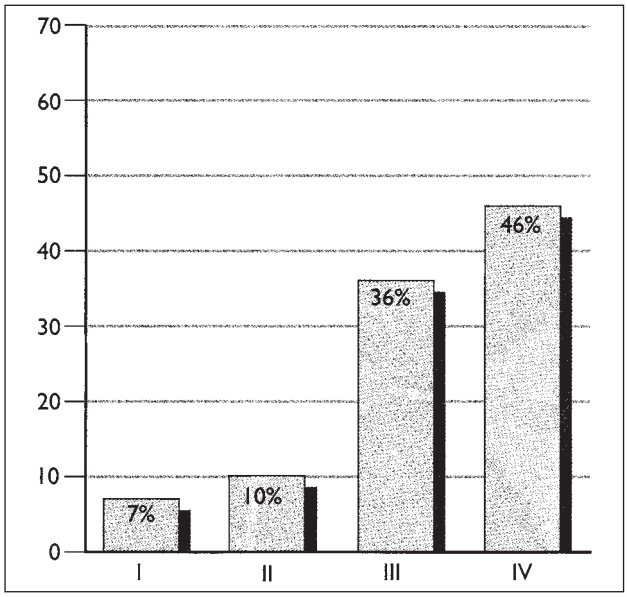


Figure 12.8
Patient angina class (TEC Registry).

cent had a history of cigarette smoking, 23% diabetes, 51% hypertension, 26% hypercholesterolemia and 72% multivessel coronary disease.

In the 1614 patients, 1870 lesions were attempted. Of these, 784 were located in native coronary arteries (41.9%) and 1086 lesions were located in saphenous vein grafts (58.1%) (Fig. 12.9). Of the 772 native lesions reported, 512 (65.3%) were de novo lesions and 260 (33.2%) were restenotic lesions. Of the 1049 reported grafts lesions, 851 were do novo and 198 were restenotic lesions. Clearly, the type of vessel treated by TEC atherectomy is different from that treated by other second-generation interventional devices in that TEC atherectomy was employed to treat a much higher proportion of lesions in saphenous vein grafts. Of the lesions located in vein grafts, 82% were located in old grafts (>3 years old). Twenty-seven percent were >10 mm long and 48% of the patients had angiographic evidence of thrombus within the

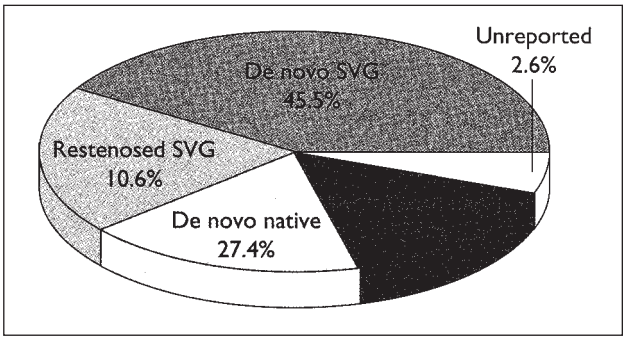


Figure 12.9
Lesion location (TEC Registry).

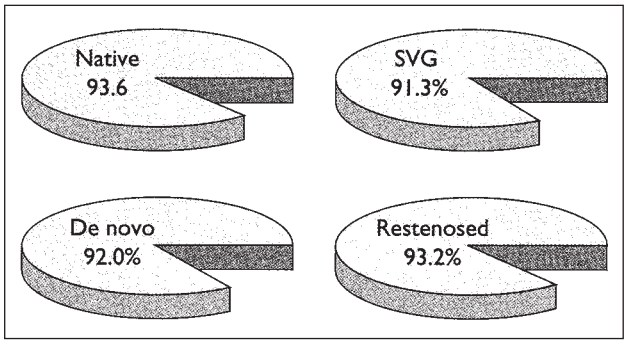


Figure 12.10
Success rates (TEC Registry).

vein graft. The cohort of patients undergoing TEC atherectomy to vein grafts was older than their counterparts undergoing TEC atherectomy in native vessels. Moreover, they had a greater incidence of multivessel coronary artery disease and an increased incidence of congestive heart failure.

Because the TEC catheter produces a lumen only as large as its nominal size, a successful procedure must be defined on the basis of what can be expected. The TEC Registry defines *technical success* as where the TEC device alone was able to cross the entire lesion with a reduction of the stenosis by at least 20% of the luminal diameter and improvement in flow by at least one TIMI grade. *Procedure success* is defined as the final diameter stenosis of <50% at the end of the procedure, whether or not adjunctive PTCA was performed. *Clinical success* means that the result qualified as a procedural success and occurred without reocclusion, reinfarction, post-infarction angina, coronary artery bygass graft (CABG), emergency medical or surgical intervention or procedure-related death.

Of 1870 lesions, 1726 (92.3%) were treated successfully (Fig. 12.10). Of 784 native coronary artery procedures, 734 (93.6%) were successful and of 1086 saphenous vein graft procedures, 991 (91.3%) were successful. Successful procedure rates for de novo lesions and restenotic lesions were 92.0% (1253 of 1363) and 93.2% (473 of 507) respectively.

NACI Registry

In the NACI Registry between 1990 and 1992, 240 lesions in 211 patients were treated by TEC atherectomy.[11] The patients were of mean age 63.9 years and 70% were male. Fifty-eight percent had unstable angina and 55% had three-vessel disease. Sixty-four percent of lesions were in saphenous vein grafts, 20.4% in the right coronary artery, 10% in the left anterior descending artery and 2.9% in the left circumflex artery. Thirty-four percent of lesions were >10 mm long, 68.4% were eccentric and 41.1% had associated thrombus. Twenty-two percent were restenotic lesions. The results showed a device success of 47.5% but 88.8% success after adjunctive PTCA.

Complications

The complications reported in the TEC Registry are similar to those seen after conventional PTCA. Table 12.4 summarizes the complications seen after TEC in native coronary arteries and saphenous vein grafts.

Of the 713 reported patients in whom native coronary arteries were treated, acute myocardial infarction occurred in

Table 12.4 Complications: TEC Registry

	Native 713	(%)	*Graft 901*	(%)	*All 1614*	(%)
In-hospital deaths	14	(2.0)	28	(3.1)	42	(2.6)
Q-wave MIs	7	(1.0)	11	(1.2)	18	(1.1)
CABG	21	(2.9)	21	(2.3)	25	(1.5)
Dissections	126	(17.7)	72	(8.0)	199	(12.3)
Occlusions	66	(9.3)	41	(4.6)	107	(6.6)
Perforations	7	(1.0)	8	(0.9)	15	(0.9)
Embolizations	17	(2.4)	76	(8.4)	98	(6.1)
Non-Q-Wave MI	11	(1.5)	22	(2.4)	34	(2.1)

7 (1.0%), CABG in 21 (2.9%) and death in 14 (2.0%). Dissection occurred in 126 (17.7%), occlusion in 66 (9.3%), perforation in 7 (1.0%), embolization in 17 (2.4%), and non-Q-wave MI in 11 (1.5%).

For saphenous vein grafts, major complications in 901 reported patients included: acute myocardial infarction in 11 (1.2%), CABG in 21 (2.3%), and death in 28 (3.1%). Dissection occurred in 72 (8.0%), occlusion in 41 (4.6%), perforation in 8 (0.9%), embolization in 76 (8.4%), and non-Q-wave AMI in 22 (2.4%). Table 10.4 also lists the range of complications for all 1614 patients collectively.

In the NACI Registry, complications occurred in 7.1% of 211 patients. Death occurred in 5.7%, Q-wave MI in 1.4%, emergency CABG in 0.9% and non-Q-wave MI in 3.3%.

Clinical and angiographic follow-up

Clinical follow-up data at 6 months are available for 1134 patients in the Registry, 524 of 637 (82.3%) in native coronary arteries and 610 of 787 (77.5%) patients with saphenous vein graft disease. Overall, 460 of 1134 (40.4%) patients demonstrated clinical restenosis (Fig. 12.11). Patients unable to return for follow-up catheterization and for whom follow-up angina was not greater than pretreatment angina or who had negative stress and/or thallium tests were considered to be clinically non-restenosed. Clinical restenosis was seen in 206 of 524 (39.3%) native coronary artery and 253 of 610 (41.5%) saphenous vein graft patients.

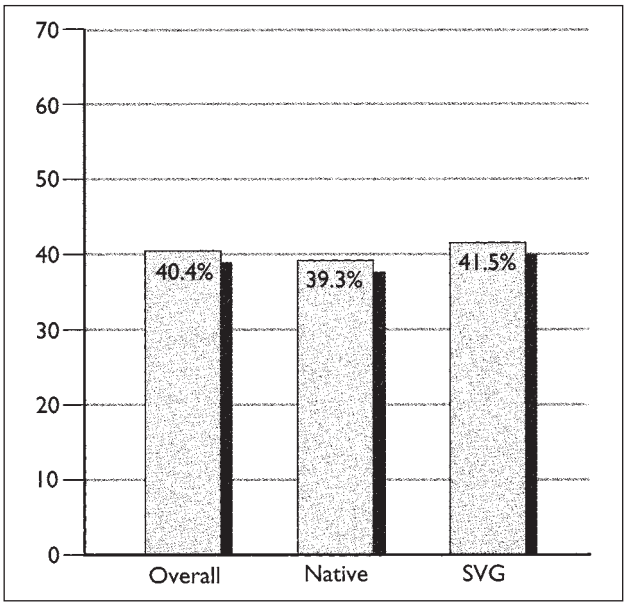


Figure 12.11
Clinical restenosis (TEC Registry).

Angiographic follow-up data at 6 months are available for 386 of 637 (60.6%) patients in whom native coronary arteries were treated and on 373 of 787 (47.4%) patients with saphenous vein graft disease. This constitutes only 53.2% (759 of 1424) of the total number of reported patients. This may produce a higher restenosis rate than is real. Overall, for patients with lesions treated in native coronary arteries and saphenous vein grafts, restenosis occurred in 444 of 759 (58.4%) patients. Of 386 patients treated for native coronary artery lesions, 202 (52.3%) restenosed compared to 242 of 373 (64.9%) in saphenous vein grafts (Fig. 12.12).

Figure 12.13 summarizes the TEC Registry data on restenosis (by patient).

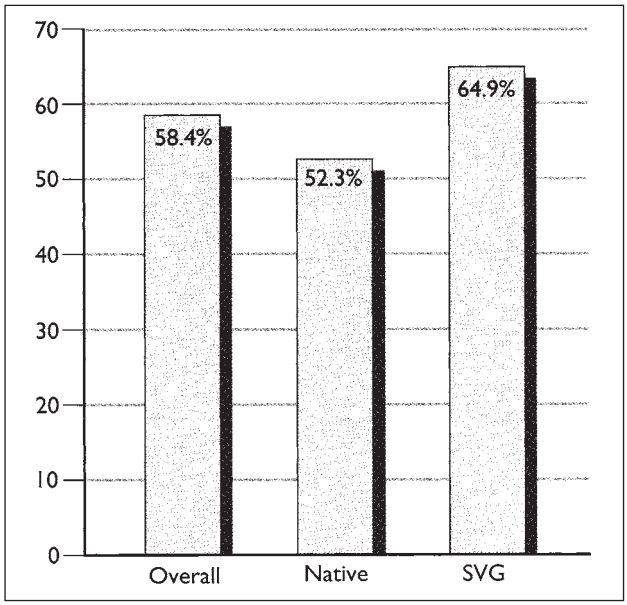


Figure 12.12
Angiographic restenosis—patients (TEC Registry).

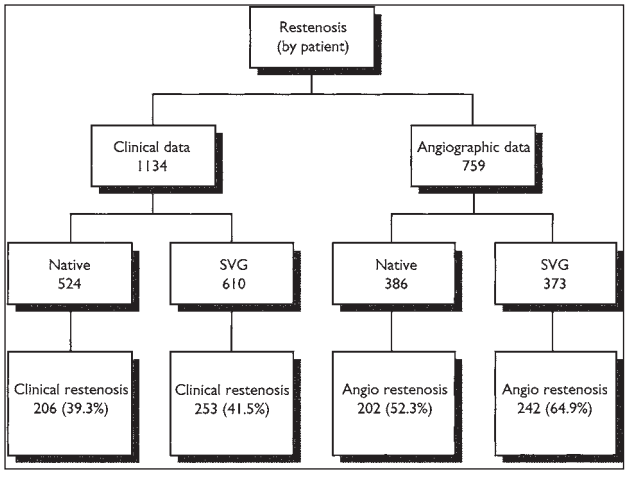


Figure 12.13
Summary of restenosis data (TEC Registry).

Angiographic follow-up data are available on 873 of 1726 (50.6%) lesions, 427 of 734 (58.2%) native lesions and 446 of 992 (45.0%) saphenous vein graft lesions. Follow-up data are also available on 604 of 1254 (48.2%) de novo lesions and 255 of 427 (59.7%) restenotic lesions. Of the 427 native lesions treated with TEC atherectomy, 232 (54.3%) restenosed. Of 604 de novo lesions, 354 (57.1%) restenosed compared to 165 of 255 (64.7%) restenosis lesions. Overall, 519 of 873 (59.5%) lesions treated by TEC, and restudied, restenosed.

Discussion

The TEC Registry data are notable for including the largest series of saphenous vein grafts treated with TEC atherectomy, and treatment of diseased vein grafts has clearly become a niche for this interventional technique.[12–18] A clinical success rate of 87% is obtained in treating these degenerated grafts (mean age of saphenous vein graft was 8.7 years). The complication and distal embolization rates after TEC atherectomy are amongst the lowest of those reported for either PTCA or the alternative new-device technology. TEC atherectomy may be particularly useful in recently occluded saphenous vein grafts associated with unstable angina.[10,12] Excision and aspiration of voluminous amounts of thrombus is successfully accomplished in these cases with low rates of distal embolization and myocardial necrosis. Such treatment often includes additional intragraft thrombolysis to dissolve any remaining thrombus and adjunctive PTCA to diminish any residual restenosis. Studies have compared the use of PTCA, urokinase or TEC atherectomy to treat recently occluded vein grafts and have recorded significantly better results with TEC atherectomy.

In native coronary arteries, the presence of thrombus again provides a rationale to perform TEC atherectomy. Acute myocardial infarction often gives rise to angiographically visible thrombus in native vessels and TEC atherectomy may have a useful role in this setting, especially if such patients are poor candidates for thrombolytic therapy, or are patients in whom thrombolytic therapy has failed.[9] Ostial lesions[15,19] and long (10–20 mm) lesions[20] may be particularly suitable. Finally, the TEC guidewire may be used to deliver other non-balloon devices, having the advantage of its stiff construction and atraumatic distal tip. [21]

Future directions

The initial experience with the TEC Registry has shown that extraction atherectomy can be performed safely and with similar risks to that of conventional PTCA.[22,23] Its greatest use has been found in the treatment of diseased saphenous vein grafts. Thrombotic, ostial and long lesions are also suitable for TEC atherectomy. Although initial restenosis data do not suggest any advantage for TEC atherectomy, improvements in equipment and technique may be useful in this regard. Currently the TEC is limited by a maximum cutter size of only 7.5 Fr (2.5 mm) and thus adjunctive PTCA is frequently needed. With the advent of larger or expandable cutting catheters, with their increased flexibility and modified cutting blades, results with TEC atherectomy should improve and may impact favourably on restenosis in specific lesion subsets.

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13

Percutaneous coronary intervention in unstable angina and non-Q-wave myocardial infarction

David R Ramsdale and Ever D Grech

The syndromes of unstable angina and non-Q-wave myocardial infarction account for approximately 2–2.5 million hospital admissions worldwide[1,2] and the evolving challenge of managing this problem is the topic of frequent discussions.[3,4] Despite recent advances in the understanding of the pathophysiology of unstable coronary artery disease and improvements in treatment,[5–7] patients still face a significant increased risk of further myocardial infarction and death in the weeks and months following the unstable episode. Because of this, it is imperative that guidelines for management and treatment of these conditions should be frequently updated[1,8] and both the British Cardiac Society and the American College of Cardiology/American Heart Association have recently published new guidelines.

Antithrombotic therapy with aspirin and heparin has dramatically improved the clinical course of patients with unstable angina[9–15] and low molecular weight heparin may be even more effective than unfractionated heparin.[15–17] Moreover, the use of the platelet glycoprotein (GP) IIb/IIIa receptor inhibitors, tirofiban[18,19] and eptifibatide[20] has been shown to reduce death, acute myocardial infarction (AMI) or recurrent angina further compared with standard therapy, thus providing a major advance in medical treatment. The pharmacology, efficacy and safety of the intravenous GP IIb/IIIa receptor antagonists in percutaneous coronary intervention (PCI) have been the subject of excellent symposia[21] and review articles in the literature.[22]

Since PTCA was introduced more than 20 years ago,[23] this technique has also been used to treat patients with unstable angina of varying severity.[24–27] The primary success rate is high but acute major complications are more common than in patients with stable angina undergoing PTCA,[28–40] probably due to the higher incidence of unfavourable clinical, anatomical and coronary morphological features in unstable patients, particularly those with rest pain or post-MI angina.[41–47] Although stenting and the new antiplatelet agents including abciximab have gone a long way to minimizing the major complications of abrupt closure, myocardial infarction and death after PTCA, even now little randomized trial data are currently available to establish an unequivocal, evidence-based, optimal treatment strategy for this serious medical problem. Controversy still exists as to whether an aggressive, early invasive and interventional approach is better than an initial conservative strategy with intervention only if symptoms continue to recur despite medical therapy. Two randomized studies were conducted in the era preceding platelet GP IIb/IIIa inhibitors and aggressive percutaneous coronary interventions with stenting but were confounded by high cross-over rates.[48–50] Although the FRISC II trial was more successful in applying the allocated treatment regimens to the invasive and conservative groups and demonstrated better outcomes for patients treated with an early invasive strategy,[51,52] current trials such as the TACTICS-TIMI 18[53] and RITA 3 may settle the issue conclusively.

This chapter focuses on the advances in the understanding and management of patients with unstable angina or non-Q-wave MI and emphasizes the role of new GP IIb/IIIa platelet inhibitors and catheter-based techniques of coronary intervention for improving outcomes in these conditions.

Pathophysiology and implications for a treatment strategy

The underlying pathology involves both atherosclerotic inflammatory disease and thrombotic mechanisms.[54–66] Inflammation promotes the erosion, fissuring or rupture of a pre-existing atherosclerotic plaque, giving rise to the aggregation and adhesion of platelets and the formation of

intracoronary thrombus that can partially or totally occlude the vessel.[67–71] However, plaque fissures are not always found beneath coronary thrombi associated with an acute fatal myocardial event. In unstable angina, occlusion of the vessel is usually subtotal and the subsequent clinical course and ECG changes are less predictable than with total occlusion.[71–74] Detachment of fragments of thrombus can cause microemboli downstream of the lesion, myocardial ischaemia and infarction. Although in most patients with unstable angina, the clinical situation stabilizes and the plaque usually heals, the underlying lesion remains and with time often becomes more severe.[57,75–78]

Clinically, unstable coronary artery disease is characterized by transient recurrent symptoms and events. The mechanical obstruction caused by the plaque, the extent of thrombus formation, the level of efficacy of collateral circulation and coronary vasomotor tone all play a part in determining whether the patient suffers myocardial ischaemia, necrosis or infarction. Numerous investigators have shown that the glycoprotein IIb/IIIa integrin mediates the final common pathway in platelet aggregation involving cross-linking of activated glycoprotein IIb/IIIa receptors on adjacent platelets by adhesive plasma proteins—primarily fibrinogen and von Willebrand factor. This understanding has led to the development of GP IIb/IIIa receptor antagonists and their use in the treatment of unstable angina and non-Q-wave MI. However, perhaps more important than the platelet thrombus which is adherent to the fissured atherosclerotic plaque is the mass of the obstructing plaque itself. Percutaneous coronary intervention (PCI) is aimed at removing or at least reducing this obstruction and improving coronary blood flow.

PTCA has been shown to be an effective method of enlarging the lumen of stenosed coronary arteries[23] which may resolve myocardial ischaemia effectively and prevent progression to total coronary occlusion in patients with unstable angina. The mechanism by which the atherosclerotic plaque is reduced is fracture of the plaque, with rupture of the intima and media and expansion of the external diameter of the artery.[79–81] Perhaps not surprisingly therefore, PTCA can be a 'two-edged sword' and aggravate thrombus formation. It has been shown that angioplasty causes endothelial denudation, platelet deposition, mural thrombus and localized vasoconstriction at the site of the arterial injury[82–84] and this may lead to vessel occlusion especially in lesions already heavily burdened by atherosclerotic plaque. This potential to intensify the ongoing thrombogenic process in patients with unstable angina partially explains the increased risk of major complications that has been reported after PTCA in such patients.[33,82–95]

The angiographic result after PTCA is not the best indicator of the vessel's true luminal diameter or its cross-sectional area and both IVUS and intracoronary angioscopy frequently demonstrate severe residual stenosis due to dissected plaque and adherent, platelet-rich thrombus.[96,97] Clinical trials have shown that anti-platelet and anti-thrombin agents can reduce the incidence of major complications after PTCA in patients with unstable angina and debulking lesions by aggressive atherectomy can also produce more predictable results than PTCA alone. However, despite excision of the unstable plaque by directional coronary atherectomy, the immediate major complication rates are probably higher in those patients with unstable, rest angina than in those with stable angina. In one study,[98] abrupt closure occurred in 5.1% and 2.6% respectively, emergency CABG surgery in 5% and 1.3% and in-hospital death in 2% and 0%. Although clinical success is very high, it is slightly lower in patients with rest/post-infarction pain (90% vs 98.7%) compared to patients with stable symptoms. Less significant differences were seen in the smaller study carried out by Umans et al.[99]

Coronary artery stenting is likely to be the best way of establishing a large post PTCA luminal diameter by mechanically displacing ruptured plaque back into the wall of the dilated coronary artery. This should minimize the effects of local thrombus formation, which can be further reduced by anti-platelet and anti-thrombotic therapy such as aspirin, clopidrogel, GP IIb/IIIa inhibitors and the anti-thrombins. Although this seems to be the case in clinical practice, randomized trial data to support this form of therapy for patients with unstable angina are still lacking. Nevertheless, it is reasonable to advocate the use of coronary artery stenting together with pharmacologic agents in such high-risk patients in a set of guidelines for treatment.

Clinical presentation

There is no universally accepted definition of unstable angina, which has been described as a clinical syndrome between stable angina and acute myocardial infarction. This broad definition includes many types of patients who present with a variable history due to varying pathophysiological mechanisms operating at different times and who have different outcomes.

Diagnosis is based on the clinical history, the admission or subsequent 12-lead ECG and cardiac enzymes or other markers in plasma. Various imaging tests can confirm myocardial perfusion or wall motion abnormalities.

The US Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guidelines for the diagnosis and treatment of unstable angina have helped to refine the assessment and management of patients.[1] Perhaps the most frequently cited classification of patients with unstable angina has been proposed by Braunwald[100] and patients usually present with one of the following patterns of symptoms:

(1) New onset (<2 months) of severe angina (CCSC Class III or IV).
(2) Abrupt worsening of previous angina, with symptoms becoming more frequent, more severe or prolonged (>15 minutes) and less responsive to nitroglycerine.
(3) Prolonged angina occurring at rest.

The ECG may show:

- ST segment depression
- transient ST segment elevation that resolves spontaneously or after GTN
- T-wave inversion
- evidence of previous MI
- left bundle branch block
- minor non-specific changes
- no abnormalities

but should not show persistent acute ST-segment elevation. Continuous ECG ST-segment monitoring provides additional information on diagnosis and risk assessment. The Prospective Registry of Acute Ischaemic Syndromes (PRAIS-UK) has shown that ECG abnormalities, particularly ST-segment depression, are important markers of risk of death or new MI[101] and the severity of ST-depression on the presenting ECG predicts survival of patients at up to 8 years, with those >2 mm having the worse outcome.[102]

C-reactive protein (CRP), an acute phase reactant marker for underlying systems inflammation, is elevated in patients with acute coronary syndromes and raised levels have been shown to be independent predictors of risk for death, acute MI and stroke.[103,104] Moreover, CRP is of additional prognostic value to troponin measurements and patients with both elevated CRP and troponin release are at highest risk.[105]

Conventional cardiac enzymes (CK, CK-MB, AST, LDH) may be normal or elevated. Detection in the blood of elevated troponin I or T concentrations is highly specific for myocardial damage and identifies patients at high risk for complications.[106–112] Normal or undetectable troponin levels >8 hours after the onset of symptoms can identify patients with a low risk of early complications.

Those patients with angina at rest, ST/T-wave abnormalities and raised troponin levels and elevated CRP who fail to settle despite hospitalization and full medical treatment have the worst prognosis, as do those with angina at rest within 48 hours of MI with reversible ECG changes.[113–118]

Management of unstable angina and non-Q-wave MI (Fig. 13.1)

For patients with a diagnosis of unstable angina or non-Q-wave infarction, the overall risk of death or further infarction is about 10% during the first 30 days and an additional 35–50% will experience recurrent ischaemia despite medical therapy.[48,119–122] Thus, patients presenting with symptoms consistent with these acute coronary syndromes should be referred urgently for further assessment and admitted to a coronary care unit or acute chest pain ward with monitoring facilities. They should be assessed by a cardiologist on the day of presentation, have a 12-lead ECG performed and blood samples for cardiac enzymes taken. Ideally, blood samples for troponin I or T should be taken immediately and a minimum of 8 hours after the onset of symptoms.

In patients admitted with suspected unstable angina but whose symptoms do not recur, the troponin is negative and the ECG remains normal (or unchanged compared to an ECG prior to symptom onset), exercise stress testing should be performed pre-discharge. If this is not practically possible, such patients can be discharged for out-patient exercise stress testing within 2 weeks.

Medical treatment involves bed rest, as well as anti-thrombotic and anti-ischaemic medication. It should be commenced immediately on admission and continued in those with probable and confirmed unstable angina.

Treatment

Anti-thrombotic

All patients should receive aspirin 75–150 mg daily unless contraindicated.[9–12] 300–600 mg aspirin should be given on presentation to those patients not currently taking it. If the patient is allergic to or intolerant of aspirin, clopidrogel 300 mg stat and then 75 mg daily should be given instead.

Intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) should be administered for at least 48 hours and for up to 1 week or longer in cases of recurrent ischaemia, in patients with extensive anterior ischaemia or where myocardial revascularization is delayed or contraindicated.[11,12,123,124] If sc LMWH has been used, patients should, if practicable, be converted to UFH in advance of invasive investigation and/or revascularization after discussion with the interventional cardiologist. UFH requires careful monitoring because of its complex pharmacokinetics, the variability in patient response and the risk of bleeding. LMWHs may be more effective than UFH,[119,124–126] have a predictable dose–response curve and can be administered without the need for monitoring blood levels—although this is not ideal if PCI is being performed.

Hirudin does not appear to have any advantages over heparin except in cases of heparin-induced thrombocytopenia.[127]

The use of thrombolytic agents in unstable angina cannot be supported.[128–144] Moreover, the use of thrombolytic therapy as an adjunct to PTCA for recurrent coronary occlusion in patients in unstable angina is also unsubstantiated and high reocclusion rates are common.[145–148]

A GP IIb/IIIa inhibitor should probably be given to:

(1) Patients with unstable angina or non-Q-wave MI with elevated troponin who are scheduled to undergo PCI using UFH.

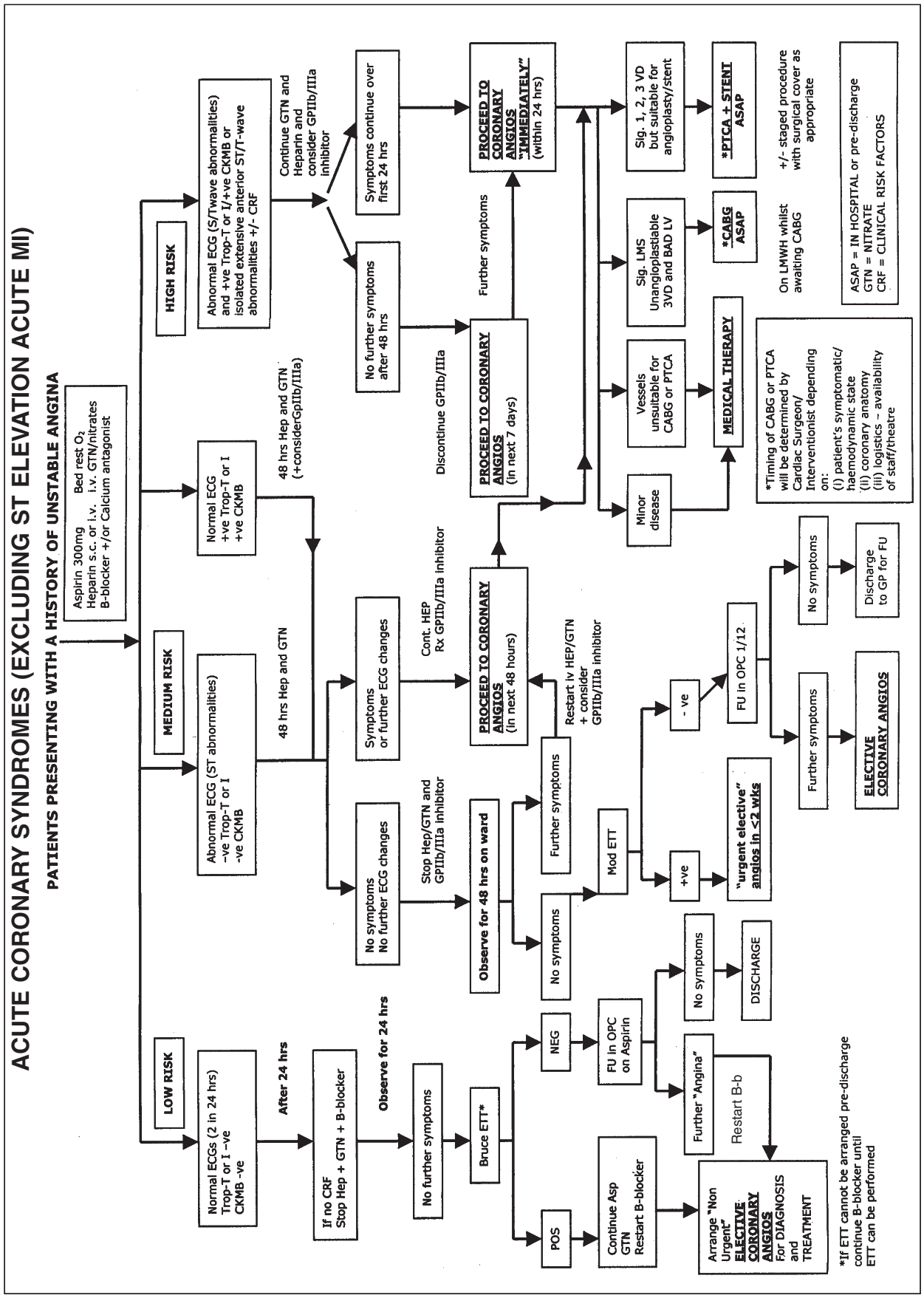


Figure 13.1
Flow chart indicating an approach to managing patients with a history of unstable angina.

(2) Patients with recurrent ischaemia refractory to aspirin and heparin for whom PCI is delayed or contraindicated.
(3) Diabetic patients with unstable angina or non-Q-wave MI requiring PCI.

However, whether these agents should be used in all patients with unstable angina remains debatable.

Four large randomized, placebo-controlled trials (the 4Ps: PRISM, PRISM PLUS, PARAGON and PURSUIT) evaluated parenteral GP IIb/IIIa antagonism in this syndrome irrespective of whether or not patients were about to undergo PCI. Table 13.1 summarizes the data for the primary endpoints for each trial.

The PRISM study of tirofiban examined the effect of short-term medical stablization of a 48-hour infusion of heparin or tirofiban.[18] At 48 hours the primary composite endpoint of death, MI or refractory ischaemia was reduced by tirofiban (3.8% vs 5.9% $P = 0.014$). At 30 days, however, the benefit was lost.

The PRISM-PLUS trial evaluated adjunctive tirofiban as part of an early invasive strategy. Originally the study was designed with three arms: tirofiban, heparin or tirofiban with heparin.[19] The tirofiban monotherapy arm was terminated prematurely owing to excess mortality at 7 days. The 7 day plus 30 day composite endpoint of death, new MI or refractory ischemia significantly favoured treatment with tirofiban plus heparin vs heparin alone (12.9% vs 17.9%; $P = 0.004$ at 7 days and 18.5% vs 22.3%; $P = 0.039$ at 30 days) and death/MI at 7 and 30 days were lower in the tirofiban plus heparin group—4.9% vs 8.3% ($P = 0.006$) and 8.7% vs 11.9% ($P = 0.03$), respectively.

The PARAGON study compared five strategies by use of a factorial design: two doses of lamifiban, each with or without heparin, and heparin alone.[149] At 30 days the primary endpoint of death or MI was similar among treatment groups; no benefit was conferred by lamifiban. When coupled with heparin, lamifiban increased haemorrhagic events without any efficacy advantage. However, for the 6 month composite endpoint, benefit emerged for patients assigned to low-dose lamifiban plus heparin (12.6% vs 17.9% for placebo plus heparin, $P = 0.025$).

The largest PURSUIT trial, randomized 10 948 patients to receive eptifibatide or placebo (in addition to standard therapy) for 72–96 hours.[20] Eptifibatide treatment significantly reduced the combined incidence of death or MI at 30 days compared with placebo (14.2% vs 15.7%, $P = 0.04$). The benefits were only present in patients receiving eptifibatide and heparin.[150]

Even pooling the data, no significant difference in mortality is seen at any time point out to 6 months. However, the placebo mortality was so low (<30%) as to make it impossible to detect without an enormous sample size. For the endpoints death/MI or revascularization, there was a significant reduction in event rates out to 6 months. Extrapolating the data to numbers needed to treat would suggest that approximately 15 deaths or MIs could be prevented by 1000 patients treated with GP IIb/IIIa antagonists in unstable angina. The cost of these agents and the modest benefit that they offer probably argues against their widespread use and high-risk subgroups probably need to be targeted—if they can be identified!

Recently the GUSTO-IV ACS trial in 7800 patients with acute coronary syndromes not undergoing PCI showed no benefit for abciximab (0.25 mg/kg bolus) when added to aspirin and heparin and followed by an infusion (0.125 μg/kg/min to a maximum of 10 μg/kg/min) for either 24 or 48 hours.[151] The composite MI/death rate was 1.5%, 1.9% and 2.2% and 8.0%, 8.2% and 9.1% at 24 hours and 30 days respectively for placebo (n=2598), abciximab given for 24 hours (n=2590) and abciximab given for 48 hours (n=2612). The reasons for this surprising result are unclear but the event rates were extremely low in all groups.

Table 13.1 Randomized trials of GPIIb/IIIa inhibitors in unstable angina and non-Q-wave MI.

Trial	*Patients*	*GP IIb/IIIa inhibitor*	*Heparin*	*30 day composite endpoint*	*Endpoint*		*p-Value*
					Placebo	*Drug*	
PRISM[18]	3 232	Tirofiban	Control	Death, MI, RI[$]	17.1%	15.9%	0.380
PRISM-PLUS[19]	1 570	Tirofiban	Yes	Death, MI, RI	22.3%	18.5%	0.039
PARAGON[149]	2 282	Lamifiban	Randomized	Death or MI	11.7%	11.3%[1]	0.804
PURSUIT[20]	9 461	Eptifibatide	Optional	Death or MI	15.7%	14.2%	0.032
ITT* pooled data[2]	16 545				15.6%	13.8%	<0.01
GUSTO IV ACS[151]	7 800	Abciximab	UFH or LMWH	Death or MI	8.0%	9.1%[#]	ns

*ITT= intention to treat
[1] Event rate for patients treated with both low- and high-dose lamifiban
[2] Includes all patients treated with GP IIb/IIIa inhibitors regardless of the dosing arm
[$] RI = Refractory Ischaemia
[#] Abciximab infusion for 48 hours

The trial evidence suggesting the benefits of giving GP IIb/IIIa inhibitors in patients with unstable angina to be treated by PCI will be discussed later.

Anti-ischaemic

Intravenous, oral or buccal nitrates should be given to relieve pain or ischaemia.[152–160] Beta-blockers should also be given to relieve pain and ischaemia when there is no contraindication such as hypotension, asthma or heart failure and calcium channel blockers can be added if further symptoms or ischaemia occur or instead of a beta-blocker if it is contraindicated.[161–165]

Risk assessment and referral for coronary angiography

Patients with unstable angina and non-Q-wave may have further serious cardiac events within the next 6 months. It is estimated that the mortality rates of patients treated medically vary from 2% at 1 month, to 4%, 6% and 10% after 3, 6 and 12 months, respectively.[166] Myocardial infarction occurs in 9% of patients during the first 6 months, most of which occur within the first month. After 1 year, an average of 14% of patients have developed MI.

Patients should have their cardiac prognosis assessed by estimating the risk of death or further cardiac events. Those deemed to be at high risk should undergo diagnostic coronary angiography which often provides the best prognostic information.

Figure 13.1 shows a flow chart which indicates an appropriate approach for managing patients presenting with a history of unstable angina. Generally:

- Patients with continued, recurrent or refractory angina despite medical treatment over the first 24 hours should be referred immediately for coronary angiography with a view to myocardial revascularization for relief of symptoms. This is based on the fact that 1–5% of these medically refractory patients will die and 2–10% will progress to MI before hospital discharge[11,12,167,168] and is supported by the FRISC-II study.[51,52]
- Patients with unstable angina or non-Q-wave MI whose symptoms have settled/stabilized but who are at intermediate or high risk of death or further cardiac events should be referred for coronary angiography for further assessment within the next 7–14 days. These include patients with reversible ECG changes and troponin positive tests or abnormally raised CK-MB and those with extensive anterior ischaemic ECG changes. They should have heparin continued until 48 hours of freedom from symptoms or new ischaemic ECG changes or until the time of angiography.
- Patients whose symptoms settle who have an abnormal ECG or troponin positive test (but not both) who have early inducible ischaemia during exercise stress testing, e.g., first two stages of Bruce protocol, should undergo coronary angiography within 2 weeks.

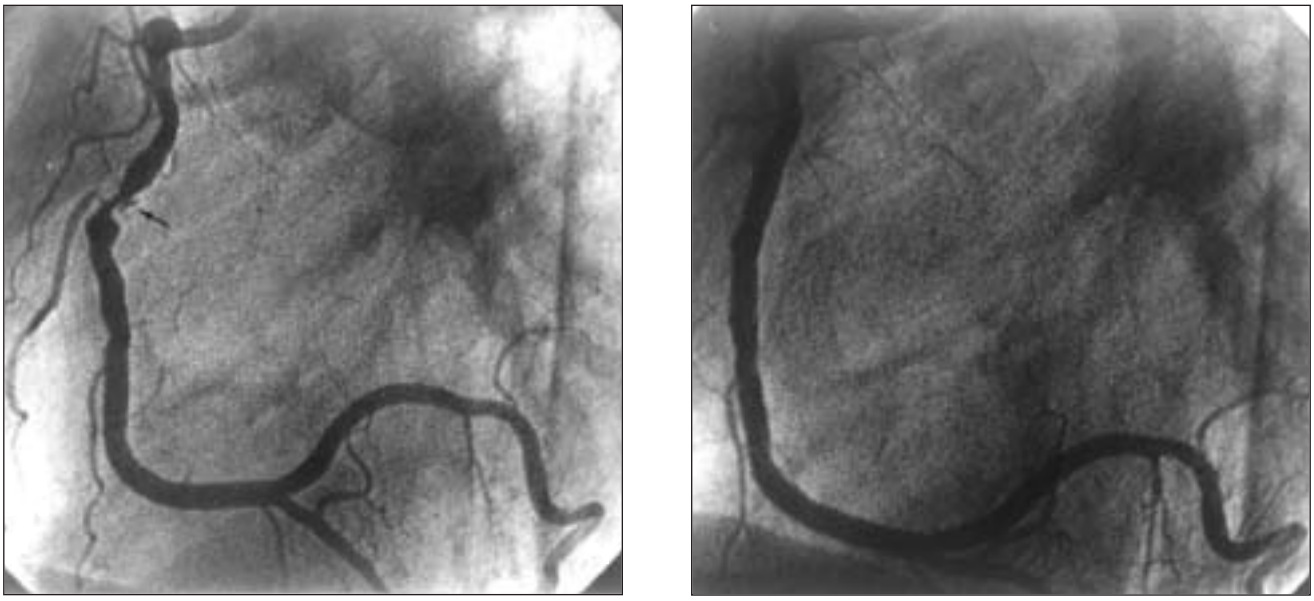
Certain other high-risk groups of patients should also be considered for early diagnostic coronary angiography and these are shown in Table 13.2.

Coronary angiographic findings

Coronary angiography in patients with unstable angina may show anything from single to multiple lesions, single or multivessel disease, recent or chronic occlusions and left main stem disease. In the TIMI-3A trial, angiography in 391 patients with unstable angina or non-Q-wave MI showed that a coronary stenosis >60% in a major vessel occurred in 0, 1, 2, 3 vessels or the left main in 15%, 27%, 31%, 20% and 4%, respectively.[169] Not infrequently, complex lesion morphology and bifurcation lesions are identified and bulky, high-grade, complex ulcerated or fissured plaques are more commonly seen in patients with unstable angina (Fig. 13.2). Lesion-associated thrombus is more often seen than in patients with stable angina symptoms. Directional coronary atherectomy has even retrieved ulcerated plaques with adherent thrombus (Figs. 13.3 and 13.4) supporting the use of vigorous antiplatelet regimens in treating this condition.

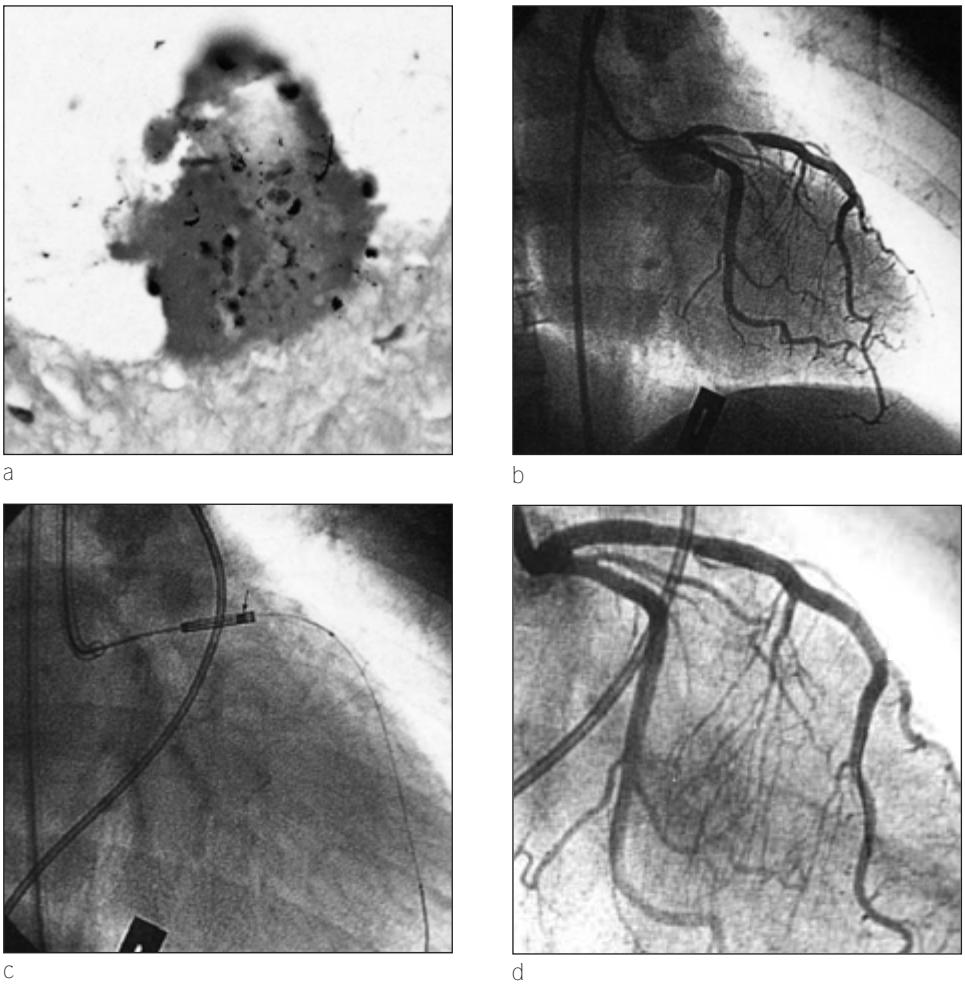
Table 13.2 High-risk patients in whom early diagnostic coronary angiography should be considered.

Continued or recurrent or refractory angina
Abnormal ECG and elevated troponin
Extensive anterior ischaemic ECG changes
Haemodynamically unstable
Previous MI
Ventricular arrhythmias
Left ventricular impairment
Age > 65 years
Co-morbidity eg diabetes mellitus
Patients presenting with abnormal ECG or troponin elevation who settle on medical treatment but who have easily inducible ischaemia on exercise stress test



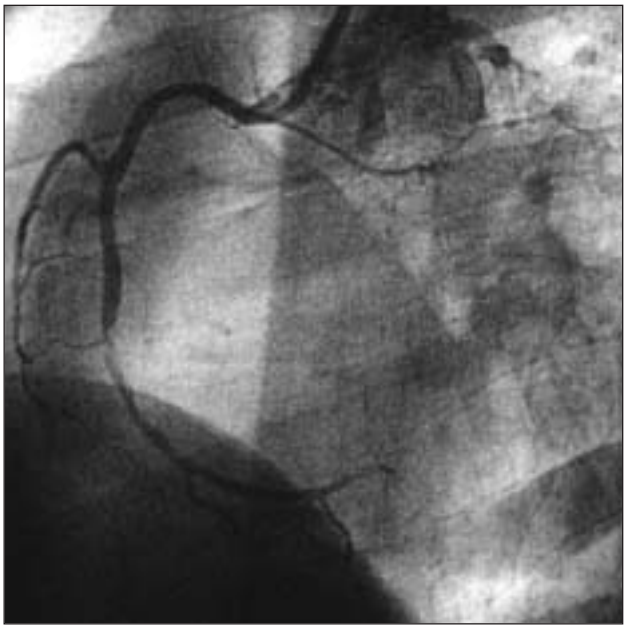
a b

Figure 13.2
(a) Angiogram showing high-grade, complex, ulcerated plaque (arrow) in right coronary artery in a patient with severe unstable angina. (b) Result after PTCA and stent implantation.



a b c d

Figure 13.3
(a) Atherectomy specimen removed by directional coronary atherectomy (DCA) showing ulcerated plaque and adherent thrombus. This 46 year old lady presented with a short history of unstable angina due to a severe proximal left anterior descending coronary artery stenosis (b). (c) Arrow shows cutter of atherectomy device at end of housing. The specimen shown above was removed from the nosecone. (d) Result after DCA.



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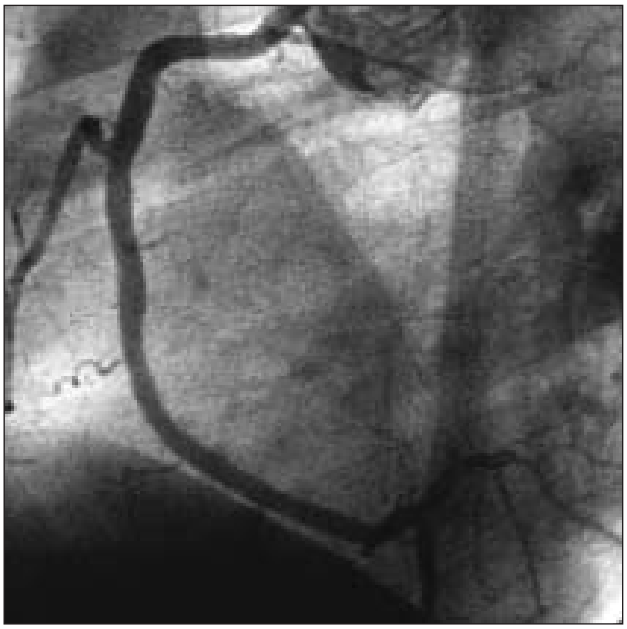

b

Figure 13.4
Acute occlusion is not uncommonly found in patients presenting with unstable angina or non-Q-wave MI as in this 53 year old man with a right coronary artery occlusion (a). Result after PTCA and stent implantation (b).

Intra-aortic balloon counterpulsation support should be considered if the patient is hemodynamically compromised or if an anatomically life-threatening lesion is present.

Strategy for PCI in unstable angina

For each individual patient, the risks and benefits of coronary intervention must be carefully assessed by the interventional cardiologist in charge of the patient,[170] and usually after discussion with cardiac surgical colleagues.

Although there are no absolute contraindications to PCI in unstable angina, left main stem stenosis and severe three-vessel disease including chronic total occlusions and impaired left ventricular function should ideally be referred for surgical revascularization. Lesions considered unsuitable for angioplasty because of vessel tortuosity, complex morphology or heavy calcification should be similarly rejected for PCI. When surgery is indicated, GP IIb/IIIa inhibitors should be stopped immediately to avoid the increased risk of bleeding complications. However, where possible PCI should be preferred to CABG surgery because of the higher operative morbidity and mortality associated with CABG surgery in acute coronary syndromes. The operative mortality and perioperative MI rate in patients with unstable angina has been reported to be between 1.8% and 7.7% and 1.0% and 16.7%, respectively.[171–179] CABG surgery for post-MI angina (<30 days) has an operative mortality rate of 0–16% and perioperative MI rate of 0–15%.[180–188]

Generally, PCI in unstable angina is performed 'ad hoc' after the diagnostic procedure.[189] PCI might necessitate multilesion/multivessel stenting, the use of alternative technologies such as atherectomy, thrombectomy or cutting balloon techniques and even staged procedures. It may be most appropriate to treat the 'culprit' lesion as an emergency to stabilize the patient's condition[190–192] and proceed to deal with other significant lesions 1–2 weeks later during a second PCI procedure or by semi-elective CABG if the other lesions present are unsuitable for PCI. However, for lesions that are suitable for PCI, stenting has provided such a degree of safety and freedom from abrupt closure that many interventionists feel comfortable at dealing with all high-grade lesions that are present at the one sitting. Wherever possible, stenting should be preferred to PTCA alone. Clopidogrel 300 mg should be given orally at the time of stent deployment and 75 mg daily thereafter for 1 month. There appears to be no value in post procedure heparinization after successful PCI.[193]

Results of PCI in unstable angina

Several reports from more than a decade ago showed that PTCA was safe and effective in patients with unstable angina.[24–27] However, success rates from PTCA in unstable and post infarct angina were slightly lower (85–89%) than for stable angina (92%) and complication rates were higher (Tables 13.3–13.6).[29,30,34–47,194–204] These included a

procedure-related mortality of 0.3–1.3%, an MI rate of 5.1–6.3% and emergency CABG surgery of 5.8–6.8% due to a higher risk of abrupt closure as a result of further endothelial injury, increased platelet and clotting activity and vasospasm related to plaque injury. Similarly, other procedures such as atherectomy had a slightly lower success rate and a higher complication rate than in patients with stable angina. The prognosis after initial successful PTCA is good with a low incidence of late mortality and a low occurrence of late non-fatal MI.[35]

Over the last 10 years balloons, guidewires, guide catheters and fluoroscopy have all been improved and new

Table 13.3 PTCA for initially stabilized unstable angina.

Author	*Year*	*No. of patients*	*Success rate (%)*	*Major complication rate*		
				Death(%)	*MI(%)*	*CABG(%)*
Quigley et al[194]	1986	25	81	4	12	12
de Feyter et al[195]	1987	71	87	0	10	12
Steffenino et al[196]	1987	89	90	0	5	5
Myler et al[29]	1990	220	85	0	6.6	6.1
Stammen et al[30]	1992	631	91	0.3	3.6	4.7
Total		1036				
Average			89	0.3	5.1	5.8

Table 13.4 PTCA for refractory unstable angina pectoris.

Author	*Year*	*No. of patients*	*Success rate (%)*	*Major complication rate*		
				Death(%)	*MI(%)*	*CABG(%)*
Timmis et al[34]	1987	56	70	5.4	7.1	12.5
de Feyter et al[35]	1988	200	89.5	0.5	8	9
Plokker et al[36]	1988	469	88	1	4.9	3
Sharma et al[37]	1988	40	88	0	0	12
Perry et al[38]	1988	105	87	2	9	4
Myler et al[29]	1990	310	79	0.3	6.5	9.4
Morrison et al[39]	1990	56	84	3.6	7.2	9
Rupprecht et al[40]	1990	202	83	2	6.5	7.9
Total		1438				
Average			85	1.3	6.3	6.8

Table 13.5 PTCA for early postinfarction angina pectoris.

Author	*Year*	*No. of patients*	*Success rate (%)*	*Major complication rate*		
				Death(%)	*MI(%)*	*CABG(%)*
de Feyter et al[41]	1986	53	89	0	8	8
Holt et al[42]	1986	70	76	2	5	12
Gottlieb et al[43]	1987	47	91	2	4	2
Safian et al[44]	1987	68	87	0	1.5	1.5
Hopkins et al[45]	1988	54	81	0	0	4
Sur'pranata el al[46]	1988	60	85	0	5	7
Morrison et al[47]	1990	66	88	3	3	3
TIMI-II[197]	1989	216	92	1	11	7.9
Total		634				
Average			88	1.1	6.3	6.5

Table 13.6 PTCA for stable angina pectoris.

Author	*Year*	*No. of patients*	*Success rate (%)*	*Major complication rate*		
				Death(%)	*MI(%)*	*CABG(%)*
Bredlau et al[198]	1985	1167	92	0.2	2.5	2.7
Hartzler et al[199]	1986	3986	91	1.2	0.9	1.8
NHLBI Registry[200] (1985–86)	1988	839	91	0.2	3.5	1.8
Tuzcu et al[201]	1988	2677	93	0.3	1.1	3.6
de Feyter et al[202]	1988	523	92	0.2	2.3	1.9
O'Keefe et al[203]	1989	404	90	1.2	4.2	3.4
Myler et al[204]	1992	533	92	0	1.7	2.1
Total		10 129				
Average			92	0.7	1.6	2.5

devices have further helped to reduce the complication rates and improve the success rates after PTCA. Stents and new anti-platelet agents have improved the outcome further, even though more complex and difficult cases are being addressed in today's clinical practice. Although there are no randomized trials in unstable angina to prove this unequivocally, Singh et al from the Mayo Clinic reviewed >7000 patients who underwent intervention in unstable angina. They showed that procedural success was better (95.9% vs 83.8%), and emergency CABG (0.9% vs 3.6%) and death (1.4% vs 2.6%) were less frequent after stenting than after PTCA alone. Moreover after 1 year, angina (23.5% vs 47.4%), Q-MI (0.4% vs 1.9%), CABG (6.5% vs 19.6%) and a repeat procedure (13.8% vs 30.6%) were all less common after stenting/new interventional techniques than after PTCA alone.[205,206]

Data from Marzocchi et al[207,208] and most recently from the FRISC II Investigators[51,52] showed that in the current era of stenting and new anti-platelet agents, stenting had a high (95%) primary success rate in unstable angina. Moreover, the latter study showed that an early invasive strategy of treatment with percutaneous coronary intervention or CABG surgery produced a significantly better outcome than in patients undergoing a non-invasive treatment strategy. Not only was death and MI reduced at 6 months in patients in the 'early invasive group' but they had less angina and severe heart failure, required less medication for angina and fewer hospital readmissions for angina, MI and revascularization.

Trials of GP IIb/IIIa antagonists in PCI

Six large randomized placebo controlled trials of intravenous GP IIb/IIIa antagonists[209–214] define our current knowledge regarding the adjunctive use of these agents during coronary intervention. These trials are reviewed below. In summary, platelet GP IIb/IIIa inhibition improves outcomes in PCI, even in the era of intracoronary stenting. Pre-treatment with GP IIb/IIIa blockade for up to 24 hours prior to PCI appears to be beneficial and, in general, therapy should continue for at least 12 hours after PCI with abciximab and perhaps longer (20–36 hours) with eptifibatide and tirofiban. The benefits of treatment are seen early, are most likely related to antithrombotic effects and are durable over the long term. Convincing reductions in restenosis rates have only really been shown for diabetics receiving stenting + abciximab in the EPISTENT trial.[212] Although it has been suggested that high-risk patients derive the greatest benefit from GP IIb/IIIa inhibitors, the ischaemic complications of both low- and high-risk interventions can be reduced. Furthermore, it appears that the benefit applies to all modalities of PCI, be it PTCA alone, atherectomy or coronary stenting. Although abciximab has shown a greater magnitude of benefit compared with placebo in PCI trials than have the small molecule peptide or non-peptide inhibitors, such indirect comparisons are hazardous. The recent early termination of the ESPRIT trial[215] after the enrolment of 2064 patients due to overwhelming efficacy for eptifibatide (35% reduction in death/MI/urgent TVR at 30 days; $P = 0.003$) compared with placebo in the setting of coronary stenting is noteworthy. Studies need to compare the efficacy of the various GP IIb/IIIa inhibitors directly. Some have speculated that the unique biological properties of abciximab compared with the other two agents (ie its longer biological half-life or its ability to block integrins other than the GP IIb/IIIa receptor) might give it additional therapeutic benefit. Currently, however, the clinical relevance of these differences remains speculative. In using an equivalency design to compare the efficacy of tirofiban and abciximab in coronary interventions, the TARGET trial (do Tirofiban And Reopro Give similar Efficacy outcomes Trial) may provide some useful insights.[216]

In this trial of 4812 patients undergoing planned coronary stent implantation, the small molecule GP IIb/IIIa inhibitor,

tirofiban was associated with a significantly greater incidence of the primary combined endpoint of death, non-fatal MI and urgent target vessel revascularization at 30 days than abciximab. Patients randomized to tirofiban (n = 2,398; 10 μg/kg bolus followed by 0.15 μg/kg/min infusion for 18–24 hours) showed a 26% relative increase in the combined endpoint compared with those treated with abciximab (n = 2414; 0.25 mg/kg bolus followed by a 0.125 μg/kg/min infusion for 12 hours) (7.55% vs 6.01%; p=0.037) (death: 0.5% vs 0.4% (ns); non-fatal MI: 6.9% vs 5.4% (p = 0.04); urgent TVR: 0.8% vs 0.7% (p=ns)). The added benefit of abciximab may be due to the agent inhibiting other processes involved with platelet aggregation and atherosclerotic plaque stability by binding to receptors on monocytes including Mac-1 and vitronectin in addition to the GP IIb/IIIa integrin on platelets, whereas the small molecule agents such as tirofiban act only on the GP IIb/IIIa integrin. In this study, minor bleeding and thrombocytopaenia were commoner with abciximab than with tirofiban (5.6% vs 3.5%; p = 0.008) but major bleeding was not significantly different (0.95% vs 1.1%).

The trials related to the use of GP IIb/IIIa inhibitors in patients with unstable angina and non-Q-wave MI undergoing PCI include EPIC, EPILOG, CAPTURE, EPISTENT, IMPACT-II and RESTORE and are summarized in Table 13.7. However, it must be remembered that although CAPTURE involved 100% of patients with acute coronary syndromes, only 45% and 68% of patients in EPIC and EPILOG had intervention for this clinical condition.

EPIC[210]

The first of the PTCA trials was EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications); 2099 patients undergoing high-risk PTCA were randomized to receive either an abciximab bolus + a 12 hour infusion, an abciximab bolus + a 12-hour placebo infusion or a placebo bolus + a 12-hour placebo infusion. The primary endpoint was the 30-day composite outcome of death, MI or urgent revascularization. There was a 35% reduction in the primary endpoint with the abciximab bolus + 12-hour infusion (8.3%) vs placebo (12.8%). The abciximab bolus alone was not significantly better than placebo, suggesting that a more prolonged period of platelet inhibition was necessary for clinical efficacy.

The benefit of the abciximab bolus and infusion was maintained over the long term, with a 23% reduction in the incidence of the composite endpoint at 6 months[217] and a 13% reduction at 3 years.[218] The early reduction in outcomes was primarily related to a decrease in the incidence of periprocedural MI and the need for subsequent revascularization with little effect on mortality. However, by 3 years there was a 60% decrease in mortality (5.1% abciximab vs 12.7% placebo) in patients enrolled with refractory angina or evolving MI.

The possibility of abciximab preventing restenosis was suggested when 6-month follow-up revealed a significant decrease in target vessel revascularization (TVR) (27.0% abciximab bolus + infusion vs 35.1% placebo),[217] but supporting data are lacking. The efficacy of abciximab observed in this trial was somewhat tempered by a marked increase in bleeding risk (14% abciximab vs 7% placebo). The majority of bleeds occurred at vascular access sites and were attributed to the high doses of heparin used in conjunction with abciximab in this trial.

EPILOG[211]

The EPILOG (Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade) trial was a

Table 13.7 Randomized trials of GPIIb/IIIa inhibitors in PCI

Trial	*Patients*	*%ACS**	*GP IIb/IIIa inhibitor*	*30 day composite endpoint*	*Endpoint Placebo*	*Drug*	*p-Value*
EPIC[210]	2099	43%	Abciximab	Death, MI, UR[$]	12.8%	8.3%	0.009
EPILOG[211]	2792	68%	Abciximab	Same	11.75%	5.2%	<0.001
EPISTENT[212]	2399	33%	Abciximab	Same	10.8%	5.3%	<0.001
IMPACT-II[213]	4010	41%	Eptifibatide	Same	11.4%	9.3%	0.060
RESTORE[214]	2141	100%	Tirofiban	Death, MI, TVR[$]	12.2%	10.3%	0.160
CAPTURE[209]	1265	100%	Abciximab	Death, UR	15.9%	11.3%	0.012
ESPRIT[215]	2064	18%	Eptifibatide	Death, MI, UTVR[$]	10.5%	6.8%	0.003

*ACS = acute coronary syndromes
[$] UR = Urgent Revascularization
[$] TVR=Target Vessel Revascularization
[$] UTVR=Urgent Target Vessel Revascularization

follow-up trial to the EPIC trial and was designed to assess whether the benefits of abciximab could be extended to a broader range of patients undergoing PCI. It also sought to assess whether a less aggressive, weight-based heparin-dosing regimen could decrease the high rate of bleeding seen in EPIC. Patients were randomized to: (1) abciximab bolus + 12 hour infusion + weight-adjusted, low-dose heparin (70 U/kg); (2) abciximab bolus + 12 hour infusion + weight adjusted, standard-dose heparin (100 U/kg) or (3) placebo + weight-adjusted, standard-dose heparin (100 U/kg). The primary outcome was the composite of death, MI and urgent revascularization at 30 days.

The trial was terminated prematurely with 2792 patients enrolled after an interim analysis revealed a 57% decrease in the composite endpoint associated with abciximab treatment (5.2% low-dose heparin, 5.4% standard-dose heparin) vs placebo-treated patients (11.7%). There was no difference in the composite between the two abciximab treatment groups, and no significant differences in bleeding rates between any of the three treatment regimens; placebo (3.1%), abciximab + low-dose heparin (2.0%) and abciximab + standard-dose heparin (3.5%).

Follow-up at 1 year suggested a sustained benefit of abciximab over placebo, but no effect was seen on TVR rates at 6 months. This lack of benefit with respect to TVR was in contrast to the EPIC study, thereby creating some doubt that abciximab prevented restenosis.[219] However, in the wake of the EPIC trial, EPILOG reconfirmed the efficacy of abciximab and showed that the drug's benefits could be extended to a much broader range of patients undergoing PCI, with an acceptably low bleeding risk when used with weight-adjusted, low-dose heparin.

CAPTURE[209]

The CAPTURE (c7E3 Antiplatelet Therapy in Unstable Refractory Angina) trial was designed to assess the efficacy of abciximab in high-risk unstable angina patients who were candidates for PCI. The purpose of this trial was to assess a strategy of initiating GP IIb/IIIa inhibition prior to coronary intervention in patients with unstable coronary disease and angiographically-suitable lesions. After diagnostic coronary angiography and prior to coronary intervention, patients were randomized to receive abciximab or a placebo infusion for 18–24 hours prior to, and continuing for 1 hour after, the procedure.

After the recruitment of 1265 patients, the trial was terminated prematurely due to the observation of a statistically significant 29% reduction in the 30-day composite endpoint of death, MI and urgent revascularization favouring abciximab infusion (11.3% abciximab vs 15.9% placebo). Further analysis showed that abciximab reduced the risk of MI prior to angioplasty (0.6% vs 2.1%) and the greatest benefit was seen in patients with elevated troponin levels. These observations generally support the practice of using 'upstream' GP IIb/IIIa inhibition for acute coronary syndromes, particularly in those patients at highest risk (ie troponin-positive patients) who are candidates for PCI. These results have also raised abciximab's potential efficacy as an agent to improve outcomes associated with unstable angina, independent of coronary intervention. Although current data and drug approval are limited to patients in whom PCI is planned, future studies will extend abciximab's evaluation to ACS patients undergoing medical therapy with only provisional PCI. Interestingly, later follow-up showed that the early clinical benefits observed in the CAPTURE trial were actually lost over time, with no difference in the composite outcome at 6 months (31.0% abciximab vs 30.8% placebo). This observation has led some to question the adequacy of the short (1 hour) post procedural abciximab infusion in terms of maintaining durable benefits over the long-term. In addition, when considered with the EPILOG trial results, these 6-month results suggest that abciximab's effect on restenosis after PTCA is, at best, minor.

EPISTENT[212]

Until recently, abciximab was the only parenteral GP IIb/IIIa inhibitor to be evaluated in the setting of coronary stenting. The EPISTENT (Evaluation of Platelet IIb/IIIa Inhibition for Stenting) trial assessed the therapeutic benefits of abciximab in a broad range of patients undergoing PTCA and stenting. This trial is relevant to current interventional treatment as it is the first published study to have examined the incremental benefit of adding GP IIb/IIIa inhibition to coronary stent procedures.

In the trial, 2399 patients were randomized to receive: (1) stenting + placebo infusion; (2) stenting + abciximab bolus and infusion or (3) PTCA + abciximab bolus and infusion. The primary endpoint was the 30-day composite of death, MI or urgent revascularization. Based on the EPILOG results, patients randomized to abciximab therapy were treated with low-dose heparin (70 U/kg), while those receiving placebo (stent alone) received high-dose heparin (100 U/kg).

The primary 30-day endpoint occurred in 10.8% of stenting + placebo, 5.3% of stenting + abciximab patients and 6.9% of PTCA + abciximab patients ($P = 0.001$). Thus, there was a 51% reduction in ischaemic complications resulting from abciximab administration in patients receiving a coronary stent. Indeed, even patients undergoing PTCA had a 23% risk reduction when receiving abciximab compared with patients who underwent stenting without GP IIb/IIIa inhibition. The improvement in clinical outcomes observed with abciximab was primarily attributable to a reduction in death and large MI.

The long-term follow-up of EPISTENT patients revealed some interesting results.[220,221] It was apparent that the effects

of GPIIb/IIIa inhibition and coronary stenting were complimentary over time such that the combination produced the best 6-month clinical outcomes. At 6 months, the incidence of the composite outcome was significantly lower for patients receiving a stent + abciximab (5.6%), compared with patients assigned to PTCA + abciximab (7.8%), or those assigned to stent + placebo (11.4%). Long-term complementary effects were most notable among patients with diabetes, where the combination of stenting + abciximab was associated with a dramatic reduction in 6-month TVR rates (8.1%) compared with stenting + placebo (17%) ($P = 0.02$), or PTCA + abciximab (18%) ($P = 0.008$). Indeed, in diabetics, who traditionally have higher restenosis rates, a strategy of potent platelet inhibition combined with arterial scaffolding of stents improved the acute gains in arterial diameter and reduced late losses due to intimal hyperplasia. These effects brought the 6-month revascularization rate in diabetic patients close to that seen in non-diabetics.[220] Moreover, a significant reduction in 1-year mortality, which is most dramatic in diabetic patients, has been reported with the stenting + abciximab combination.[221]

IMPACT –II[213]

Shortly after abciximab's clinical studies were initiated, other work began evaluating the two short-acting, competitive GP IIb/IIIa inhibitors: eptifibatide and tirofiban.

The IMPACT-II (Integrilin to Manage Platelet Activation and Coronary Thrombosis) study evaluated the efficacy and safety of two doses of eptifibatide in preventing ischaemic complications in patients undergoing elective, urgent or emergency PCI. Patients were randomized to receive: (1) eptifibatide bolus (135 μg/kg) + a 20–24 hour high-dose infusion (0.75 μg/kg/min); (2) eptifibatide bolus (135 μg/kg) + a 20–24 hour low-dose infusion (0.5 μg/kg/min) or (3) a placebo bolus and infusion. PTCA was begun within 60 minutes of the initiation of study drug infusion in 4010 patients. All patients received concomitant aspirin and IV heparin. In a treatment-received analysis, the low-dose infusion eptifibatide regimen was shown to produce a significant reduction in the primary composite endpoint of death, MI, unplanned surgical revascularization or repeat PTCA or stenting for abrupt closure (9.3% eptifibatide vs 11.4% placebo) ($P = 0.035$). The higher dose regimen, however, produced a less substantial, and statistically insignificant reduction (9.9% vs 11.4%) ($P = 0.18$). It is quite likely that the small benefit seen in this trial was attributable to underdosing, because later pharmacodynamic studies confirmed that the doses used were at the low end of the efficacy–response curve. As a result, higher doses were subsequently studied, including the 180 μg/kg bolus and 2.0 μg/kg/min infusion regimen used in the PURSUIT (Platelet IIb/IIIa in Unstable Angina Receptor Suppression using Integrilin Therapy) trial, and the double bolus 180/180/2.0 regimen used in the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) coronary stent trial.[215]

The ESPRIT study was stopped prematurely when it was revealed that the combined incidence of death, MI and urgent TVR at 30 days in patients undergoing stent implantation was 35% lower in the 1040 patients treated with eptifibatide (double-bolus regimen), aspirin and heparin compared to the 1024 patients treated with aspirin, heparin and placebo (6.8% vs 10.5%; $p=0.003$). However, it must be remembred that the patients in this study were undergoing elective stent implantation and were not patients with acute coronary syndromes.

RESTORE[214]

The RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) trial evaluated the efficacy and safety of tirofiban in patients with ACS undergoing PTCA within 72 hours of presentation. A total of 2141 patients were randomized to either a tirofiban bolus of 10 μg/kg followed by a 36-hour infusion of 0.15 μg/kg/min or a placebo bolus and infusion. All patients received concomitant aspirin and intravenous heparin for the coronary intervention. The primary outcome was the composite of death, MI and TVR at 30 days.

Although the primary outcome was significantly reduced in the tirofiban group at 48 hours (38% relative risk reduction; $P = 0.005$) and 7 days (27% relative risk reduction; $P = 0.022$), the early benefits were attenuated over time, such that event rates were not significantly different at 30 days (10.3% tirofiban vs 12.2% placebo; relative risk reduction 16%; $P = 0.16$). The effect was predominantly due to the accumulation of non-urgent repeat revascularization procedures in both groups. When the data were reanalysed to include only urgent revascularization (as opposed to any TVR) in the composite endpoint, there was a more convincing 24% reduction with tirofiban (8% vs 10.5%).

Bleeding complications associated with GP IIb/IIIa inhibitors

The clinical trials of GP IIb/IIIa inhibitors in PCI have shown that the risk of major bleeding is 1.5–5.3% (excluding EPIC) and can be minimized by careful monitoring of heparin therapy. In general, bleeding complications with these agents are usually mild-to-moderate and are more readily reversible with the newer GP IIb/IIIa inhibitors such as eptifibatide. The femoral access site remains the predominant site of bleeding

complications and guidelines for medical and nursing care of patients undergoing PCI should be strictly adhered to. These are shown in Table 13.8. Certain risk factors for bleeding exist and it is prudent in this situation for the cardiologist to weigh the possible benefits against the risks for each individual case. If CABG surgery is necessary and cannot be delayed in patients who have already received GP IIb/IIIa inhibitors, several precautions are appropriate. Operating 'off pump' may prevent some of the haematologic disruption associated with cardiopulmonary bypass. If bypass is used, heparin dosing should be reduced on the basis of the ACT. The activity of small-molecule GP IIb/IIIa inhibitors is largely washed out by the end of surgery and platelet transfusion may not be necessary. In patients treated with abciximab, platelets should be given, if necessary, when the patient is 'coming off' the pump to prevent their consumption during cardiopulmonary bypass.

Timing of PCI for unstable angina

Although evidence suggests that PTCA within 48 hours of pain is associated with an increased complication rate and that these could be reduced by 'stabilization' over a 1–2 week period,[29,30] data are conflicting.[34–40,222–225] Coronary artery stenting and the newer anti-platelet and anti-thrombotic regimens have probably changed the frequency of such complications.

The impact of prolonged stabilization on the logistics of patient management and costs is substantial. Not only is it extremely costly to keep patients on an ITU/CCU for many days, but intravenous therapy and expensive agents such as Reopro and Integrilin, and the necessary repeated investigations add to the cost. Moreover the risk of delaying too long until the culprit vessel suddenly occludes causing its own major complications and the need for primary PTCA or emergency CABG surgery make early investigation and treatment an attractive alternative.

The FRISC II data[51,52] would suggest that although early intervention (<7 days) is associated with a higher event rate (procedural-related) during the first 2 weeks compared to the non-invasive group, after the first 2 weeks the event rate is lower in the invasive group and the hazard curves cross after about 4 weeks. Thereafter the event rate is consistently lower for death and MI in patients treated by early intervention.

Table 13.8 Guidelines for managing patients treated with GPIIb/IIIa inhibitors undergoing PCI.

Femoral artery puncture
- anterior approach recommended
- avoid 'through and through' approach
- limit attempts
- avoid venous sheath
- suture in arterial sheath

Heparin control
- initial bolus of 70 U/kg (weight adjusted) recommended
- do not exceed 7000 U bolus
- monitor with ACT
- maintain ACT close to 200 seconds
- discontinue heparin after PCI
- remove arterial sheath when ACT is < 175 seconds (4 hours post PCI)
- experienced operator to remove sheath
- careful observation of puncture site is necessary after sheath removal

Early invasive vs conservative treatment strategy in unstable angina and non-Q-wave myocardial infarction

Controversy exists regarding the optimal management strategy. Until recently, only two randomized trials TIMI IIIB[48,49] and VANQWISH[50] had compared an early invasive vs a conservative treatment strategy in the management of patients with unstable coronary disease.

The TIMI IIIB trial[48,49] randomized patients to either angiography within 48 hours of admission followed by revascularization as appropriate (740 patients) or to a more conservative medical strategy with revascularization being undertaken only when necessary for recurrent ischaemia (733 patients). The trial demonstrated similar clinical outcomes for patients in the invasive and conservative treatment groups. Death, non-fatal MI or signs of ischaemia on exercise stress testing at 6 weeks occurred in 16.2% and 18.1% of patients, respectively. The incidence of death or MI at 1 year was also similar in the two groups—10.8% vs 12.2%, respectively. The conservatively treated group of patients had longer hospital stays and more frequent readmissions than the early intervention group.

The VANQWISH trial[50] of men with non-Q-wave MI randomized patients to either invasive or conservative treatment strategies within 72 hours of onset of symptoms. The investigators reported a higher rate of in-hospital (7.8% vs 3.3%) and 1 year (24% vs 18.6%) mortality in the early invasive strategy group compared to those managed initially conservatively.

Unfortunately, both of these trials and their conclusions are flawed and cannot be used to guide us on whether patients with unstable angina or non-Q-wave MI should undergo immediate invasive investigation and PCI or not. Both trials were trials of strategies rather than treatments and there were high cross-over rates. A high proportion of patients in the

'conservative' groups received intervention while relatively few in the invasive group did. For example, in TIMI IIIB, in the 'conservative' and 'invasive' groups, angiography was performed in 64% vs 98%, PTCA in 26% vs 38%, CABG in 24% vs 25% and any revascularization in 49% vs 61%. In VANQWISH, a large number of patients underwent investigation and treatment in the 'conservative group'. For example, angiography was performed in 48% vs 96% and revascularization in 33% vs 44% in the 'conservative group' and 'invasive groups', respectively. Moreover, in the invasive group having revascularization, 60% had CABG rather than PTCA and most of the deaths occurred in this group. PTCA deaths only occurred in the 'conservative' group (3.6%) and none in the 'invasive group'. Finally, both studies were conducted in the era preceeding platelet GP IIb/IIIa inhibition and aggressive percutaneous coronary intervention with stenting.

The more recently performed Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial[51,52] demonstrated that in the era of stenting and newer antiplatelet agents, an 'early invasive' strategy (PCI or CABG) produced a better outcome (reduced death/MI, less angina, fewer anti-anginal drugs, less III/IV heart failure) at 6 months than those treated non-invasively. In this study, 2457 patients were randomized to early invasive or non-invasive treatment strategies and each group then to subcutaneous dalteparin treatment for 3 months. The results showed that a high proportion of those allocated to 'early invasive' treatment received it within 7 days compared to few in the non-invasive group (42% PCI and 35% CABG vs 17.8% PCI and 18.8% CABG, respectively at 6 months). A 65% stent rate was reported in the PCI group. Table 13.9 shows a comparison of revascularization rates in the three trials. There was a significant decrease in the composite endpoint of death and MI at 6 months with an early invasive treatment strategy (death/MI 9.4% vs 12.1%; MI 7.8% vs 10.1% for the 'invasive' and 'non-invasive' groups, respectively). There were no PTCA/stenting deaths and 2% deaths after CABG. In VANQWISH, CABG deaths were 7.7%.

The study also showed that during the first 2 weeks, event rates were higher in the 'early invasive' group (and lowest in the non-invasive dalteparin group), but after 2 weeks, event rates were lower in the 'early invasive' group. Moreover, at 6 months, patients in the 'early invasive' group had less angina, were on fewer anti-anginal drugs, had less III/IV heart failure and 50% fewer readmissions. Patients in the non-invasive group required more readmissions for angina (50% requiring invasive assessment), MI and further revascularization (23% of the 'non-invasive' group required revascularization in the 6-month follow-up period compared to 5.6% in the 'early invasive' group).

The study also showed that the low molecular weight heparin, dalteparin, minimized cardiac events over the first 2–4 weeks in patients with unstable angina and non-Q-wave MI (death/MI 3.1% dalteparin vs 5.9% placebo).

The treatment with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) trial[53] has also set out to establish whether an invasive or conservative treatment strategy results in the best clinical outcome in the current era of platelet GP IIb/IIIa inhibition and contemporary intervention and the relative cost of these two treatment strategies.

A total of 2200 patients were randomized within 24 hours of the last episode of chest pain. In the early invasive strategy, cardiac catheterization (usually PTCA) was carried out 4–48 hours after randomization whereas in the early conservative strategy, only medical treatment was given unless a patient experienced one or more of the pre-specified clinical criteria for proceeding to an invasive procedure. All patients were treated with aspirin, B-blockers, cholesterol lowering drugs and tirofiban. Results showed that the early invasive strategy significantly reduced the incidence of the primary endpoint—a composite of death, MI or rehospitalization for worsening angina—compared to the conservative medical strategy at 6 months (15.9% vs 19.4%; $p = 0.025$). The rate of death or MI was also significantly reduced at 6 months in the invasive strategy arm compared with the conservative treatment arm (7.3% vs 9.5%; $p < 0.05$).[226]

RITA 3 will similarly attempt to compare an invasive with a conservative management strategy for patients with unstable angina and non-Q-wave MI.

Table 13.9 Comparison of revascularization rates in the 'invasive' and 'non-invasive' groups.

Study	*Invasive*	*Non-invasive*
FRISC-II (7days)	77%	9%
FRISC-II (<6 months)	77%	37%
TIMI IIIB (6 weeks)	61%	49%
VANQWISH (12 months)	44%	33%

Restenosis after PTCA for unstable angina

The data on restenosis rates in patients undergoing PTCA for unstable angina compared to stable angina are conflicting.[40,227–230]

In a quantitative angiographic study of 339 consecutive patients with angiographic follow-up of 85%, Luyten et al[227] found that the restenosis rate was similar in 133 patients with unstable angina and 206 patients with stable angina. Rupprecht et al[40] found that the restenosis rate was higher for 185 patients with unstable angina than 379 with stable angina (37% vs 24%; $P = <0.01$). Duke University reported higher restenosis rates in patients who had symptoms <24 hours

prior to PTCA.[228] Univariate analysis of 18 patient-related variables performed in the CARPORT Restenosis Study revealed that unstable angina and angina duration <2.3 months were associated with a larger loss in minimal luminal diameter at follow-up. However, multivariate analysis only retained the duration of angina <2.3 months.[229] Data from the MARCATOR restenosis study also demonstrated that duration of angina (of <6 months) was associated with a higher loss of MLD at follow-up.[230] In conclusion, it appears that the available data suggest a higher restenosis rate for patients with unstable or recent-onset angina.

Coronary artery stenting is likely to reduce restenosis rates but data are currently limited for patients specifically with unstable angina.

Conclusions

The diagnosis of unstable angina or non-Q-wave MI demands urgent hospital admission and monitoring on a coronary care unit. The clinical history, 12-lead ECG and troponin estimations are the essential tools in making the diagnosis and in risk stratification.

Bed rest, aspirin, heparin, intravenous nitrates and oral anti-anginal agents are the mainstay of treatment. Those patients who continue to have symptoms and those at high risk of further cardiac events should be considered for treatment with a GP IIb/IIIa inhibitor and undergo coronary arteriography with a view to coronary revascularization. Those deemed suitable for PCI should undergo the procedure, with the prime aim being to treat the 'culprit' lesion—if this can be identified. PTCA should probably be accompanied by stent implantation wherever possible. Those patients unsuitable for PCI because of diffuse multivessel disease, chronic occlusions or left main stem stenosis should be referred for CABG surgery. There seems to be little merit in prolonged 'stabilization' of patients prior to PCI and an early invasive strategy should be generally preferred to a conservative one in all patients except those at very low risk of further cardiac events. Such an approach will shorten hospital stays, improve acute and long-term outcomes and reduce the need for subsequent interventional procedures.

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14

Coronary angioplasty in myocardial infarction

Menko-Jan de Boer and Felix Zijlstra

Introduction

Since the early eighties many trials have tried to determine the role of different treatment strategies for acute myocardial infarction (AMI). The use of aspirin,[1] beta-blockers,[2] and angiotensin-converting enzyme (ACE) inhibitors[3] have all contributed to a reduction of mortality. Restoring antegrade flow through the infarct-related vessel (IRV) by means of reperfusion therapy has also been successful in infarct treatment, especially in those patients who present within 12 hours of symptom onset with ST-elevation on the ECG. Reperfusion therapy is defined as the first therapy used to restore blood flow through a suspected or known occluded coronary artery immediately at diagnosis. It includes intravenous thrombolysis, intracoronary thrombolysis, primary coronary angioplasty, or immediate coronary artery bypass surgery.[1,4–16] Currently available thrombolytic agents are all associated with certain limitations: half or more of the patients will fail to achieve early and complete reperfusion with the current regimens. The mortality rate is at least 6 to 8%, and possibly higher.[5,9,13] Reinfarction, bleeding risk (including intracranial haemorrhage), and the potential need for transfusion continue to pose concerns. Recent studies have determined the role of primary coronary angioplasty: primary angioplasty results in higher patency rates, a better preservation of left ventricular function and a reduction of mortality and recurrent infarction when compared to thrombolytic therapy.[11,14–16]

On the other hand, thrombolytic therapy has the major advantage that it can be administered in all hospitals while primary angioplasty can only be applied in hospitals with facilities for interventional cardiology. Therefore, in many patients with acute infarction the choice has to be made for treatment with thrombolytic therapy in the community hospital (or even in the prehospital phase), or transfer to a tertiary centre with interventional cardiology equipment, or a combination of both therapies.[17–19]

Thrombolytic therapy and timing of coronary angioplasty

Reocclusion at the site of the often critical residual coronary vessel stenosis within the following days after myocardial infarction led several cardiologists to perform percutaneous transluminal coronary angioplasty at varying intervals after thrombolysis and as early as 1982, Meyer and colleagues reported very encouraging results of this combination strategy.[20] Others were soon to follow.[21–23] Several studies on the combination of thrombolytic therapy and coronary angioplasty have been published.[24–27]

Definitions

1: Immediate PTCA

After or while starting a thrombolytic agent, angioplasty is performed as soon as possible. Despite the attractive concept of reducing the underlying stenosis while the thrombus is lysed, the toll that has to be paid for this combination procedure is considerable. The complication rates are higher, there is no beneficial effect on left ventricular function or mortality and the costs of this combination approach have lead to the conclusion that immediate PTCA is not the treatment of choice.[24–27] Angioplasty produces a localized injury to the arterial wall leading to plaque splitting, stretching of the arterial wall, plaque compression, thrombus 'squeezing' with release of many vasoactive mediators, and denudation of the endothelium. This can be regarded as an ideal 'target' for rethrombosis. In combination with thrombolytic agents and their potential to activate thrombin and platelets, these factors may contribute to the high

incidence of complications of immediate PTCA.[28–30] However, if reocclusion can be prevented, immediate angioplasty may be beneficial in selected patients.[31]

2: Rescue PTCA

Thrombolysis can accomplish initial reperfusion defined as TIMI flow grades 2 or 3 of the IRV in 70 to 75% of the patients. When there is clinical evidence for coronary artery occlusion more then 90 minutes after starting thrombolytic therapy, mechanical reopening of the IRV should be considered and this is called 'rescue' PTCA. Failed thrombolysis followed by PTCA showed an initial high success rate for achieving vessel patency, ranging between 73 and 96 percent.[32–37] On the other hand, mortality is high in patients in whom rescue angioplasty failed.[33–36] This is probably a subgroup of patients with more complex lesions and pathology. The role of rescue PTCA has been addressed in one randomized study of patients with anterior wall myocardial infarction. In this study problems with the inclusion of patients were encountered as interventional cardiologists from many centres who were invited to participate felt it unethical to withhold coronary angioplasty from a patient in case an occluded IRV was found.[35] An important problem to be solved is the identification of non-invasive markers of reperfusion after thrombolytic therapy. Time delay after failure of thrombolytic therapy may result in further damage of myocardial tissue. A subanalysis of the GUSTO data demonstrated, that patients undergoing rescue PTCA have a dismal prognosis.[36,37]

3: Early, deferred and routine PTCA

A 'cooling down' period of at least 18–48 hours is allowed after thrombolysis and angiography is performed in all patients. The lesion held responsible for the infarction is dilated if it is suitable for angioplasty. The primary goal of this approach is to prevent recurrent ischaemia after thrombolytic therapy. In the TIMI-II study, patients were also randomized to a conservative approach, and angiography with or without angioplasty were only performed when there were signs of recurrent ischaemia (angina pectoris at rest or after exercise or if myocardial ischaemia could be provoked). This last strategy is often referred to as:

4: Elective PTCA

This issue has been addressed in several studies. However, if an occluded vessel was found, angioplasty was not performed in many of these studies and these patients may have had considerable benefits of the procedure. Despite these limitations most of these trials suggest that 'prophylactic' angioplasty will not confer benefits in terms of clinical or functional results, even from a successful procedure.[38–41] Data from the DANAMI study however, suggest that an invasive strategy in post-AMI patients with inducible ischaemia will result in a reduction in the incidence of reinfarction, re-admissions for unstable angina, and a lower prevalence of stable angina. According to these data, patients with inducible ischaemia before discharge who have received treatment with thrombolytic drugs for their first AMI should be referred for coronary arteriography and revascularized accordingly.[41]

From these studies we may conclude that PTCA during or shortly after thrombolytic therapy is not necessary in patients with a patent IRV and no beneficial effects may be expected from routine PTCA of a residual stenosis of the IRV. However, 'rescue' PTCA in the new millennium may need reconsideration as with newer thrombolytic agents (or regimens) and newer and more refined interventional equipment better clinical results may be obtainable.[42]

Primary (or direct) coronary angioplasty

Hartzler and colleagues were the first to report on the results of primary or direct coronary angioplasty (i.e. angioplasty without antecedent or concomitant thrombolytic therapy) as a general treatment modality for myocardial infarction.[22] The primary success rate of this procedure is very high for single vessel coronary artery disease (99%) as well as for multivessel disease (90%).[43–45] They found few procedural complications, a low in-hospital mortality and a three-year follow-up survival rate of 87–92%. In patients with previous coronary bypass surgery primary angioplasty also appeared to be effective and safe.[46] Combined results from nine, non-randomized, descriptive studies of primary coronary angioplasty with data from 2015 patients demonstrated an in-hospital mortality between 5 and 14%, probably reflecting the heterogeneity of the patient groups.[47] This stressed the need for randomized comparisons of thrombolytic therapy and primary angioplasty therapy for myocardial infarction.

The first trial that assigned patients to undergo primary PTCA or to receive thrombolytic therapy (intracoronary streptokinase) on a randomized, prospective base, was the study by O'Neill and colleagues.[48] This demonstrated more effective preservation of myocardial function and a less severe residual stenosis of the IRV in patients treated with primary coronary angioplasty. Coronary reperfusion was established in 83% of the patients treated with angioplasty and in 85% of those treated with thrombolysis. The time from symptom

onset to reperfusion was the same in both groups. Marco and co-workers also demonstrated the effectiveness, safety and beneficial effects on left ventricular function of primary coronary angioplasty in a non-randomized group of 43 patients with myocardial infarction.[49] Primary angioplasty is an effective means of complete recanalization in patients with acute myocardial infarction with reduction of the residual stenosis of the IRV and with the potential to eliminate thrombus ('squeezing the thrombus'). Bleeding complications, especially intracranial haemorrhage, may be significantly less than for thrombolytic therapy. Primary angioplasty may also be useful in patients beyond the traditional time window of 4–6 hours, especially when there are signs of ongoing ischaemia.[50,51]

An overview of the first reports on primary angioplasty is given in Table 14.1. Primary coronary angioplasty, when performed by experienced operators, restores normal, Thrombolysis in Myocardial Infarction (TIMI) 3 blood flow in over 90% of patients[52–54] and reocclusion rates after primary angioplasty are low.[53,55] This compares favourably with the 50–70% of patients who achieve normal flow after thrombolytic therapy.[7,55] As illustrated in Fig. 14.1, a comparison is made between the angiographic data of the GUSTO-1 (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries) trial and the 'Zwolle' trial.

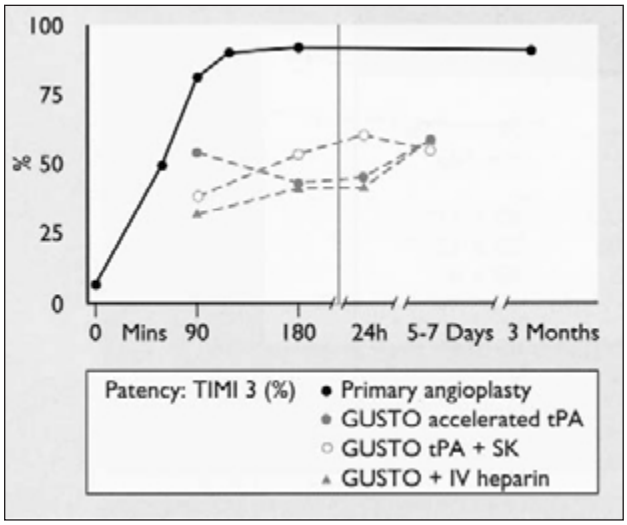


Figure 14.1
Graphic display of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow immediately after randomization: comparison of the angiographic results from the Zwolle and GUSTO trials. The data on TIMI flow in the GUSTO trial were gathered from different patients, who were randomly assigned to angiography at different time intervals after start of therapy. GUSTO: the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries study; tPA: tissue plasminogen activator; SK: streptokinase

Table 14.1 The early studies of primary coronary angioplasty for acute myocardial infarction.

Study (Ref)	*N*	*Success (%)*	*Reocclusion # (%)*	*Restenosis (%)*	*In-hospital death (%)*
Hartzler 1984[108†]	78	90	15		8
Kimura 1984[109]	58	88	16		NR
O'Neill 1986[48*]	29	83	8.3		6.8
Rothbaum 1987[110]	151	87	9	31	7
Marco 1987[49]	43	95	22	30	9.3
Miller 1987[111]	81	92	7.9	35	7.8
Flaker 1989[112 ‡]	93	78	11	34	14
DeWood 1989[113*]	18				NR
O'Neill 1992[114*]	63	93	11	37	6.5
Zijlstra 1993[14*]	70	98	9	24	2
Grines 1993[15*]	195	97			2.6
Gibbons 1993[16*]	47	93			4
Ribeiro 1993[115*]	50	90	2.5		6
Saito 1994[82]	198	93	7.5		8
O'Keefe 1993[116]	1000	94	13		8
O'Neill 1994[68]	271	92			4
de Boer 1994[52–54*]	152	97		28	2

#, indicates early or late reocclusion, depending on study design; *, indicates if the study was a prospective randomized trial; the numbers are based on the intention to treat principle; † some patients in the whole study group also received thrombolytic agents; ‡, only anterior wall infarcts were included. NR = not reported.

Myocardial salvage by primary coronary angioplasty

Myocardial salvage can be assessed by determining enzymatic infarct size and by measuring regional or global left ventricular function. In the 'Zwolle' trial, enzymatic infarct size was calculated from serial measurements of lactate dehydrogenase.[52] Infarct size was 23% smaller in patients randomized to angioplasty compared to streptokinase and this difference was more pronounced in patients admitted to the hospital within 2 hours after the onset of symptoms and in patients with an anterior wall myocardial infarction. Global and regional left ventricular function were measured with a radionuclide technique. Wall motion was better preserved by angioplasty again with a strong relation between time from symptom onset to admission and myocardial salvage. These results are shown in Table 14.2. The enzymatic infarct size and left ventricular function data strongly favour angioplasty especially in patients with anterior wall infarctions and patients presenting soon after symptom onset.[52,54]

Mortality and clinical outcome after primary coronary angioplasty

Although data from two of the three trials suggested a mortality benefit for angioplasty over thrombolytic therapy,[14,15] none of these studies were large enough to unequivocally answer this crucial question. However, a pooled analysis of these three trials, makes it clear that clinical outcome after primary angioplasty is better than after thrombolytic therapy.[56,57] The mortality rate in the thrombolytic groups was 6.4% (comparable with the GUSTO data), whereas the mortality in the angioplasty groups was 2.5%, $P = 0.008$. This represents a ratio for risk reduction of 2.5 (95% confidence interval (CI) 1.2 to 5.6). Similarly, a 3.9 risk ratio reduction for reinfarction (2.0% versus 7.9%, $P < 0.001$, CI 1.8 to 8.4) for angioplasty patients was found. Finally, angioplasty resulted in a 9.7 risk ratio reduction (0.3% versus 2.5%, $P = 0.007$, CI 1.3 to 75.6) in the incidence of stroke. Freedom from any of these events was observed in 95% of angioplasty patients compared to 85% of patients randomized to thrombolytic therapy. Patients with anterior wall infarctions and/or signs of left ventricular dysfunction derived the most benefit from angioplasty.[56,57]

Table 14.2 Global left ventricular ejection fraction (%) in the first Zwolle trial.

	Angioplasty	*P*	*Streptokinase*
EF all patients	50 ± 9	< 0.001	45 ± 11
EF anterior wall MI	46 ± 12	0.002	39 ± 12
EF non-anterior wall MI	53 ± 9	0.02	49 ± 9
Time from symptom onset to admission:			
< 2 hours: EF, %	51 ± 10	< 0.001	45 ± 11
> 2 hours: EF, %	48 ± 12	0.04	44 ± 12

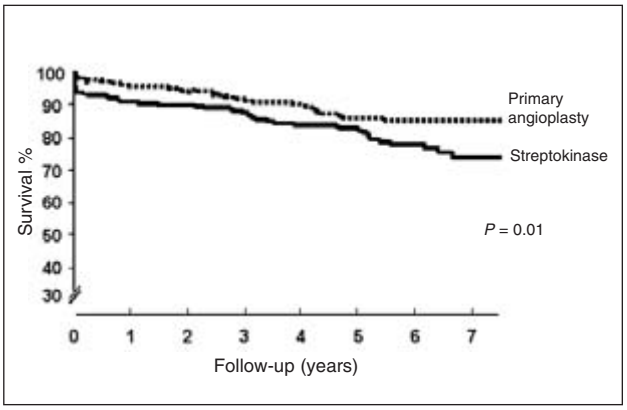
EF: ejection fraction; MI: Myocardial Infarction.

Long-term follow-up data from the Zwolle studies

The frequency of restenosis after primary angioplasty has not been studied extensively. The available quantitative angiographic data in the first Zwolle study suggest a restenosis frequency around 30%, but reocclusions are relatively rare.[53,55] Follow-up data show low rates of post-infarction angina, few reinfarctions and a rate of interventions and hospital readmissions that is, in fact, lower than after thrombolytic therapy. [58,59] If we look at the combined rate of death and non-fatal recurrent myocardial infarction a highly significant difference in favour of primary angioplasty is evident very soon after randomization, which is sustained during a longer period of follow-up (Fig. 14.2). As compared with thrombolytic therapy using streptokinase, primary coronary angioplasty is associated with better clinical outcomes over 5 years.[59]

Stents in primary angioplasty

The implantation of metallic stents has emerged as a mature technique for the percutaneous catheter-based therapy of coronary lesions.[60] Improved clinical outcome, reduced incidence of restenosis and the subsequent need for target vessel revascularization (TVR) have been demonstrated extensively for selected patient groups. The reluctance to place stents at the culprit lesion site in AMI was initiated by the fear of high thrombogenicity of both the device and the vascular trauma in a thrombotic environment. We compared the use of stents and balloon angioplasty in selected patients with AMI: excluded were patients with small infarct-vessels (less than 3 mm), diffuse atherosclerotic disease, severe tortuosity of the vessel or anticipated problems with stent delivery. The cardiac event-free survival rate in the stent group was significantly higher than in the balloon angioplasty group (95% versus 80%; $P = 0.012$) and this could be mainly attributed to a significant reduction in the need for TVR and a lower



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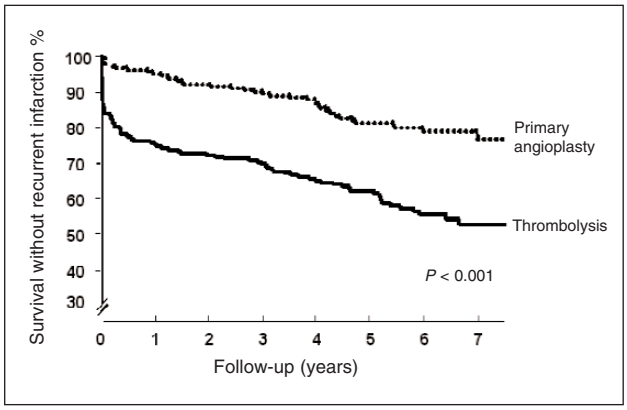

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Figure 14.2
Survival ((a) $P = 0.01$), and survival *without* non-fatal recurrent myocardial infarction ((b) $P < 0.001$) in 402 patients with acute myocardial infarction, randomized to treatment with thrombolysis (——) or primary angioplasty (. . . . .)

incidence of reinfarction.[61] The FRESCO (Florence Randomized Elective Stenting in acute Coronary Occlusions) study group used a somewhat different approach: patients were randomized after an optimal angiographic result of the culprit lesion was obtained with balloon angioplasty, but these investigators also found a better clinical outcome after stent placement.[62] Finally the Stent Primary Angioplasty in Myocardial Infarction investigators have demonstrated a better clinical outcome of a larger cohort of patients, and who were candidates for stent placement in AMI, when compared to 'stand-alone' balloon angioplasty.[63] The reduced rate of TIMI 3 flow after stent placement (89%) when compared with balloon angioplasty (92%) was a puzzling observation and this may be an explanation for the slightly higher six-month mortality rate of 4.2% in the stent group, compared to 2.7% in the angioplasty group ($P=0.27$).[63] We could confirm this observation in our study where the TIMI 3 flow rates were 87% versus 94% respectively (unpublished core-lab data). This observation may be an important one, and needs further evaluation.

Cost-effectiveness of primary angioplasty

In the 'Zwolle' trial total medical costs of all patients were calculated including hospital costs, professional charges, procedures and medication. After 1 year of follow-up the costs were DFL 27.485 per patient in the angioplasty group and DFL 26.478 ($P = 0.22$) in the streptokinase group. The efficacy of both treatment modalities can be addressed by calculating the average cost per event free survivor (i.e. without recurrent infarction and where revascularization procedures are not considered to be events): DFL 29.280 for angioplasty patients versus DFL 34.941 for streptokinase patients, making angioplasty a very good investment.[58,59]

Furthermore, these data demonstrate superior clinical outcome in patients after primary coronary angioplasty when compared with thrombolytic therapy, at approximately the same costs per patient in the first year. When assessed in relation to survival without recurrent infarction or stroke, it is apparent that treatment of acute myocardial infarction with angioplasty is more efficient than thrombolytic therapy. Additional savings of angioplasty treatment may be expected during longer follow-up (Fig. 14.3). It has been demonstrated that rehospitalizations were significantly less frequent in the patient group managed invasively. These results may help to encourage introduction of primary angioplasty as a treatment modality for patients with acute myocardial infarction in hospitals with existing interventional cardiology programmes.[58,59,64–67]

Primary coronary angioplasty and cardiosurgical standby

The role of the catheterization laboratory staff, the coronary care and intensive care unit, the cardiovascular surgeons, and the cardiovascular anaesthesiologists cannot be overemphasized. All recently published results should be seen in this light. Sometimes the most difficult part of the emergency procedure is to identify the infarct-related vessel and serious complications can be induced by performing angioplasty of non-infarct-related vessels. If there is doubt about the 'culprit'

lesion, immediate consultation with other interventional cardiologists and cardiac surgeons is warranted. The need for surgical intervention has been between 3 and 5 percent[14,15,54,68–70] although after a 'learning curve' for performing primary angioplasty as an interventional team this number may be lower. In our opinion this is one of the most important reasons to perform primary angioplasty only in centres with a large experience in interventional cardiology. Recently, several investigators have reported excellent results from centres without on-site cardiac surgery.[71,72] The performance of primary angioplasty in these centres may extend the availability of this effective reperfusion therapy.

Who should be offered coronary angioplasty for AMI?

Although there are overwhelming data that coronary angioplasty is a highly effective treatment, a large group of patients with myocardial infarction will fare well with modern thrombolytic therapy. Patients with large anterior wall infarctions, patients in cardiogenic shock and probably all patients in Killip class 2 or more, are candidates for primary coronary angioplasty.[14,57,73–76] Easy obtainable parameters for early decision making have to be identified and the ECG therefore plays a pivotal role. Two-dimensional doppler-echocardiography on admission is a technique that can provide information on extent of jeopardized myocardium, regional and global systolic wall motion and valvular function, without further discomfort for the patient. However, skilful interpretation is required. An advantage of thrombolytic therapy is that it can be started by general practitioners and paramedical ambulance staff before the patient reaches the hospital, which may result in a reduction of time to start of treatment (pre-hospital thrombolytic therapy).[77–79] We introduced ambulance ECG facilities for pre-hospital triage for direct transfer to our hospital for immediate angiography and subsequent angiography-guided therapy. Preliminary data from this registry show that a pre-hospital ambulance ECG is able to identify patients with myocardial infarction. Intravenously administered heparin and aspirin did not lead to any major bleeding complication and contraindications for thrombolytic therapy were good reasons for inclusion in the primary angioplasty protocol. Pre-hospital thrombolytic therapy is still hampered by strict inclusion criteria, bleeding complications, a modest reperfusion rate and worse clinical outcome when compared with primary angioplasty. The logistics and problems with referral for primary intervention for acute myocardial infarction from hospitals without angioplasty facilities have been described by us.[80] By equipping and training ambulances using our Pre Hospital Infarct Angioplasty Triage (PHIAT) protocol, in regions normally serving hospitals without angioplasty facilities, patients with large myocardial infarctions can be directly referred to our interventional centre. Preliminary data suggest that pre-hospital ambulance triage for immediate angiography-guided reperfusion therapy is feasible, effective and safe in the treatment of acute myocardial infarction (Fig. 14.4).

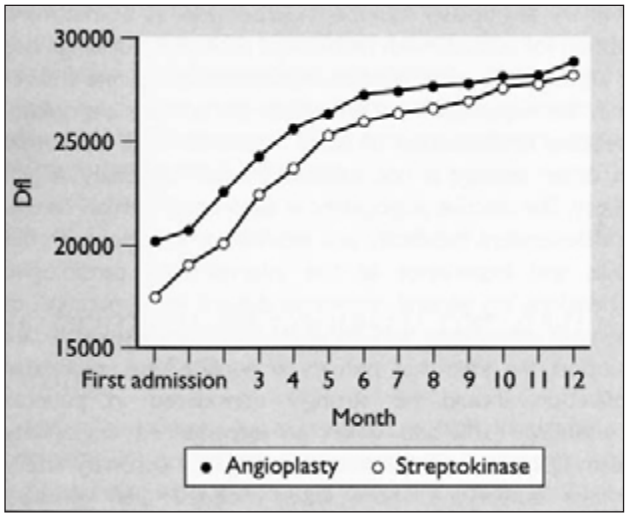


Figure 14.3
Total cumulative costs during the first year per patient, including in-hospital costs and costs of pharmacological treatment (in surviving patients) in both treatment arms of the first Zwolle Study. Dfl. = Dutch Guilders.

Is there an age-limit for patients that should be offered primary coronary angioplasty?

In our experience with primary angioplasty, in very old patients we encountered many problems ranging from difficult vascular access, massive bleeding at vascular puncture sites and other vascular complications, to difficulties in decision making when severe coronary artery disease, not suitable for angioplasty, was found. The absolute gain in life years is lower and the burden for hospital organization and house-staff is high. However the elderly seem to benefit even more from primary angioplasty compared with thrombolytic therapy as was demonstrated by the results from a pooled analysis from three major studies on primary PTCA and our own data.[57,81] In the very old but otherwise very fit patients, primary coronary angioplasty should not be denied if they present with large myocardial infarctions.

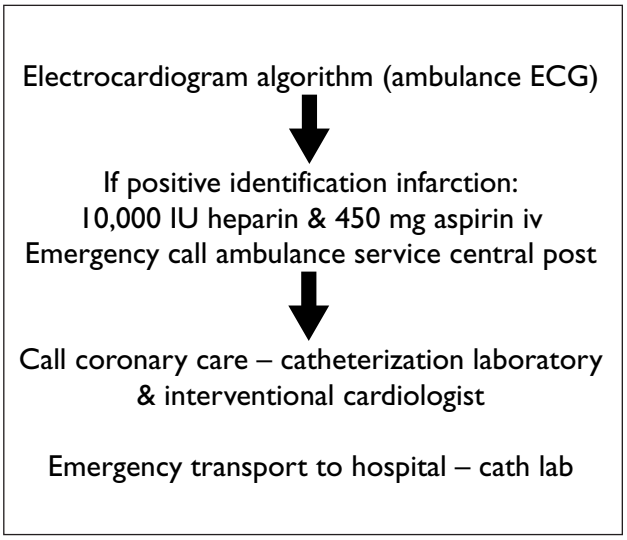


Figure 14.4
PHIAT: PreHospital Infarct Angioplasty Triage

Where, when and who should perform primary coronary angioplasty?

We all need to examine our local logistics to decide how primary angioplasty can be incorporated as a treatment option for patients with myocardial infarction. Although this is arguably the most important question, no definite answer may be expected from any study on primary angioplasty because extrapolation of study results to other operators in other settings is not justified. Primary coronary angioplasty, like elective angioplasty, is associated with an operator-dependent morbidity and mortality that varies with the skills and experience of the interventional cardiologist.[69] Therefore, no general recommendations for application of primary angioplasty can be given. However, several data support the idea that primary angioplasty for myocardial infarction should strongly be considered in patients presenting early and when an experienced angioplasty team is available. Furthermore, emergency coronary artery bypass surgery is more often needed after primary coronary angioplasty compared with elective angioplasty. In the first Zwolle study, 3% of the angioplasty assigned patients underwent bypass surgery within the first few hours after admission for myocardial infarction and the majority of patients survived and did well.[70] On-site cardiosurgical standby is therefore in our view a prerequisite for safe performance of primary coronary angioplasty and data from the primary angioplasty studies cannot be extrapolated to hospitals without these facilities.

Is there a place for new devices in the treatment of myocardial infarction?

Some reports suggested promising results of DCA (Directional Coronary Atherectomy) and TEC (Transluminal extraction atherectomy) applied in small groups of patients[82,83] but the skills and costs required for these techniques, the loss of time to achieve adequate flow through the infarct-related vessel due to technical preparations and the risk of not reaching the culprit lesion, are major limitations. The excellent results of balloon angioplasty, with or without stent placement, are difficult to beat. A diverse array of drills, lasers, shavers, burrs and other exotic interventional devices have been proposed but not yet investigated thoroughly in the setting of myocardial infarction. The use of an intra-aortic balloonpump (IABP) as an adjunct to reperfusion therapy has been evaluated in several trials and the benefits of this assist device were demonstrated in high-risk patients.[84–88] An increase in diastolic coronary blood flow velocity may prevent reocclusion and recurrent thrombus formation. However, we could not confirm the benefits of the *routine* use of an IABP in a larger series of high-risk patients.[88] Further investigations are needed to define the role of IABP during and after primary coronary angioplasty for myocardial infarction.

Is primary angioplasty for AMI really safe?

Gacioch and Topol have reported a high incidence of complications and death after angioplasty in patients with AMI and occlusion of the right coronary artery, attributed to a higher reocclusion rate, an exaggerated Bezold–Jarisch reflex, and reperfusion injury.[89] This could not be confirmed by data on complications of angioplasty in the setting of AMI, although minor catheterization related events were more common in patients presenting with an occlusion of the right coronary artery.[43] This finding was confirmed by our own group and major events were rare in our experience with primary angioplasty.[53] Little is known about the occurrence of adverse events in patients treated with primary coronary angioplasty although the results of the studies from experienced centres suggest that primary coronary angioplasty can be carried out safely. However, we do not know if patients might even be harmed by primary angioplasty, but if this subgroup exists, it will probably be small. Case reports on adverse events are rare (see Fig. 14.9).[90] Finally, the pooled data from the major trials on primary angioplasty give strong support to the theory that the incidence of stroke is greatly reduced with this approach.[57] Procedural failure is infrequent and tends to cluster around patients with high-risk baseline characteristics.[91]

How do we monitor patients after successful primary angioplasty?

Reocclusion seems to be a relatively rare phenomenon after primary angioplasty but if it occurs it is a serious threat for these patients. The small number of patients in Killip class 3 and 4 and those with TIMI 2 flow immediately after angioplasty are probably more susceptible for reocclusion.[53] Assessment of initial reperfusion after intravenous thrombolytic therapy has its limitations,[92] but primary angioplasty gives the unique opportunity to document patency angiographically, still regarded as the 'gold standard' for success of therapy. Noninvasive monitoring of markers that can indicate reocclusion after successful reperfusion include clinical signs (chest pain, haemodynamic deterioration), recurrence of ST elevation on the electrocardiogram, monitoring of specific cardiac proteins in plasma and continuous 12 lead and/or vectorcardiographic monitoring.[93–95] An example of a practical approach for non-invasive monitoring is the Myocardial Infarction Diagnosis and Analysis (MIDA) system, that has been routinely used in our coronary care unit since 1992. This is a computerized system with on-line dynamic analysis of the QRS complex and ST segment changes using eight electrodes placed according to the Frank method. Three orthogonal leads X, Y and Z are continuously monitored and analysed. Electrocardiac signals from the above mentioned electrodes compare the averaged complex to the initial complex and displays this information in trend graphs, that are continuously updated. The two most important parameters are the ST vector magnitude (ST-VM) which reflects the extent of ischaemic tissue at risk and the QRS vector difference (QRS-VD) reflecting changes in the shape of the QRS complex. All these data can be stored on a computer internal hard-disk for further analysis; decision making by the physician in charge can be guided by the graphic display. An example of a MIDA scan during and after primary coronary angioplasty is depicted in Fig. 14.5.

Prognostic markers after successful primary angioplasty

The success of reperfusion therapy has commonly been assessed by grading the extent of epicardial flow (TIMI classi-

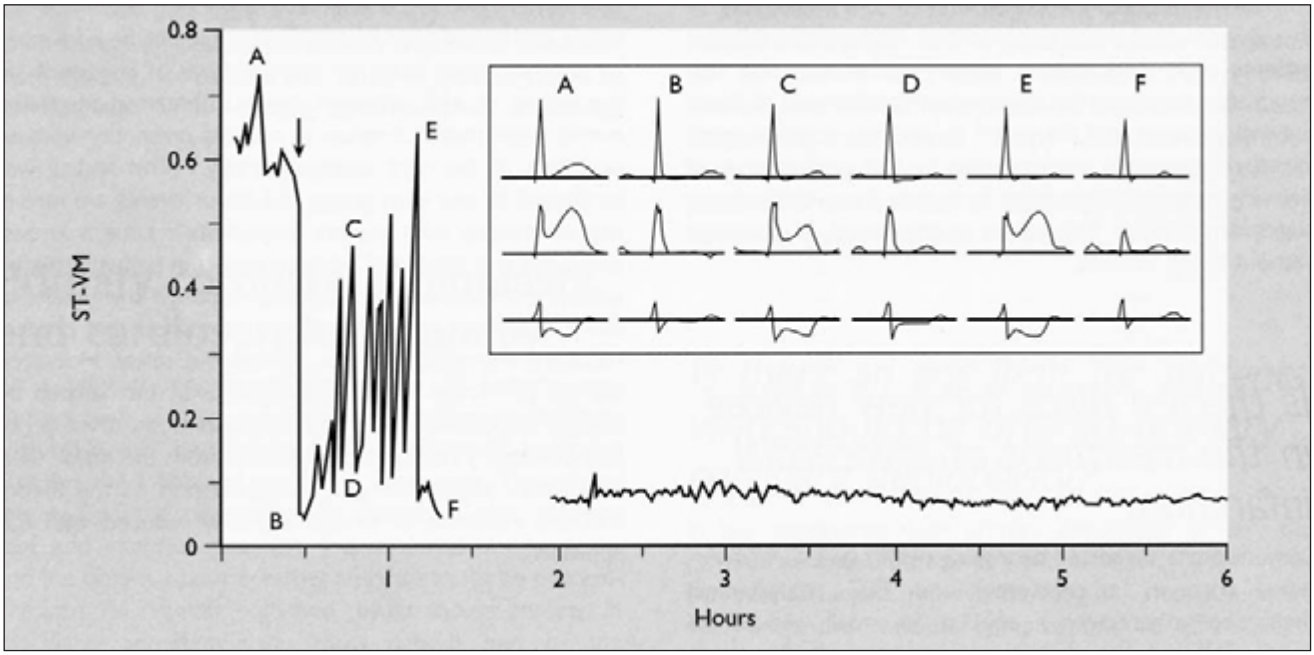


Figure 14.5
Continuous monitoring of six hours duration of ST vector magnitude (ST-VM) changes in a 59-year-old patient with an acute infero-posterior infarction undergoing primary angioplasty of an occluded right coronary artery. The vector ECG leads X, Y and Z more or less resemble V5, II and V2. On arrival in the catheterization laboratory the sum of ST-segment deviation is 0.7 mV (A). The arrow indicates the first deflation of a 3.5 mm balloon and an immediate decrease of ST-segment deviation with subsequent relief of chest pain and angiographic TIMI 3 flow (B). C and E indicate some of the multiple repeat balloon inflations and recovery of the ST-segments thereafter (D and F). During transportation of the patient to the coronary care unit (CCU) the registration was temporarily interrupted. On the CCU the ST level stabilizes and ischemic episodes remained absent. Accordingly, the QRS-vector difference (not presented here) did not indicate additional myocardial necrosis after successful reperfusion.

fication). However, from a pathophysiological point of view, not the epicardium, but myocardium and endocardium should be targets of reperfusion therapy. Therefore, simple parameters which reflect myocardial reperfusion are warranted. We investigated the prognostic value of two easily obtainable markers of reperfusion.

1. The 12 lead ECG

The prognostic value of the 12-lead electrocardiogram has been documented for patients treated with thrombolytic therapy,[96,97] but not all patients will have early and sustained successful reperfusion of the infarct-related vessel. We demonstrated, that 50% of patients treated with primary angioplasty had persistent ST-segment elevation despite TIMI-3 flow of the infarct vessel.[98] These patients will have a considerably worse outcome when compared with patients in whom ST-segment elevation had disappeared, alongside successful opening of the infarct vessel. Our study showed, that by means of simple 12-lead electrocardiography important information can be obtained about the success of myocardial reperfusion. It was possible to risk stratify patients at a very early stage after the acute event (Fig. 14.6a) and there was a strong correlation with enzymatic infarct size.

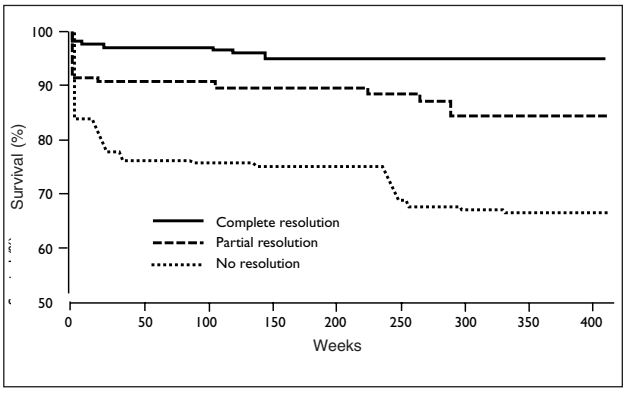
2. Myocardial blush grade

To be able to assess reperfusion of the myocardium using angiography we developed the angiographic myocardial blush grade based on the visually assessed contrast density in the infarcted myocardium after reperfusion. The angiographic myocardial blush grades are analogous to the TIMI grade classification for flow through the epicardial infarct vessel. Myocardial blush grades were defined as follows: 0, no myocardial blush or contrast density; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct related coronary artery; and 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct related coronary artery. Kaplan–Meier curves on survival, according to myocardial blush grade immediately after restoration of blood flow through the epicardial vessel, are depicted in Fig. 14.6b.[99] A new standard for success of reperfusion therapy has been proposed: '90% TIMI 3 flow at 90 minutes'.[100] We think that the future standard should include the phrase: 'with evidence of adequate reperfusion on the myocardium level'.

Recurrent ischaemic events occur far less frequently after angioplasty compared with thrombolytic therapy, and early discharge seems to be a feasible approach. Early discharge of patients after infarcts treated with primary angioplasty was reported from several studies[101–103] and readmissions for recurrent ischaemia were reduced significantly resulting in substantial cost savings without additional risks.

What is the best treatment after successful reperfusion therapy for myocardial infarction?

Late angioplasty of occluded infarct-vessels after failed thrombolysis may have benefits with regard to left ventricular function and survival but 'rescue PTCA' has a disappointing outcome. However, coronary angiography and subsequent



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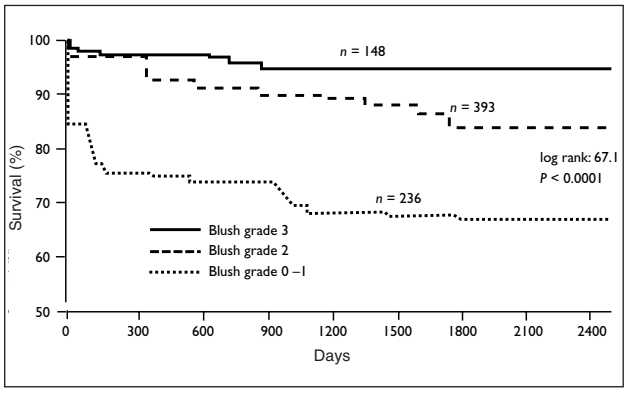

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Figure 14.6
(a) 12-lead ECG resolution after successful reperfusion therapy for AMI (n = 403).
(b) Myocardial blush grade (n = 777).

'tailored' therapy should be considered in all patients with severe problems after any kind of reperfusion approach. We do not know the optimal moment to perform angioplasty of an occluded infarct vessel late after failed reperfusion therapy and maybe it is appropriate to introduce a period of 'cooling down' in asymptomatic patients, when angioplasty is considered. However, the reocclusion rate may be considerably higher than with primary coronary angioplasty.[104] Coronary artery restenosis in response to arterial injury is the Achilles' heel of angioplasty and prevention remains a clinical challenge after primary angioplasty especially because thrombus is thought to induce neointimal proliferation.[105] New pharmacological interventions may reduce the incidence of restenosis. Despite this limitation, in our experience, patients rarely present with an occluded vessel at follow-up angiography and repeat coronary angioplasty can be carried out safely if restenosis occurs. Concomitant and/or additional treatment with glycoprotein IIb/IIIa blockers has been the subject of investigation, but no definite proof has been gathered, to recommend the routine use of these agents.[106,107] Several trials are underway to answer this important issue.

Practical guidelines

There is no definite formula to perform primary angioplasty. Every cardiologist should feel at ease with his or her own local situation. Time and procedural success are predominant factors in all decisions made in the often hectic and chaotic circumstances. Primary angioplasty is never a stand-alone procedure and maybe the most important rule is to ask opinions from other workers in the field whether they are colleagues, nurses or ancillary personnel.[69] However, some general statements can be made, derived from our own experience with more than 2000 primary angioplasty procedures.

- Optimal visualization of the coronary anatomy is necessary and digital angiographic assessment of the coronary artery tree is highly desirable; one of the worst things that can happen is dilatation of a non infarct-related lesion. In our catheterization laboratory we start the angiography procedure with visualization of the coronary artery that is not suspected to be the culprit lesion; a left ventricular angiogram is not routinely performed.
- In the very sick patients, immediate consultation of the cardioanesthaesiologist and his team is urgently needed. While concentrating on treating the lesion the interventional cardiologist is at risk of overlooking the patient's respiratory and haemodynamic problems that occur frequently after massive myocardial infarction. Support of cardio-respiratory function should be managed by an experienced team and this will enable the cardiologist to focus his or her attention to the restoration of adequate blood flow to the infarct-zone.
- In all patients with right coronary (or large circumflex) artery involvement, an external pacemaker and up to 2 mg of atropine should be at hand to overcome the characteristic conduction abnormalities and blood-pressure drop encountered in these patients after successful reperfusion.
- Any type of hypotension should be treated aggressively as this condition predisposes to reocclusion. Monitoring with a Swan–Ganz catheter is an excellent tool to tailor therapy: additional fluid expansion, inotropic support or intra-aortic balloon pumping are the most common and effective measures.
- If severe three vessel or left-main disease is found, an experienced cardiosurgical team can 'safely' perform acute bypass surgery as was shown in our own experience as well as in the experience of others; this therapy should always be considered as potential part of reperfusion therapy.
- An estimated balloon to vessel ratio of at least 1.0 is recommended.[43] This also requires an optimal visualization of the culprit lesion. On-line quantitative coronary arteriography can be of help; vessel size should be reassessed after multiple doses of intracoronary nitrates.
- Any major obstruction distal or proximal from the culprit lesion, that could be responsible for diminished flow through the treated segment should be considered for dilatation; if in doubt however one should be very reluctant.
- In our experience the need for selective adjunctive thrombolytic treatment is negligible. It is remarkable that a sometimes a very large 'thrombotic burden' literally melts away by adequate flow after reduction of the responsible lesion.
- The ECG may be an insensitive tool after primary angioplasty as even with widely patent vessels and TIMI 3 flow marked ST-elevation may be observed. Trend analysis with vectorcardiographic monitoring (see Fig. 14.5) is far more reliable in detecting failed angioplasty or reocclusion.

How to perform primary angioplasty: 10 rules to remember

1. In suspected MI, initial assessment should be performed within 15 min:
   TIME = MUSCLE = LIVES.
2. When the diagnosis of MI is confirmed before hospital arrival, transfer the patient directly to the cath lab, and not to emergency room or CCU.
3. Do not forget aspirin, heparin, nitrates (or β-blockers, if not contraindicated).
4. Visualize both coronary arteries.

5. Use a balloon and perhaps a stent; forget about other techniques.
6. Consider conservative management and acute or elective CABG.
7. Be sure that somebody looks after the patient when you perform angiography and angioplasty.
8. Beware and prepare for reperfusion arrhythmias, bradycardia and hypotension
9. Do not undersize your balloon.
10. Stent the plaque, not the vessel.

Illustrated cases

Figures 14.7–14.13 illustrate the effectiveness of primary PTCA in acute myocardial infarction as well as the broad range of problems that may be encountered.

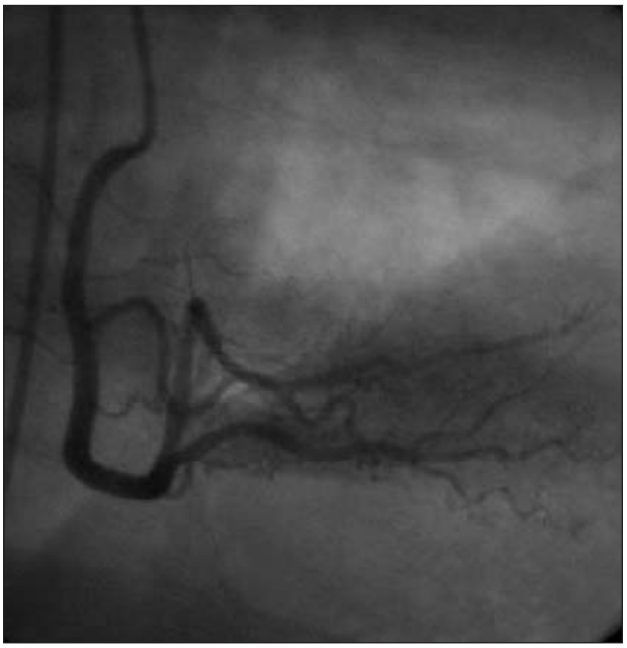
Conclusions

The life-saving effect of reperfusion therapy for myocardial infarction has been well established: early reperfusion leads to enhanced salvage of myocardium and a better clinical outcome. The beneficial effects of primary coronary angioplasty in this regard can be summarized as follows:

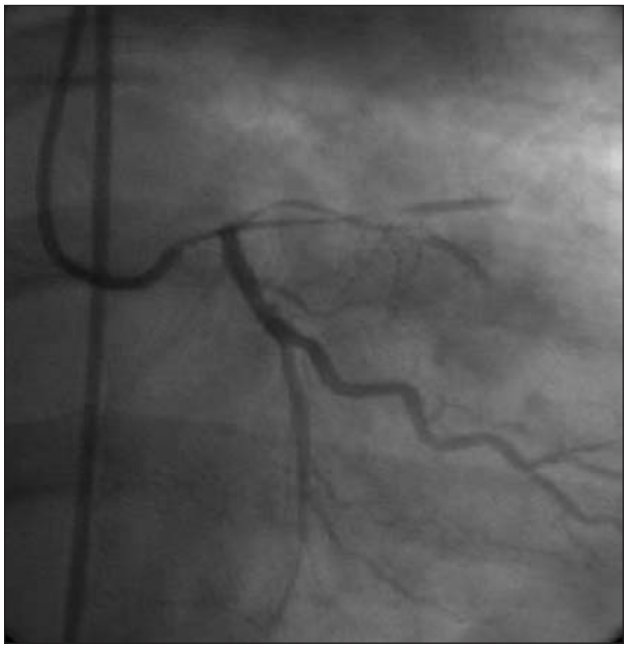
Primary angioplasty, when compared with intravenous thrombolytic therapy results in:

a. a higher patency rate of the infarct-related vessel,
b. improved myocardial preservation as evident from enzymatic infarct size and ejection fraction measurements,
c. a better immediate as well as long-term clinical outcome resulting in:
d a shorter hospital stay,
e. a reduction in readmissions and reinfarctions,
f. a lower mortality

In hospitals with existing facilities for interventional cardiology, these results can be obtained without additional cost. Patients presenting with large infarcts, those in cardiogenic shock or who have a contraindication to thrombolysis are without any doubt best treated with primary angioplasty. Referral of these patients from community hospitals to centres with experience in performing primary angioplasty should always be considered.

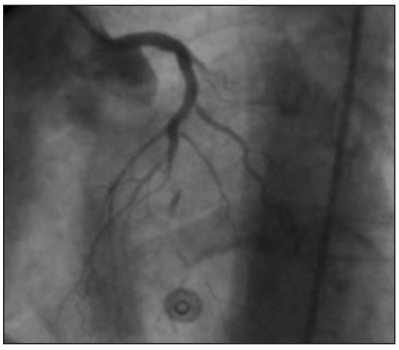


a



b

Figure 14.7
A 56-year-old man was admitted 2 hours after the onset of symptoms. He had no previous history of cardiovascular disease. On acute angiography, the right coronary artery had no significant narrowing (a) whereas collaterals to the LAD were observed (Rentrop class 1). The left coronary artery showed a severe narrowing of the main stem, and a dissecting occlusion of the LAD (b). It was decided to perform acute surgery and a dissection of the entire ascending aorta was found, advancing into the left coronary artery. Despite additional measures, the patient could not be weaned from extracorporeal circulation and died.



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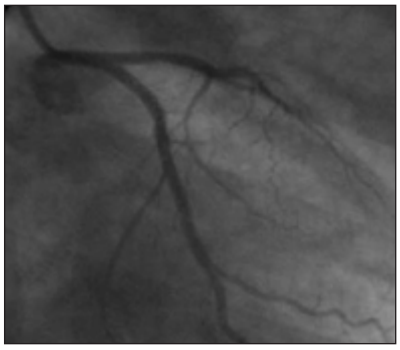

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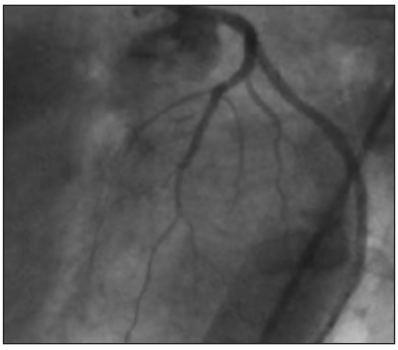
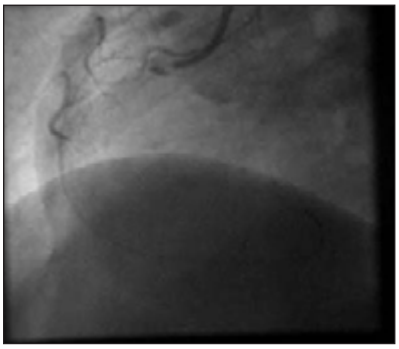


c

Figure 14.8

After a positive infarct identification using the PHIAT (PreHospital Infarct Angioplasty Triage) ambulance protocol, a 35-year-old woman was admitted one hour after the onset of severe chest pain. The ambulance-electrocardiogram showed a large inferior wall MI. The left coronary artery showed complete occlusion of the LAD *and* circumflex artery (see a). The RCA had only minor disease. From the angiographic and ECG-infarct localization data it was decided that the circumflex artery was the infarct-related vessel: a 3.5 mm diameter, 18 mm long stent was placed in this vessel with complete restoration of flow and resolution of pain (see b). However, the patient remained haemodynamically unstable. The LAD was also opened in the same session and a 2.75 mm diameter, 18 mm long stent was inserted also with good angiographic result and TIMI-3 flow (see c). Afterwards the patient was treated with an IABP and a glycoprotein IIb/IIIa blocker (Tirofiban). This case demonstrates that it is sometimes necessary to accomplish complete revascularization in severly ill patients, although the golden rule to dilate only the infarct-related segment should be kept in mind. The patient recovered well.



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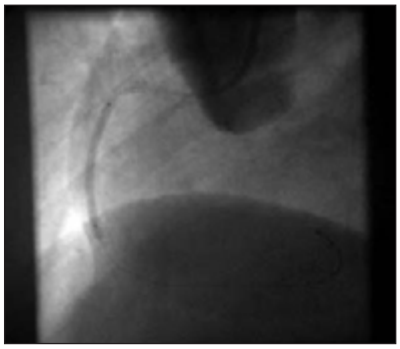

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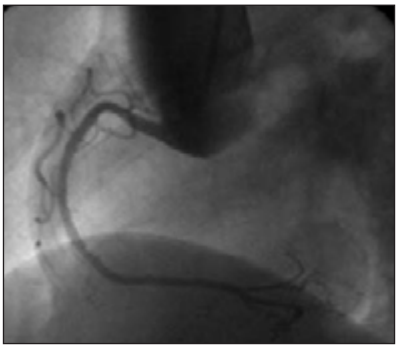

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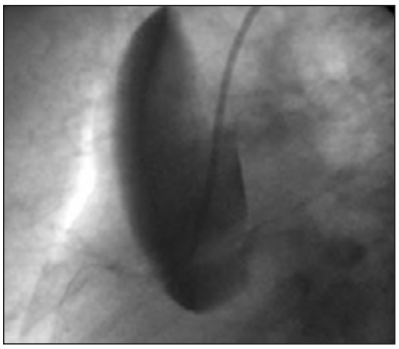
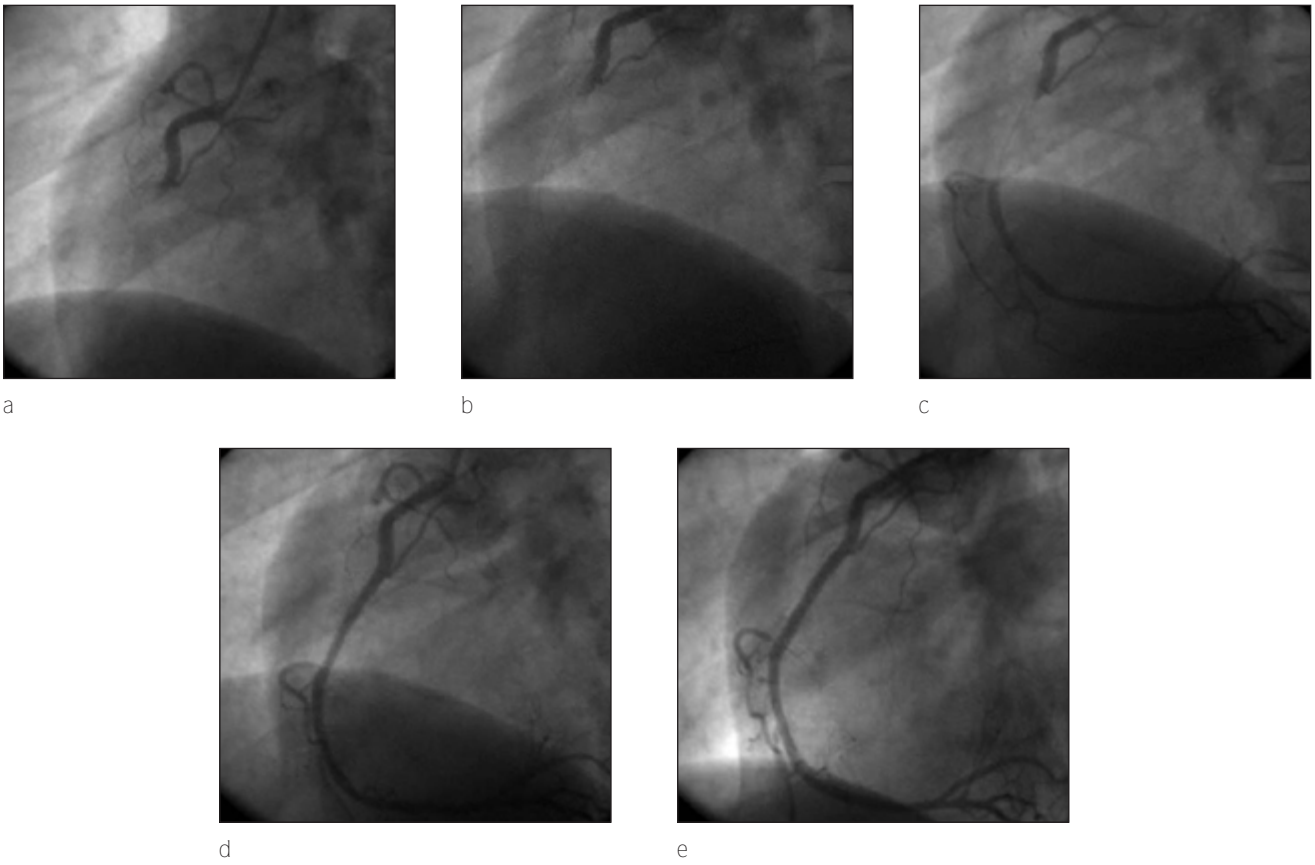


d

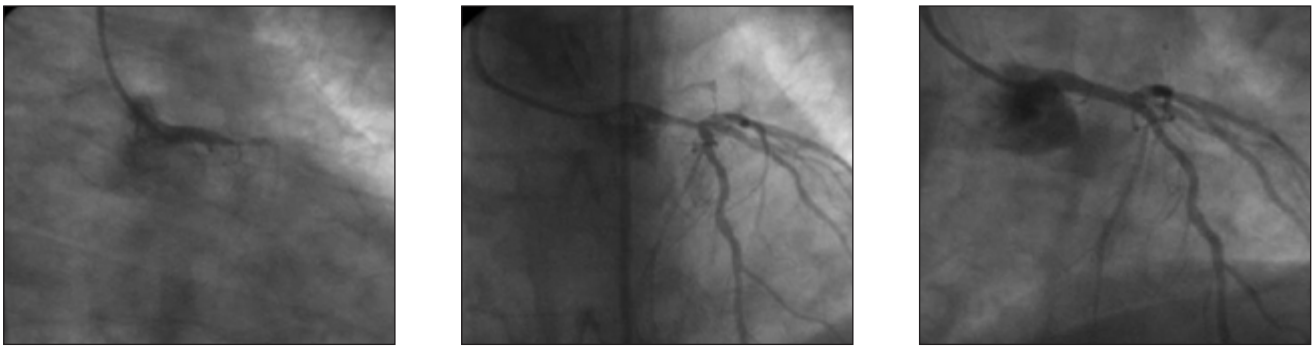
Figure 14.9

A 61-year-old woman was brought in from another hospital to undergo primary angioplasty for acute inferior MI. The ostium of the RCA was dissected (a) without further significant coronary artery disease. During manipulation of the guiding catheter and placement of three stents, a large amount of dye was accumulating in the ascending aorta (b–d) despite a good result of the procedure (c). The patient was asymptomatic and there were no signs of aortic regurgitation. After consultation with the thoracic surgeon it was decided to perform replacement of the ascending aorta (the aortic valve appeared to be normal during surgery) and one bypass graft to the RCA, two days after the index infarction. The patient did well and had a complete recovery. A good result was demonstrated on a MRI scan 6 months later.



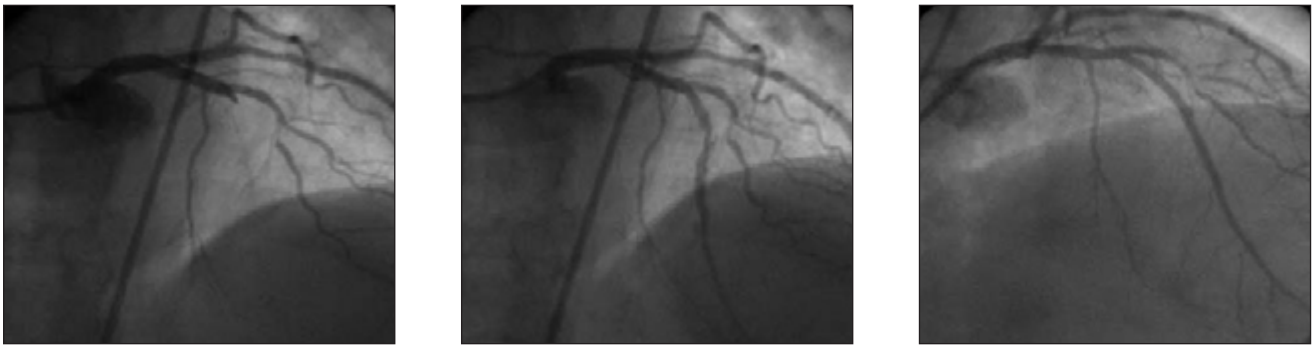
a b c d e

Figure 14.10
A 39-year-old man was admitted for acute inferior wall myocardial infarction, three hours after symptom onset. An occluded RCA was found (a) and after multiple balloon inflations no antegrade flow could be seen (b). Using an over-the-wire balloon with injection of dye through the distal balloon lumen together with contrast injection through the guiding catheter it was demonstrated that a long area of dissection (mechanical, about 30 mm long) was responsible for the no-reflow phenomenon (c). After placement of a 33 mm stent (3.5 mm diameter) there is an indication of 'undersizing' (d) and in stent inflations with a high pressure 4 mm diameter balloon accomplished a nice angiographic result (e). This case demonstrates (1) if a no-reflow phenomenon is found, the presence of a mechanical dissection should be considered (as was proven with the over-the-wire balloon) and (2) sizing of balloon or stent can only be reliably done after restoration of antegrade blood flow, preferrably combined with multiple intracoronary injections of nitroglycerin.



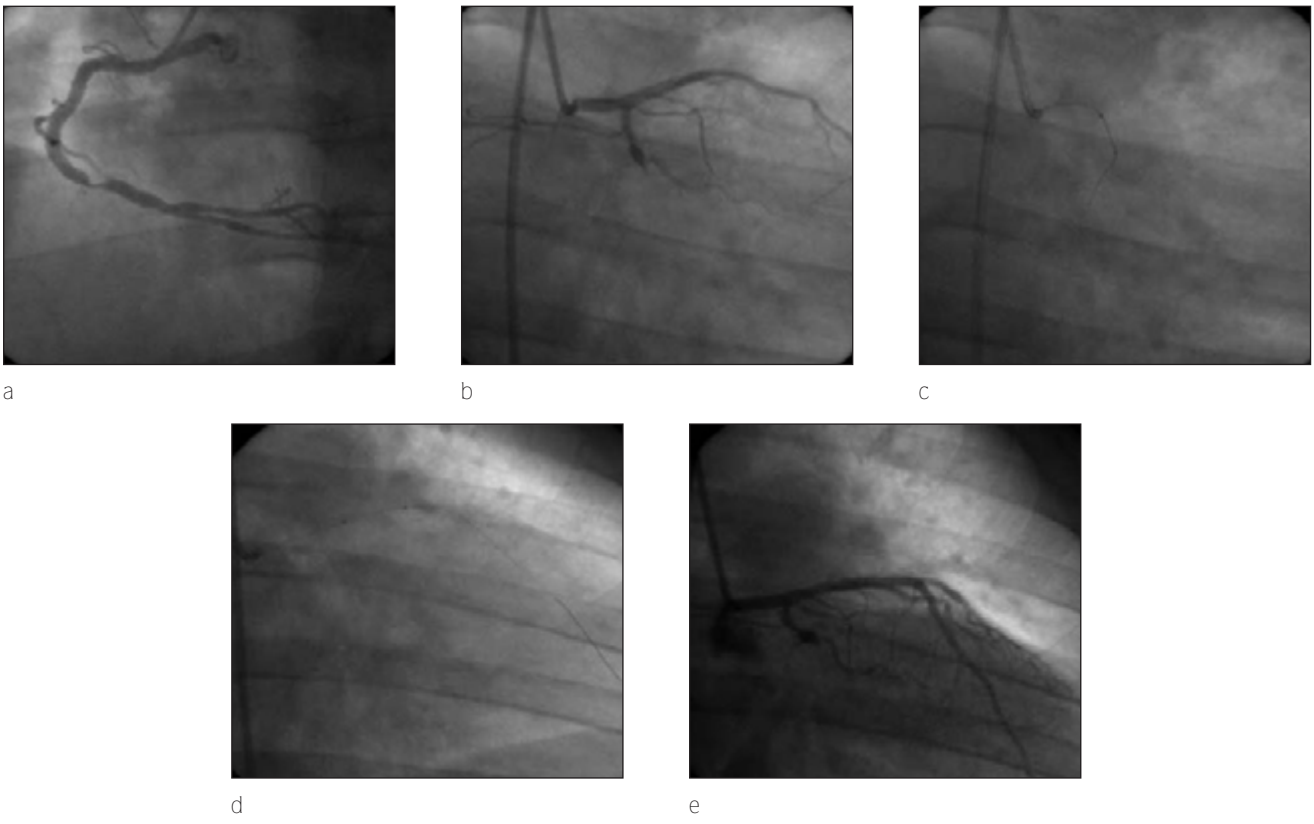
a b c

Figure 14.11
A 47-year-old male was admitted in severe cardiogenic shock and chest pain lasting one and a half hours. The ECG was non-conclusive with broadening of the QRS-complex. Immediate angiography revealed a total occlusion of the left main stem (a). After multiple balloon (3.5 mm) inflations, flow was restored and the clinical situation improved dramatically (b). It was decided to put a 4 mm stent in the left main stem extending to the proximal LAD. An optimal angiographic result, with normal myocardial blush, and without occlusion of sidebranches was obtained (c).



a b c

Figure 14.12
A 57-year-old man was admitted six hours following the onset of symptoms. The ECG showed anterior wall myocardial infarction. The right coronary artery was apparently normal whereas the left anterior descending artery was occluded after the bifurcation of a large, narrowed diagonal branch (a). Multiple balloon inflations resulted in a local dissection with considerable residual stenosis (b). It was decided to place a stent (3.5 mm diameter) with an angiographically good result (c). Although the TIMI flow was normal, the myocardial blush was considerably reduced, probably reflecting a long period of ischaemia and extensive damage on myocardial tissue level. The ejection fraction measured after 5 days with radionuclide techniques was 35%.



a b c

d e

Figure 14.13
A 43-year-old man was admitted with chest pain and dyspnoea 2.5 hours after symptom onset. He was hypotensive and appeared to be in cardiogenic shock. The ECG showed marked ST-depression in the precordial leads. On angiography the RCA was severely diseased (a), whereas both the circumflex and the left anterior descending artery were occluded (b). The ECG was compatible with an acute occlusion of the circumflex artery but despite several attempts with an over-the-wire balloon it was not possible to cross the lesion (c). With the same wire and balloon the occlusion of the LAD was crossed without any problems (d) and after placement of a stent the LAD had normal flow with complete resolution of the patient's chest pain and marked improvement of the ECG. The patient was treated with an IABP and a glycoprotein IIb/IIIa blocker. He recovered well and five months later a successful PTCA of the RCA was performed. The stent in the LAD looked excellent. This case demonstrates the importance of stepwise clinical decision making and the fact that the ECG is not always reliable (especially in multi-vessel disease).

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15

Adjunctive pharmacotherapy and coronary intervention

Derek P Chew and A Michael Lincoff

Introduction

The past two decades have witnessed dramatic progress in interventional cardiology. The diversification of technology has enabled the treatment of lesions with greater complexity, while providing commensurate declines in adverse ischemic outcomes. However, coronary interventions are inherently thrombogenic, with each technique resulting in various degrees of controlled vascular injury, generating a milieu primed for coronary thrombus formation and cellular proliferation. Since many patients undergoing percutaneous coronary interventions (PCI) present with acute coronary syndromes, coupled with the continued evolution of catheter-based reperfusion for acute MI and the proliferation in stent usage, the pharmacological suppression of early and late thrombotic events remains a critical consideration. Fortunately, pharmacological developments have paralleled the growth in interventional device technology. While pharmacological solutions to the problem of restenosis remain elusive (discussed elsewhere), the array of anti-thrombin and anti-platelet therapies available to the clinical interventional cardiologist continues to broaden. Furthermore, attempts to improve the outcomes from PCI have moved beyond the target lesion and towards the coronary microvasculature. The currently available anti-thrombin and anti-platelet therapies will be presented in this chapter, focusing on the evidence supporting their use in the catheterization laboratory and the controversies that surround their clinical application.

Anti-thrombin therapy

Heparin and LMWH

Pharmacology

Heparin is a glycosaminoglycan that indirectly inhibits thrombin via a high affinity interaction with antithrombin III.[1,2] Binding of heparin to antithrombin III accelerates this enzyme's inactivation of thrombin, factor Xa and factor IXa, with anti-thrombin activity being the most prominent. Heparin's anti-thrombin effect requires the simultaneous binding of heparin, anti-thrombin III, and thrombin.[3] Molecules of less than 18 saccharides lack sufficient length to simultaneously span antithrombin III and thrombin, and therefore lack anti-thrombin activity. In contrast, the anti-factor Xa activity of the heparin–antithrombin III complex is not dependent on heparin bridging the factor Xa and anti-thrombin III molecules. Therefore the anti-factor Xa effect of heparin is retained over a broad spectrum of molecular size.

Heterogeneity in unfractionated heparin's anticoagulant effect and pharmacological profile is the consequence of diversity in molecular weight (5000 to 30 000 daltons, mean 15 000 daltons). Up to two-thirds of administered heparin has no anti-thrombin activity due to insufficient saccharide length.[4] Molecules of higher molecular weight are cleared more rapidly and differential clearance results in the greater decline in anti-thrombin activity compared with antifactor Xa activity.[5] Therefore, the relationship between the activated partial thromboplastin time (APTT) and in vivo anti-coagulant effect is imperfect. Thrombin inactivation by heparin also occurs via heparin–cofactor II, an enzyme with specific activity for thrombin, but requires much higher heparin levels than the heparin-antithrombin III pathway. Intravenous administration of heparin provides a prompt onset of effect. Clearance is complex, with initial rapid but saturable metabolism within

endothelial cells and macrophages (zero-order kinetics) followed by slower renal clearance (first order kinetics), resulting in the variable plasma half-life of 30–150 minutes depending on dose.[6]

Low molecular weight heparin (LMWH) offers an alternative anti-thrombin approach. Chemical or enzymatic depolymerization of unfractionated heparin provides heparin fragments with a mean molecular weight one-third of that of unfractionated heparin. Nevertheless, molecular size (1000–10 000 daltons, mean 4000–5000 daltons) and therefore anti-coagulant characteristics remain heterogeneous.[7] Smaller fragments do not bind thrombin, but retain the anti-factor Xa activity via antithrombin III. However, between 25% and 50% of the heparin molecules retain anti-thrombin activity and the ratio of anti-thrombin:anti-factor Xa activity ranges from 1:2 to 1:4 among the specific preparations. Compared to unfractionated heparin, reduced non-specific plasma protein binding provides a more predictable dose–response while reduced binding to endothelial cells and macrophages increases the plasma half-life (2–4-fold longer).[7] Less platelet and platelet factor 4 interaction leads to lower rates of heparin-induced thrombocytopenia[8] and may contribute to less 'rebound' in thrombin activity. Clearance is by renal excretion, and the biological half-life is increased in those with renal failure[9] (Fig. 15.1).

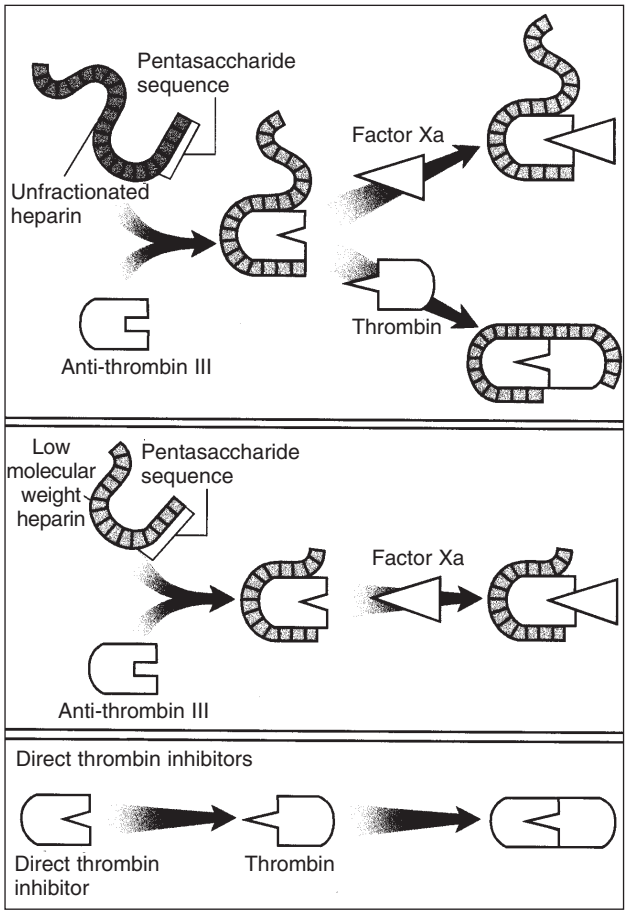

Figure 15.1
Pharmacological approaches to thrombin inhibition. Unfractionated heparin bridges anti-thrombin III and thrombin, while acting as a catalyst for the anti-thrombin III enzyme to increase anti-thrombin and anti-factor Xa activity. Low molecular weight heparin is unable to span and therefore augment the anti-thrombin III activity against thrombin, but retains anti-factor Xa activity. Direct thrombin inhibitors bind and inhibit thrombin without the need for anti-thrombin III. (Reproduced with permission from Weitz[7])

Efficacy and limitations of heparin therapy

Heparin effectively suppresses thrombin generation in patients undergoing angioplasty for stable angina when adequate anti-coagulation is achieved,[10] but efficacy for the entire spectrum of patient acuity has not been well established. While lesion complexity and unstable angina appear to predict relative insensitivity to heparin, no relationship between lesion complexity and continued thrombin generation was observed following angioplasty or directional atherectomy when the activated clotting time (ACT) was maintained >300 seconds.[11] In contrast, a correlation between a larger area of endothelial injury and increased thrombin generation despite adequate heparin therapy has been observed[12] (Table 15.1).

Several factors limit the efficacy of unfractionated heparin. Variable bioavailability results from non-specific binding of plasma proteins that are secreted by platelets and endothelial cells stimulated by thrombosis and the vascular inflammatory response.[13,14] The large molecular size of the heparin–anti-thrombin complex compromises the access to thrombin and factor Xa bound within thrombus or associated with the prothrombinase complex on platelet phospholipid surfaces.[15,16] Heparin's efficacy is subject to the availability of anti-thrombin III.[17] Prothrombotic effects have also been implicated. Platelet activation by unfractionated heparin has been observed,[18] and may contribute to a prothrombotic state following cessation of therapy.[19] Lastly, binding to platelet factor 4 leads to heparin-induced thrombocytopenia in 1–3% of patients.[8]

Alternatively, LMWH offers the advantages of more predictable dose–response,[4] greater duration of action, and possibly less marked platelet activation.[18] Supported by a large body of animal data,[20–27] demonstrating reduced neo-intimal proliferation with prolonged treatment with LMWH, initial clinical studies focused on the prevention of restenosis. However, these trials were uniformly disappointing.[28–32] Superior efficacy of LMWH over unfractionated heparin in acute coronary syndromes[33] has spurred interest in these agents for peri-procedural anti-coagulation. Initial observational studies suggest an acceptable level of clinical efficacy with low rates of bleeding with and without glycoprotein

Table 15.1 Pharmacological differences between unfractionated heparin and LMWH.

Property	*Unfractionated heparin*	*Low molecular weight heparins*
Mean molecular weight (Daltons)	15 000	5000
Mean saccharide units	45	15
Anti-Xa:anti-IIa activity	1	2–4
Half-life (h)	1	2–4
Bioavailability	+ to +++	++++
Subcutaneous absorption	++	++++
Binding to endothelium	+++	+
Binding to plasma proteins	+++	+
Binding to platelets/macrophages	++	+
Antigenicity	++	+
Clearance	Renal	Renal
Protamine neutralization	++++	++

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Table 15.2 Randomized trials of LMWH in percutaneous coronary intervention.

Author/study	*Year*	*Drug*	n	*Primary endpoint*	*Relative risk reduction*
ERA[30]	1994	Enoxaparin	458	Angiographic or clinical restenosis	2% (NS)
REDUCE[31]	1996	Reviparin	612	6 mth death/MI/revasc	4% (NS)
FACT[32]	1997	Nadroparin	354	3 mth angiographic restenosis	6% (NS)
ENTICES[199]	1998	Enoxaparin	123	Stent thrombosis	
NICE 1	1999	Enoxaparin	827	Anti-thrombotic efficacy (Unpublished) 1 mg/kg enoxaparin	
NICE 4[36]	2000	Enoxaparin	817	Safety 0.75 mg/kg enoxaparin with abciximab	

ERA: Enoxaparin Restenosis trial. REDUCE: Reduction of Restenosis After PTCA. Early Administration of Reviparin in a Double-Blind, Unfractionated Heparin and Placebo-Controlled Evaluation. FACT: Fraxiparine Angioplastine Coronaire Transluminale. ENTICES: ENoxaparin and TIClopidine after Elective Stenting. NICE: National Investigators Collaborating on Enoxaparin. NS = Non-significant.

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IIb/IIIa therapy.[34–36] Despite promising results,[36,37] the optimal dose of LMWH in patients undergoing PCI is uncertain, the required dose adjustment in patients receiving prior LMWH is unclear and the response to protamine, in the event of bleeding, is less predictable. Moreover, routine use of LMWH during PCI is hampered by the present lack of a rapid 'point-of-care' test, since ACT and APTT are not representative of anticoagulant efficacy with these agents. Several studies are currently exploring the role of these agents in the catheterization laboratory, including the potential synergistic role with glycoprotein IIb/IIIa antagonists, while development of a point of care test is under investigation (Table 15.2).

Practical issues and controversies

Since the inception of PCI, peri-procedural unfractionated heparin combined with aspirin has been the mainstay of anti-thrombotic strategy. Despite this wealth of experience, uniform practice recommendations have not developed and the optimum ACT remains uncertain. Most target ACT recommendations are empiric and derived from retrospective, non-randomized studies.[38,39] Furthermore, optimal levels in specific clinical presentations[40] or for interventional device modalities have not been fully explored and may differ significantly. Nevertheless, ischemic events have been inconsistently associated with low ACT levels, while bleeding risk clearly correlates with high ACT levels, total heparin dose, age, gender and renal insufficiency. Reinforced by the inter-individual variation in dose–response, these associations suggest that dose adjustment based on the ACT remains a standard of care.

Divergence in heparin dose–response results from variation in patient acuity (thrombus stimulated release of heparinase and platelet factor 4),[41] lesion complexity,[42] and concomitant medications.[43] Individualization of the heparin dose with weight-adjusted dosing provides a rational approach to attenuating this variability.[44] However, an

attempt to define the benefits of weight-adjusted dosing compared to higher fixed dosing in a randomized trial of 400 patients failed to determine superior efficacy or safety with either approach,[45] although earlier sheath removal was permitted by the weight-adjusted approach.

Observational data support pretreatment with heparin in acute coronary syndromes and in those with thrombus-containing lesions.[46–48] However, no randomized studies have been performed and the relative benefit of heparin pretreatment in the era of coronary stenting and glycoprotein IIb/IIIa inhibition is unknown. Nevertheless, heparin treatment as medical management prior to PCI in patients with acute ischemic syndromes remains a relatively low-cost and low-risk strategy. However, routine intravenous or subcutaneous heparin therapy after PCI cannot be advocated. Several studies demonstrate no incremental benefit with prolonged heparin therapy following coronary intervention,[49–52] while bleeding events, particularly vascular access site complications and length of stay, are increased.

Direct anti-thrombin therapy

By directly binding thrombin, this class of agents circumvents many of the putative limitations of heparin therapy. Direct thrombin inhibitors act independently of anti-thrombin III, are active against thrombin either bound within fibrin or in the fluid phase, and demonstrate less plasma protein binding, allowing a more predictable dose–response.[53] Platelet stimulatory effects may also be less prominent with this class of agents when compared to unfractionated heparin,[18] avoiding immune-mediated thrombocytopenia. The prototypical agent is hirudin, derived from the saliva of *Hurido medicinalis* (medicinal leech),[54] but currently produced by recombinant technology. Synthetic analogs include bivalirudin, an antagonist with many similarities to the parent molecule, as well as several non-covalent inhibitors (argatroban, napsapatran, and inogatran) and reversible-covalent inhibitors of the thrombin active site (efegatran).[55]

Hirudin is a 65 amino acid peptide-binding thrombin at the thrombin catalytic site and the anion exosite.[56] Multiple points of contact between the molecules enable a high affinity interaction. Binding is slowly reversible, providing stable thrombin inhibition and secondary prevention of platelet activation, factor V and VIII generation, and endothelin release. Potential advantages of hirudin-mediated thrombin inhibition include continued activity within platelet-rich thrombus and the lack of direct platelet interaction. However, rebound activation of coagulation may still occur with this agent.[57]

Animal studies with the direct thrombin inhibitors demonstrated superior suppression of thrombin generation and subsequent reduction in neo-intimal hyperplasia.[58–61] Encouraged by initial clinical studies showing fewer acute complications[62,63] and less troponin elevation in patients undergoing angioplasty,[64,65] the HELVETICA trial[66] investigated the role of hirudin in the prevention of ischemic events and angiographic restenosis. Despite a significant reduction in early cardiac events favoring intravenous followed by 3 days of subcutaneous hirudin therapy in this 1141 patient randomized study, no differences in 7-month event-free survival or angiographic indices of restenosis were observed. Early bleeding events were slightly increased with hirudin in this study, corroborating the increased bleeding events seen in the acute coronary syndrome trials with this agent.[67,68] In the 503 patients undergoing primary angioplasty in GUSTO IIb randomized to either heparin or hirudin, 30-day death, MI or stroke was reduced by 23% ($P = 0.37$), without a significant increase in bleeding[69] (Table 15.3).

Bivalirudin (hirulog)[70,71] retains the two terminal binding domains of hirudin (for the active site and the exosite) in a 20 amino acid molecule, providing highly specific binding but lower affinity due to fewer points of contact. In contrast to hirudin, thrombin is able to cleave the amino-terminal

Table 15.3 Randomized trials of direct thrombin inhibitors in percutaneous coronary intervention.

Author/study	*Year*	*Drug*	n	*Primary endpoint*	*Relative risk reduction*
Van den Bos et al[63]	1993	Hirudin	113	MI and CABG	87%, $P = 0.048$
Topol et al[62]	1993	Hirulog	291	Abrupt closure	59%, $P = 0.01$
Rupprecht et al[65]	1995	Hirudin	61	48 hour MI (troponin)	2% (NS)
HELVETICA[66]	1995	Hirudin	1141	7 mth death/MI/revasc	7% (NS)
Bittl et al[72]	1995	Hirulog	4098	In-hosp death/MI/revasc	7% (NS)
			704	Post-MI subgroup	36%, $P = 0.04$
GUSTO-IIb[69]	1997	Hirudin	503	30 Day death/MI/CVA	23% (NS)
Lewis et al[77]	1997	Argatroban	50	Adverse outcome	

HELVETICA: Hirudin in a European Trial versus Heparin in the Prevention of Restenosis after PTCA trial. GUSTO: Global Utilization of strategies to open Occluded Arteries. ns = non significant.

domain of bivalirudin, removing the active site inhibition, therefore offering transient anti-thrombin effects that may contribute to an improved safety profile.[55] Bivalirudin also augments the generation of protein C, a natural anticoagulant.[55] This agent undergoes extensive metabolism and almost no renal excretion, with a half-life of approximately 30 minutes.

The Hirulog Angioplasty Study randomized 4098 patients undergoing angioplasty for unstable angina or post-infarction angina to either adjunctive heparin or bivalirudin therapy.[72] In-hospital death, MI, abrupt closure or rapid deterioration due to cardiac cause was not significantly reduced by hirulog in the overall population. Subanalysis of the post-MI patients demonstrated a more prominent reduction in the primary endpoint with bivalirudin therapy (5.1% vs 10.8%, $P = 0.004$), suggesting superior efficacy of direct anti-thrombin therapy in the higher risk setting. In contrast to the hirudin experience, a statistically significant reduction in bleeding was noted with bivalirudin therapy (3.8% vs 9.8%, $P = 0.001$). Interestingly, the relationship between acute closure and ACT seen with heparin was not observed with bivalirudin, implying less dose–response variability with this agent and raising the possibility of safer anti-thrombin therapy without the need for anticoagulant monitoring.[73]

Overall, lower rates of bleeding (possibly improving procedural safety, especially with glycoprotein IIb/IIIa inhibition) and a superior dose–response relationship (possibly translating to less need for glycoprotein IIb/IIIa inhibition) make bivalirudin an attractive alternative to unfractionated heparin. Furthermore, when heparin is contraindicated, such as with heparin-induced thrombocytopenia, several reports attest to the efficacy of these agents.[74–77] However, before bivalirudin could become a broadly used anti-thrombin therapy for PCI, randomized data comparing bivalirudin to the current standard of heparin with routine glycoprotein IIb/IIIa inhibition are required. The CACHET study will address this question.

Anti-platelet therapy

Aspirin

Supported by evidence from numerous clinical trials, aspirin remains an integral component of medical therapy for both acute coronary syndromes and PCI.[78,79] Aspirin inhibits prostaglandin G/H synthase resulting in irreversible inhibition of cyclo-oxygenase activity, thereby decreasing thromboxane A2 production.[80] Other actions, such as the enhancement of fibrinolysis,[81] may also contribute to its anti-thrombotic effects, but these mechanisms play a secondary role. Aspirin is rapidly absorbed in the stomach and upper intestine, with peak plasma levels achieved in 30–40 minutes (although longer for enteric-coated preparations). The circulating half-life is short, 10–20 minutes, while platelet inhibition persists for the life-span of the exposed platelets (7–10 days). Therefore, 50% platelet function returns in approximately 5 to 6 days.

The role of aspirin in percutaneous coronary interventions is based on both retrospective observations[82,83] and randomized data.[79] A randomized comparison of aspirin and dipyridamole with placebo in 376 patients demonstrated a 77% risk reduction in peri-procedural MI ($P = 0.003$).[84] Subsequently, concurrent dipyridamole was shown to confer no additional benefit.[85] Comparisons between low and high dose aspirin have not demonstrated incremental benefits from increased doses. No impact of aspirin on restenosis has been observed. Overall, aspirin provides compelling benefits combined with a favorable safety profile at low cost. Thus, it is the primary anti-platelet therapy for percutaneous coronary interventions and provides the minimum standard upon which all new therapies should demonstrate incremental benefit.

ADP-receptor antagonists

As adjunctive platelet inhibition following coronary stenting, the thienopyridines provide effective intermediate-term suppression of subacute stent thrombosis,[86–88] thus facilitating the rapid growth in stent utilization worldwide. These orally active agents bind to the ADP-receptor and inhibit ADP-mediated platelet activation[89] and shear-stress-induced platelet aggregation.[90] Furthermore, attenuation of P-selectin and activated fibrinogen receptor expression, both predictors of subacute stent thrombosis following coronary stenting,[91–96] have also been documented. Synergy with aspirin supports this combined anti-platelet approach in stented patients.[97]

Ticlopidine is orally active but requires metabolism, as evidenced by its delayed onset (48–72 hours), which persists despite intravenous administration.[98] Maximum prolongation of the bleeding time occurs at 5–6 days and recovery of platelet function following discontinuation requires up to a week. Ticlopidine is associated with a relatively high rate of intolerance. Diarrhea occurs in up to 20% of patients, and rash in a smaller proportion (12%). Neutropenia is reported in 1–4% of patients, requiring frequent assessment of the white cell count. Ticlopidine induced thrombotic thrombocytopenic purpura is also described, with a recent series of patients documenting an overall mortality rate of up to 33%.[99]

Clopidogrel confers similar efficacy as ticlopidine with an improved safety profile. This agent is also orally active with a more rapid onset of action, particularly when an oral loading dose is given.[100] Clopidogrel 300 mg produces significant platelet inhibition within 2 hours of dosing. Gastrointestinal symptoms (4%) and rash (6%) are the most common side-effects, but are less common than with ticlopidine. Neutropenia (0.1%) and thrombocytopenia (0.3%) are very rare. In the CAPRIE trial,[101] overall bleeding rates with

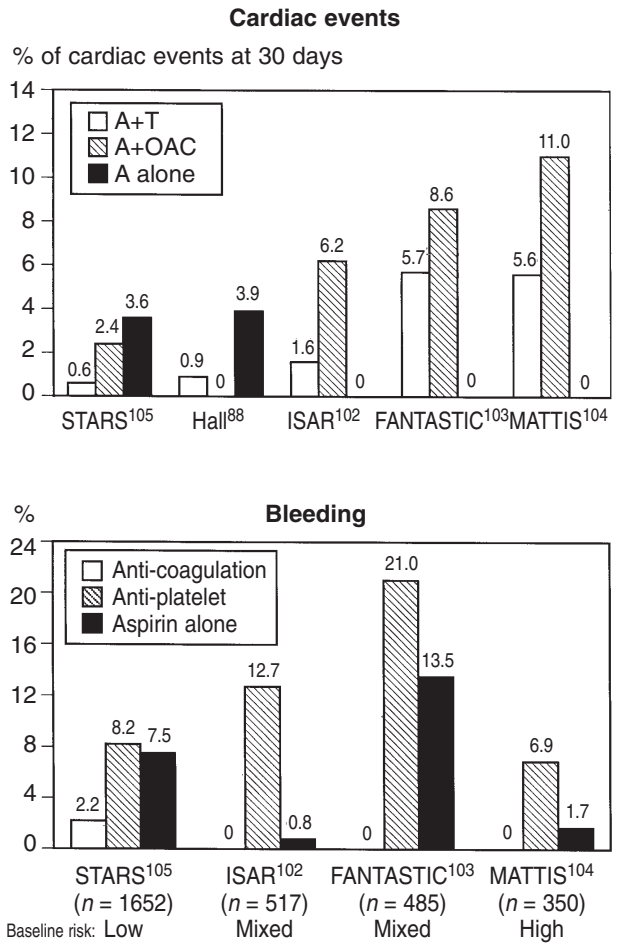

Figure 15.2
The five randomized trials of combined anti-platelet therapy compared with anti-coagulation following coronary stenting. ISAR: Intracoronary Stenting and Antithrombotic Regimen trial. STARS: Stent Anticoagulation Restenosis Study. FANTASTIC: Full Anticoagulation Versus Aspirin and Ticlopidine. MATTIS: The Multicentre Aspirin and Ticlopidine Trial after Intracoronary Stenting. A = aspirin; T = ticlopidine; OAC = oral anticoagulation.

clopidogrel were similar to aspirin (9.27% versus 9.28%), and gastrointestinal hemorrhage was slightly less common when compared with aspirin.

The evidence supporting the combination of aspirin and ticlopidine following coronary stenting has been established by five randomized trials.[88,102–105] These trials demonstrate a striking and consistent reduction in cardiac events coupled with reductions in bleeding complications and improved tolerance with the combination anti-platelet approach[106] when compared with heparin followed by coumadin or aspirin alone.[88,105] Patients with clinical[107] and procedural markers[104] of increased risk for stent thrombosis derive a greater absolute reduction in adverse ischemic events. No effect on restenosis has been demonstrated[108] (Fig. 15.2).

As an alternative to ticlopidine, clopidogrel is associated with more rapid onset, improved tolerability and fewer hematological complications. A direct comparative trial of 700 patients randomized to ticlopidine or clopidogrel after coronary stenting documents improved tolerance, but noted a non-significant increase in cardiac events with clopidogrel (clopidogrel: 3.1% vs ticlopidine 1.7%; $P = 0.24$).[109] However, the larger CLASSICS trial randomized stented patients to either ticlopidine or clopidogrel with and without an oral loading dose, finding a similar rate of adverse cardiac events in each group. Again, the safety end-point (bleeding, neutropenia, thrombocytopenia and drug discontinuation) occurred more frequently with ticlopidine therapy (ticlopidine: 9.1%, clopidogrel 75 mg daily 6.3%, clopidogrel 300 mg bolus/75 mg daily: 2.9%). No thrombocytopenia was seen with clopidogrel.

Practical issues and clinical controversies

Non-randomized data document reduced peri-procedural CK elevations following stenting with combined aspirin and ticlopidine pretreatment and show that the magnitude of benefit correlates with the duration of ticlopidine pretreatment.[110] This clinical evidence is reinforced by ex vivo evidence of superior thrombin and platelet suppression when ticlopidine is begun >24 hours prior to planned stenting.[111,112] These data support early pretreatment with thienopyridines whenever feasible, but raise the concern of excessive bleeding if emergent bypass surgery is required. Fortunately, with the advent of stenting, the need for emergent surgery continues to decline. A shorter post-procedural duration of therapy (2 weeks rather than 4 weeks) with clopidogrel has been advocated,[113] but is as yet unsupported by randomized data.

Glycoprotein IIb/IIIa antagonists

The glycoprotein IIb/IIIa receptor is a heterodimeric molecule with extracellular binding domains for fibrinogen, fibronectin and von Willebrand factor, representing the final common pathway for platelet aggregation.[114,115] In addition, an intracytoplasmic tail transmits 'outside-to-inside' signals involved in platelet degranulation and clot retraction, while an alternate binding site for prothrombin facilitates thrombin generation.[116] Receptor activity is dynamic and dependent on prior platelet activation.[117] Current approaches to glycoprotein IIb/IIIa inhibition include a monoclonal antibody fragment (abciximab) and competitive inhibition with small molecule antagonists (eptifibatide and

tirofiban). This recent shift in focus away from thrombin inhibition towards potent platelet inhibition with these agents has led to substantial reductions in the adverse ischemic outcomes associated with PCI.[118]

Abciximab

Abciximab is a chimeric (human-murine) monoclonal Fab antibody fragment targeting the β_3 integrins, glycoprotein IIb/IIIa and $\alpha_v\beta_3$ (the 'vitronectin receptor').[119,120] Affinity for both the activated and inactivated receptor is high. Receptor binding is reversible but dissociation is slow. Normalization of platelet function occurs in 24–36 hours after discontinuation of the drug.[121] The target level of >80% platelet inhibition (correlating with >80% glycoprotein IIb/IIIa receptor occupancy[121]) occurs with the 0.25 mg/kg bolus in >90% of patients.[122] The half-life of unbound abciximab is quite short (26 minutes) and a maintenance infusion is required to provide sustained receptor blockade, particularly since up to 50% more glycoprotein IIb/IIIa receptors may be externalized from α-granules in response to strong antagonists.[123,124] In the setting of angioplasty, the addition of abciximab to standard heparin and aspirin therapy demonstrates superior suppression of thrombin generation, indicating inhibition of platelet procoagulant activity.[125,126] This effect may account for the 30–40 second prolongation of the ACT by abciximab when administered with heparin.[127] Elimination occurs with platelet clearance and through transfer to new unoccupied platelets[128] (Table 15.4).

Clinical data from the abciximab trials constitute the majority of evidence supporting the use of glycoprotein inhibition IIb/IIIa as adjunctive pharmacotherapy for PCI. The initial study, EPIC,[129] investigated the role of abciximab in patients undergoing high-risk angioplasty and demonstrated a 35% relative risk reduction in the 30-day composite end-point (death, MI or any revascularization), at the cost of increased bleeding events. Subsequent trials[130] have enrolled a broader population of patients in a more contemporary interventional practice setting (coronary stenting),[131] and have demonstrated a remarkably consistent 50–60% reduction in death, myocardial infarction and urgent revascularization at 30 days. Furthermore, the use of concurrent low dose (70 units/kg) weight-adjusted heparin and the abolition of post-procedural heparin have eliminated the increased bleeding events without compromise of clinical efficacy. These benefits extend to each component of the composite end-point, and to all demographic subgroups, regardless of patient acuity, baseline clinical factors, lesion complexity[132] or interventional techniques.[133–135]

Several aspects of the abciximab clinical experience are unique among the available anti-thrombotic therapies used in the cardiac catheterization laboratory. Firstly, the early benefits observed in these trials are maintained at long-term follow-up, with reduction in the composite end-point observed at 3 years in the initial EPIC study.[136] Secondly, the trend towards a reduction in long-term mortality observed in the EPIC and EPILOG studies is confirmed by a significant reduction at 12 months in EPISTENT (stent + placebo = 2.4% vs stent + abciximab = 1.0%, $P = 0.037$). Whether this benefit is wholly attributable to reductions in peri-procedural myocardial infraction is unclear. A clinically meaningful effect on target vessel revascularization, promised by early studies,[129] remains uncertain.

Table 15.4 Overview of abciximab in percutaneous coronary intervention: 30-day relative risk reduction in composite end-points from the abciximab trials.

Trial	n	*Population*	*Randomized therapy*	*30 Day composite end-point RR (%)*	P *value*
EPIC[129]	2099	High risk PCI	Bolus Abx	10	0.43
			Bolus and infusion Abx	35	0.008
EPILOG[130]	2792	PCI	Heparin 70 units/kg	56	<0.0001
		PCI	Heparin 100 units/kg	54	<0.0001
EPISTENT[131]	2399	PCI	PTCA/ Abx vs stent	36	0.007
			Stent Abx vs stent	51	<0.001
CAPTURE[161]	1265	Unstable angina:	Abx pretreatment	29	0.012
RAPPORT[152]	429	AMI	Primary PTCA	48	0.03
ADMIRAL	300	AMI	Primary stent	50	

EPIC: Evaluation of c7E3 for the Prevention of Ischemic Complications. EPILOG: Evaluation in PTCA to Improve Long term Outcome with abciximab GPIIb/IIIa blockade. EPISTENT: Evaluation of IIb/IIIa Platelet Inhibitor for Stenting. CAPTURE: C7E3 FAB Anti-Platelet Therapy in Unstable Refractory Angina. RAPPORT: ReoPro and Primary PTCA Organization and Randomized Trial. ADMIRAL: Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up. AMI = Acute Myocardial Infarction. Abx = abciximab

Eptifibatide

Eptifibatide is a heptapeptide based on the modified KGD (Lys·Gly·Asp) sequence demonstrating competitive inhibition of the fibrinogen receptor.[137] As opposed to abciximab, its specificity is confined to the glycoprotein IIb/IIIa receptor. Early studies established a promising pharmacodynamic profile with immediate onset of action and rapid dissociation, providing swift return of platelet function with the cessation of therapy (within 4 hours).[138] Clearance is primarily by renal excretion and dose adjustment in renal impairment is required but not well defined.

Initial studies of eptifibatide in PCI have been confounded by dose uncertainties. The IMPACT II trial randomized 4010 patients to two doses of eptifibatide compared with placebo.[139] Despite clinical benefits demonstrated at the end of the 24-hour course of therapy, only a trend towards reduction in the primary composite end-point (death, MI, urgent revascularization and bailout coronary stenting) was evident at 30 days. This modest treatment effect may have been largely explained by inadequate dosing. Sodium citrate, the anti-coagulant used for platelet aggregation measurements, lowers ionic calcium and inhibits fibrinogen binding while exaggerating the efficacy of eptifibatide compared with measurements performed at physiological concentrations of calcium. Therefore, the doses used in IMPACT II based upon ex vivo platelet aggregation studies in citrated blood actually produced only 30–40% platelet inhibition in response to ADP.[137,140]

More recent studies using higher doses of eptifibatide have established a more substantial clinical benefit with this agent. The PURSUIT study investigated the role of eptifibatide in patients with acute coronary syndromes.[141] The most prominent benefit was observed in those undergoing PCI within 72 hours (while on eptifibatide), with a 30% reduction in the composite end-point of death and MI at 30 days (16.8% vs 11.8%, P = 0.013).[142] Furthermore, the recently completed ESPRIT trial, using a high-dose double bolus and infusion regimen of eptifibatide established convincing reductions in ischemic end-points for patients undergoing coronary stenting (Table 15.5).

Tirofiban

Tirofiban, a tyrosine analog, is a small non-peptide molecule mimicking the geometric and charge characteristics of the RGD (Arg·Gly·Asp) sequence involved in fibrinogen binding. This agent also provides competitive inhibition of the glycoprotein IIb/IIIa receptor.[143,144] Like eptifibatide, binding is specific, with rapid onset and reversibility of effect. The half-life is short (1.2 hours) with 80% renal clearance resulting in diminished platelet inhibition at 4 hours and normalization at 8 hours after drug cessation.[143] Reduced doses are required in those with renal impairment. Synergistic platelet inhibition has been documented with aspirin and ADP antagonists.[145]

The RESTORE trial[146] randomized 2141 patients with unstable angina undergoing PCI to either tirofiban or placebo. Again, prominent treatment effects were observed at 2 days, but by 30 days only a trend favoring a reduction in death, MI and target vessel revascularization with tirofiban was documented (relative risk reduction: 16.2% at 30 days, P = NS). More promising results were observed in the PRISM-PLUS study[147] investigating the role of tirofiban as empiric therapy for non-ST elevation acute coronary syndromes. Among 475 patients undergoing early revascularization, a 43% reduction in death or MI at 30 days was observed (10.2% vs 5.9%, P = NS).

Practical issues and controversies

High-risk PCI

Although all patients seem to benefit from glycoprotein IIb/IIIa blockade, efficacy may be enhanced in certain high risk subgroups. The increased risk of adverse events observed in diabetic patients undergoing PCI is negated with glycoprotein IIb/IIIa therapy. From EPILOG, the diabetic subpopulation receiving abciximab experienced adverse event rates for death and myocardial infarction comparable to the non-diabetic

Table 15.5 Overview of eptifibatide in percutaneous coronary intervention.

Trial	n	*Eptifibatide dose*	*Primary end-point*	*Relative risk reduction (%)*	P *value*
IMPACT II[139]	4010	135 μg/kg + 0.5 μg/kg/min	30 day death/MI/urgent	19	0.063
		135 μg/kg + 0.75 μg/kg/min	revasc/stent for AVC	13	0.220
PURSUIT[142]	1228	180 μg/kg + 2 μg/kg/min	30 day death/MI	30	0.013
ESPRIT[200]	2007	180 μg/kg,180 μg/kg + 2 μg/kg/min	48 hour death/MI/urgent revasc	36	0.005

AVC: Acute vessel closure.
IMPACT II: Integrelin to Manage Platelet Aggregation to combat Coronary Thrombosis II. PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrelin Therapy. ESPRIT: Enhanced Suppression of the Platelet glycoprotein IIb/IIIa Receptor using Integrelin Therapy.

Table 15.6 Results of the 30-day reduction in death, MI and urgent revascularization with abciximab (bolus and 12 hour infusion) in patients presenting with acute coronary syndromes.

Trial	n	*Abciximab* (%)	*Placebo* (%)	*RR reduction* (%)	P *value*
EPIC[129]	470	3.8	13.1	71	0.004
EPILOG[130]	1312	4.8	12.2	69	0.05
EPISTENT[131]	864	4.5	14.8	70	
RAPPORT[152]	429	5.8	11.2	48	0.03

EPIC: Evaluation of c7E3 for the Prevention of Ischemic Complications. EPILOG: Evaluation in PTCA to Improve Long term Outcome with abciximab GP IIb/IIIa blockade. EPISTENT: Evaluation of IIb/IIIa Platelet Inhibitor for Stenting. RAPPORT: ReoPro And Primary PTCA Organization and Randomized Trial.

patients at 6 months, while these event rates were 48% higher in the diabetic population compared with the non-diabetic population receiving placebo.148 A prominent mortality benefit at one year (~50%) has also been observed in a combined analysis of diabetics in EPIC, EPILOG and EPISTENT using abciximab. Whether similar benefits can be expected from the other agents of this class is less certain and awaits the final analysis of trials currently incomplete. In patients undergoing PCI for acute coronary syndromes, abciximab is associated with a greater relative risk reduction in death and myocardial infarction at 30 days when compared with stable patients. From the EPIC trial, the end-point of death, MI and target vessel revascularization was reduced by 71% at 30 days (P = 0.004),149 effectively eliminating the increased relative risk of adverse ischemic events observed in these patients. Furthermore, among acute coronary syndrome patients, troponin elevation may identify patients who derive greater benefit from glycoprotein IIb/IIIa therapy150 (Table 15.6).

Acute myocardial infarction

As either peri-procedural pharmacotherapy for primary PCI or in combination with reduced dose fibrinolysis leading to facilitated PCI, glycoprotein IIb/IIIa inhibition has contributed to the continued evolution of catheter-based reperfusion for acute MI. Adjunctive use of abciximab in the primary PCI strategy confers greater recovery in coronary flow (implying a microvascular effect) with corresponding improvement in regional wall motion abnormalities.[151] These improvements translate to a 50% relative risk reduction in death, myocardial infarction and urgent revascularization at 30 days for patients undergoing either primary angioplasty[152] or primary stenting. Alternatively, superior procedural success rates for catheter-based reperfusion associated with initial vessel patency (TIMI grade 2 or 3 flow)[153] have driven attempts to improve initial pharmacological reperfusion with early abciximab therapy[154] or combined glycoprotein IIb/IIIa therapy and low-dose fibrinolytic therapy. While the phase II studies have shown promising results,[155,156] assessment of the impact of these strategies on clinical outcomes awaits the results of ongoing large-scale trials, and combined glycoprotein IIb/IIIa inhibitor and fibrinolytic regimens cannot be currently recommended in clinical practice.

Differences between the agents

Disparity in the magnitude of benefit, durability of effect and impact on target vessel revascularization observed among the clinical trials raises the question of real efficacy differences between the agents. While observations can be made, definitive conclusions are difficult to draw in the absence of direct comparative trials. Whether heterogeneity results from: (a) variation in receptor binding characteristics;[157] (b) differences in thrombin inhibition;[158] (c) inadequate dosing;[140] (d) or non-glycoprotein IIb/IIIa[159] and prothrombotic effects[160] remains uncertain. The TARGET trial, directly comparing tirofiban to abciximab in stented patients, and the final results of the ESPRIT placebo-controlled trial of eptifibatide in coronary stenting will further define comparative efficacy of these agents.

Target vessel revascularization

Whether a reduction in target vessel revascularization (TVR) and 'clinical restenosis' results from therapy with abciximab remains a contentious issue. The 26% reduction in TVR at 6 months with abciximab reported from EPIC[129] has not been consistently replicated in subsequent studies,[130,161] although improvements in angioplasty technique associated with lower restenosis rates in the later trials may make any real difference more difficult to demonstrate. Interestingly, diabetics in the EPISTENT trial[131,162] enjoyed a ~50% reduction in TVR with stenting and abciximab compared with stenting alone. Nevertheless, the mechanism of this benefit remains unknown in light of the ERASER study[163] of 241 stented patients randomized to abciximab or placebo. Angiographic and intravascular ultrasound follow-up at 6 months demonstrated no reduction in neo-intimal hyperplasia or target vessel revascularization. The small molecule antagonists have also failed to produce a reduction in clinical or angiographic restenosis.[164,165]

Concurrent heparin and bleeding

Bleeding may be increased with glycoprotein IIb/IIIa inhibition, with vascular access site complications representing the majority of events. No increase in intra-cerebral bleeding has been observed in any of the randomized studies. Glycoprotein IIb/IIIa inhibition decreases concurrent heparin requirements[125,126] and bleeding complications can be largely avoided by reducing the concurrent heparin dose. With abciximab, the EPILOG trial[130] demonstrated similar efficacy but superior safety when heparin was administered at 70 units/kg as compared with 100 units/kg. Major bleeding rates with abciximab and low-dose heparin are equal to or lower than full-dose heparin without abciximab. When abciximab therapy is planned, an empiric target ACT of >200 seconds is suggested. A weight-adjusted heparin dose targeting an ACT level of >300 seconds appears optimal when abciximab is not planned, avoiding excessively prolonged ACTs if abciximab is required. However, the bailout use of abciximab is currently only supported by non-randomized data.[166] Optimal ACT levels with the other glycoprotein IIb/IIIa agents, planned or unplanned, are not well defined.

In addition to reduced heparin doses, attention to vascular access site care, sheath removal at 4–6 hours (when ACT < 175 seconds or APTT < 150 seconds) and avoidance of venous sheaths reduces the likelihood of bleeding events. Vascular closure devices do not appear to increase overall bleeding rates in the setting of glycoprotein IIb/IIIa inhibition in a non-randomized series, though retroperitoneal bleeding may be increased.

Nevertheless, bleeding risk remains of concern when the use of glycoprotein IIb/IIIa antagonists is unplanned, such as 'bailout' administration following full-dose heparinization. Careful reversal of heparinization after glycoprotein IIb/IIIa inhibition with protamine[167] may attenuate the bleeding risk if ACT levels are particularly elevated. Similarly, during 'rescue' PCI for failed full dose thrombolysis close monitoring of the ACT and reduced concurrent heparin doses is prudent.

Cardiac surgery

Glycoprotein IIb/IIIa therapy does not markedly increase the risk of major blood loss with urgent cardiac surgery. Reversal of abciximab's effect can be achieved with platelet transfusions. The increase in receptors available for abciximab binding reduces mean platelet inhibition below 60–80%, with a commensurate decrease in skin bleeding time. Both eptifibatide and tirofiban have shorter half-lives of therapeutic effect and usually require only cessation of infusion to reduce the bleeding risk. Interestingly, platelet counts following cardiac surgery with prior abciximab or eptifibatide therapy show relative preservation, suggesting glycoprotein IIb/IIIa inhibition mediates protection from cardiac bypass pump platelet consumption.

Thrombocytopenia

Between 0.4% and 1% of patients experience profound thrombocytopenia following glycoprotein IIb/IIIa therapy, observed more commonly with abciximab than with the small molecule antagonists. This phenomenon differs from heparin-induced thrombocytopenia by its early onset (within 24 hours) and precipitous nature. The precise mechanism is unclear, but immune clearance is suspected and supported by an association between ligand-induced binding site expression and lower platelet counts.[93] Interestingly, the combination of LMWH and abciximab appears to be associated with lower rates of thrombocytopenia, suggesting platelet activation by unfractionated heparin has a role.[36] Cessation of therapy allows platelet counts to return towards normal by 20 000–30 000/day, with little evidence of ongoing platelet clearance. Platelet transfusions are safe and protective of bleeding events, and should be considered for platelet counts < 20 000/dl.

Re-administration

Human anti-chimeric antibodies (HACA) occur in 5–6% of patients within the first month of abciximab therapy, raising the question of the safety of re-administration. Prospective studies have not shown increases in hypersensitivity reactions, anaphylaxis, or reduced clinical efficacy.[168] A slight increase in thrombocytopenia has been reported with the re-administration, but HACA antibody positivity is not predictive of these events.[168] No antibody response has been reported with either tirofiban or eptifibatide, while rates of thrombocytopenia with repeat administration are unknown.

Economic considerations

Economic constraints limit the routine use of these agents in practice, but cost-effectiveness analyses suggest that routine use is economically favorable. In the EPIC data set, the routine use of abciximab conferred a $600–700 in hospital saving, which was somewhat offset by the costs of increased bleeding complications ($550).[169] Elimination of excess bleeding complications improved the costs and cost effectiveness, as demonstrated in EPILOG, while the overall reduction in mortality observed with the stent and abciximab strategy in EPISTENT extrapolates to a cost-effectiveness ratio of $6213 per life-year added.[131] This cost effectiveness compares satisfactorily with other accepted therapies in medicine, such as the $7000 per life-year estimated for coronary artery bypass grafting for left main disease. In patients at high risk, such as those with diabetes and acute coronary syndromes,[149] cost effectiveness may be even more attractive. The cost effectiveness of the small molecule antagonists has thus far been difficult to assess, owing to the lack of mortality benefit in the clinical trials. A better appreciation of the economic value of the small molecule antagonists awaits the analysis of the more current PCI trials.

Pharmacotherapy for the microvasculature: the next frontier

Current adjunctive pharmacological therapy for PCI has been directed towards the suppression of lesion-associated thrombus. However, mechanical vascular injury and micro-embolism lead to microvascular occlusion and myonecrosis in up to 30% of patients undergoing coronary revascularization,[170–172] with an associated proportional increase in long-term mortality.[173–176] The development of investigative modalities capable of imaging the microvasculature (myocardial contrast echocardiography, magnetic resonance imaging, and positron emission tomography) has shifted attention towards protection of the distal vascular bed.[177]

'No-reflow', the gross manifestation of microvascular disruption, occurs in ~2% of interventions,[178] and is associated with increased mortality (8–15%).[178,179] Although initially attributed to profound microcirculatory vasospasm, its prevalence during acute infarct angioplasty (12%), saphenous vein graft intervention (4%), rotational (7%) and directional atherectomy (4.5%)[178] indicates that distal embolization[180–184] and ischemia-induced leukocyte adhesion[185–186] contribute to the pathophysiology. Treatment with intra-coronary boluses of nitroglycerin, papavarine,[187] verapamil[178,188] and nitroprusside are supported by small studies. Recent anecdotal reports also suggest a role for glycoprotein IIb/IIIa inhibition in these patients.[166,189]

Although supported by animal data, many attempts to institute routine pharmacological protection of the coronary microvasculature have met with disappointment in the clinical environment, attributed to unanticipated toxic effects or the lack of clinically meaningful benefits. Some approaches depend on distribution to the vascular micro-environment before the ischemic injury or reperfusion, and such agents may be better suited to the prevention of peri-procedural events. Strategies that remain promising include targeting inflammatory cell or adhesion molecule activity in the distal microcirculation (glycoprotein IIb/IIIa,[151,159] p-selectin[190] and complement inhibition[191]), and the prevention of destructive ion fluxes across ischemic endothelial and myocyte cell membranes (cariporide,[192] adenosine,[193–196] and nicorandil[197,198]). By maintaining the integrity of the distal circulatory bed, such therapies are likely to provide important further reductions in peri-procedural ischemic events.

Recommendations for anti-thrombotic therapy

(1) Aspirin 75–325 mg in all patients. Clopidogrel 75 mg daily or ticlopidine 250 mg BID is a reasonable alternative in aspirin-intolerant patients.

(2) Unfractionated heparin in all patients:
   - No concurrent glycoprotein IIb/IIIa inhibition planned: 100 units/kg with additional boluses as necessary to achieve and maintain an ACT > 300 seconds.
   - Concurrent glycoprotein IIb/IIIa inhibition planned: 70 units/kg with additional boluses as necessary to achieve and maintain an ACT > 200 seconds.

(3) There is no support for the use of post-procedural anti-thrombin therapy.

(4) Bivalirudin is an effective alternative for patients with heparin sensitivity such as heparin-induced thrombocytopenia.

(5) Glycoprotein IIb/IIIa inhibition is indicated in all patients, and will be particularly beneficial in high-risk patients, including those with acute coronary syndrome and diabetes, multi-lesion and multi-vessel PCI, rotational and directional atherectomy, increased lesion complexity, and where a large myocardial territory is at risk.

(6) Following coronary stenting, clopidogrel 75 mg should be administered for 4 weeks. Pretreatment with ADP antagonists is advocated when feasible. Clopidogrel 300 mg stat followed by 75 mg daily is recommended in those not commenced prior to PCI. Ticlopidine 150 mg BID is an acceptable alternative.

Abbreviations

ADMIRAL: Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up.
CADILLAC: Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial.
CAPTURE: C7E3 FAB Anti Platelet Therapy in Unstable Refractory Angina.
EPIC: Evaluation of c7E3 for the Prevention of Ischemic Complications.
EPILOG: Evaluation in PTCA to Improve Long term Outcome with abciximab GP IIb/IIIa blockade.
EPISTENT: Evaluation of IIb/IIIa Platelet Inhibitor for Stenting.
ESPRIT: Enhanced Suppression of the Platelet glycoprotein IIb/IIIa Receptor using Integrelin Therapy.
HELVETICA: Hirudin in a European Trial vs Heparin in the Prevention of Restenosis after PTCA.
IMPACT II: Integrelin to Manage Platelet Aggregation to combat Coronary Thrombosis II.
PRISM: Platelet Receptor inhibition in Ischemic Syndrome Management.
PRISM-PLUS: Platelet Receptor inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms.
PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy.
RESTORE: Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis.
TIMI: Thrombolysis In Myocardial Infarction.

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16

Thrombectomy and mechanical thrombolysis

Jose A Silva and Stephen R Ramee

Introduction

Acute coronary syndromes are a frequent cause of hospital admissions in industrialized nations. In the United States alone, acute coronary syndromes and myocardial infarction account for over 1.5 million hospital admissions annually.[1] These syndromes share a common pathophysiology: a cholesterol-rich atherosclerotic plaque suddenly ruptures, triggering the formation of thrombus which further compromises coronary flow.[2–5] Depending on the size of the thrombus, collateral flow, and the intrinsic fibrinolytic system, a spectrum of clinical presentations may ensue, including minimal or no symptoms, unstable or accelerated angina pectoris, myocardial infarction or even sudden death. Thrombotic lesions present a challenge for the interventional cardiologist as percutaneous treatment is associated with an increased complication rate such as abrupt occlusion, emergency bypass surgery, and death.[6,7] Thrombotic lesions also appear to play an important role in restenosis.[8,9] Consequently, removal of coronary thrombi prior to plaque intervention is desirable.

Whereas the use of pharmacologic thrombolysis before or during percutaneous coronary intervention (PCI) has yielded mixed results with some studies showing increased procedural complications,[10] the use of the GP IIb/IIIa platelet inhibitors has uniformly been shown to decrease procedural complications, when small or suspected thrombus is present.[11–14] On the other hand, when facing a large thrombus burden, mechanical approaches offer a faster and more efficient thrombus resolution.

In the present chapter, we discuss the mechanisms of action and the clinical applications of the current thrombectomy and thrombolysis devices available for the treatment of thrombotic lesions in native coronary arteries and saphenous vein grafts.

Mechanical thrombectomy

Several devices have been developed for mechanical thrombectomy, including the Possis AngioJet™ (Possis Medical, Minneapolis, MN), the Hydrolyser (Cordis Europa, Roden, The Netherlands), the Clot Buster Amplatz Thrombectomy Device (ATD, Microvena Corporation, White Bear Lake, MN), the Arrow-Trerotola Percutaneous thrombolytic device (PTD) (Arrow International, Reading, PA), and the Shredding Embolectomy Thrombectomy (SET) device (Convergenza, San Diego, CA). This chapter will concentrate on the first two devices, since they are the only devices available for the treatment of thrombotic lesions in coronary arteries and saphenous vein grafts.

Rheolytic thrombectomy with the Possis AngioJet™ System

System description

The AngioJet™ system consists of three components:[15,16] the external and portable drive unit, a disposable and single-use pulsatile pump, and a disposable and single-use catheter. The system is powered by the drive unit which provides the necessary power to operate the pulsatile pump and controls the flow of saline to and from the catheter. The pulsatile pump provides the pathway for the removal of the mixture of saline, thrombus and blood from the catheter to a collection bag which stores this effluent debris during the procedure. The catheter uses the Venturi–Bernoulli vacuum principle, by which high-speed saline jets create a low-pressure region at the tip of the catheter which acts to pull the thrombus from the vessel and propel it from the body (Fig. 16.1).

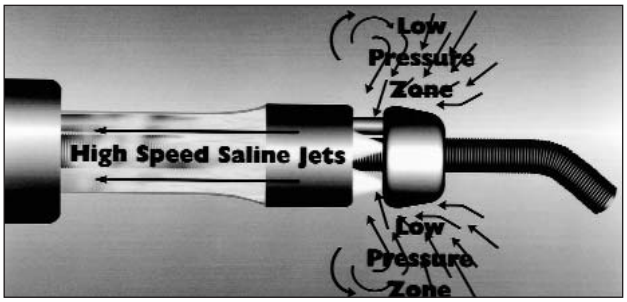

Figure 16.1
AngioJet™ catheter design.

Mechanism of action

As the system operates, the pump set provides the catheter with a heparinized sterile saline flow at the rate of 50 to 60 ml/min. The saline delivered to the catheter is at a pressure of approximately 600 atm (900 psi), and a temperature of 37°C. Passage of the saline through the long, small diameter tube results in a significant decrease of the saline pressure, so that at the tip the saline pressure has dropped to approximately 170 atm (250 psi). The tip of the catheter has a metal ring with evenly spaced holes through which the saline jets flow back toward a steel cylinder in the catheter body. The jets are aimed inward, so that they intersect at the catheter center line if extended, which avoids contact with the vessel wall. The saline jets exit from the ring at about 500 km/h. Applying the Bernoulli principle, these high-speed saline jets create a vacuum inside the tip of –760 mmHg, resulting in a gradient between the pressure at the tip of the catheter and the pressure inside the artery of approximately –860 mmHg (assuming a normal mean pressure of +100 mmHg inside the artery). This negative pressure gradient forces the surrounding mixture of thrombus, blood and saline into the opening of the tip. Once inside the jet, the thrombus is subjected to powerful mixing and is broken up into very small particles. When a jet reaches the opposite side of the tip, it contains a homogeneous mixture of thrombi debris, blood, and saline.[15,16]

Catheter delivery and procedure

The technique used to deliver the coronary AngioJet™ catheter (LF140; 140 cm long nylon dual-lumen shaft) is similar to other standard PCI techniques. Patients are pre-treated with aspirin and if possible with calcium channel blockers. Heparin is given to maintain an ACT of ≥ 300 seconds. After a 7 or 8 French guiding catheter (minimum internal diameter = 0.080 inch) is in position, a guidewire is advanced distal to the treatment site. The AngioJet™ catheters (LF140 coronary, and F105 peripheral) are 5 French devices, designed to operate over a standard 0.014 or 0.018 inch guidewire. Because transient bradycardia occurs, presumably due to the release of adenosine from hemolysed red cells,[17] the use of a prophylactic temporary pacemaker during the procedure is recommended.

The catheter is then advanced over the guidewire until it reaches the location of the thrombus. At this point the system may be activated by depressing the foot switch on the drive unit. The device is then advanced at 2 to 3 mm/s, sweeping toward the distal end and then deactivated; alternatively, the thrombus may be crossed toward the distal end with the device deactivated. After the thrombus has been crossed, the device is activated, sweeping toward the proximal end. We prefer the second approach, because we believe that it may decrease the likelihood of distal embolization. The operator should continue making passes until no further improvement of thrombus burden is seen.

Indications and contraindications for use

The coronary LF140 AngioJet™ catheter is designed to remove fresh and semiorganized thrombus, preferably less than 2 weeks old, from native coronary arteries and saphenous vein grafts in patients with acute coronary syndromes including acute myocardial infarction.[18–21] The Possis AngioJet™ has also been used successfully in thrombotic occlusion of the peripheral circulation, AV dialysis grafts, deep venous thrombosis, and pulmonary embolism.[22–24]

The coronary LF140 AngioJet™ catheter should not be used in vessels of less than 2 mm in diameter, since this increases the likelihood of vessel wall injury, dissection, and perforation. Other contraindications include vessels with previous dissections, perforations, loose atheromatous flaps, suboptimally deployed or unexpanded stents, or recent anastomosis.

Complications

In vitro and in vivo animal studies have shown that the Possis AngioJet™ catheter causes minimal trauma to the vessel wall.[16] Experimental and clinical studies have also shown that the device causes mild and transient hemolysis, usually of no clinical significance.[15,16,21] Distal embolization, transient and sustained no-reflow, and perforation are rare, although they continue to be potential complications in 2 to 5% of the patients, as reported in the VeGAS 2 trial.[22] Transient bradycardia or heart block also occurs particularly when treating the right coronary artery; for this, a prophylactic temporary pacemaker should be placed during the procedure.[15–17]

Results of clinical investigations

In the VeGAS 1 Pilot study[18] the device was tested in 90 patients (91 lesions) with acute coronary ischemia and angio-

graphic evidence of thrombus, in native coronary arteries (43%) and saphenous vein grafts (57%). The AngioJet™ was successfully delivered in all 91 lesions. Thrombus burden decreased from 81.8 ± 92.8 mm^2 at baseline to 21.4±36.2 mm^2 after rheolytic thrombectomy, and to 11.4 ± 37 mm^2 after final treatment ($P < 0.001$) (Fig. 16.2). Procedural success (TIMI 3 flow after final treatment and residual diameter stenosis <50%) was obtained in 87% and clinical success (procedural success and no death, Q-wave MI, or emergency bypass surgery during the index hospitalization) in 82%. Distal embolization occurred in 3.3% of the vessels. In the VeGAS 2 trial,[19] 346 patients with angiographically visible thrombus in native coronary arteries or a saphenous vein graft were randomized to receive either prolonged urokinase infusion or mechanical thrombectomy with the Possis AngioJet™ system (Tables 16.1 and 16.2). As noted in Table 16.2, device success, procedural success, in-hospital major cardiovascular events, bleeding, and vascular complications were significantly better in the AngioJet™ group. Similarly, the 1-year freedom from major cardiovascular events and freedom from target vessel failure were superior in the AngioJet™ group (Figs. 16.3 and 16.4). The Possis

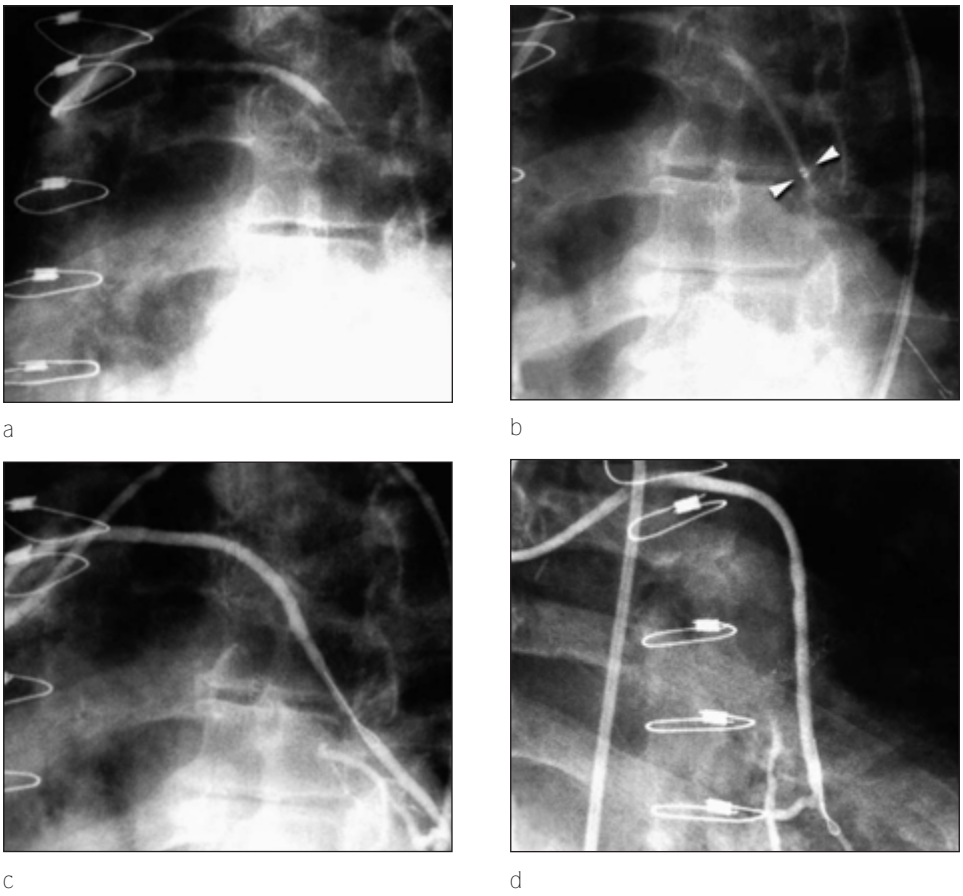

Figure 16.2
(a) Thrombotic occlusion of a saphenous vein graft. (b) Possis AngioJet™ catheter being passed through a thrombotic occlusion. (c) Angiographic results after rheolytic thrombectomy. (d) Angiographic results after final treatment with stenting.

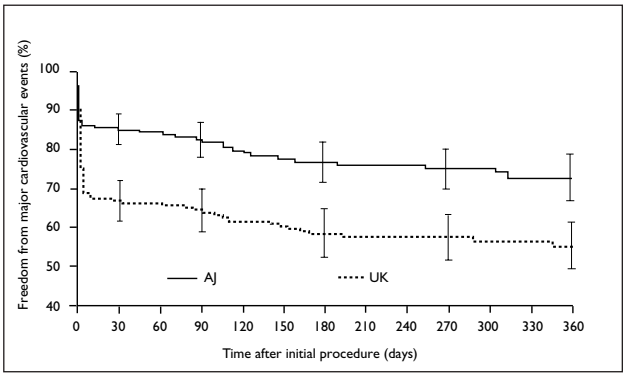

Figure 16.3
One-year freedom from major cardiovascular events. AJ, AngioJet™; UK, urokinase

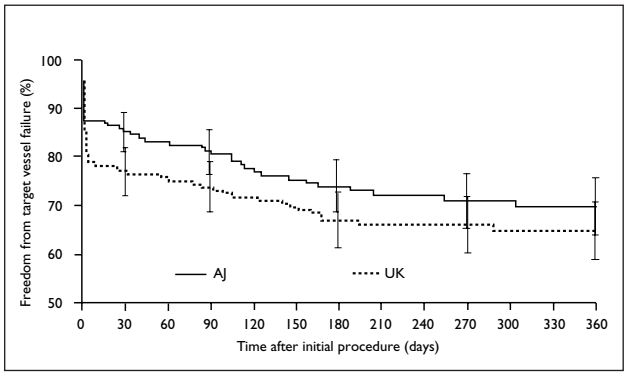

Figure 16.4
One-year freedom from target vessel failure. AJ, AngioJet™; UK, urokinase

Table 16.1 Baseline lesion characteristics of the VeGAS 2 randomized trial.

Lesion characteristic	*AngioJet™ (N = 183)*	*Urokinase (N = 169)*	*P value*
RVD (mm, mean ± SD)	3.30 ± 0.67	3.45 ± 0.77	NS
MLD (mm, mean ± SD)	0.80 ± 0.93	0.80 ± 0.96	NS
% DS (mean ± SD)	76 ± 26	78 ± 23	NS
Lesion length (mm)			
Mean ± SD (N)	15.47 ± 13.35	16.10 ± 12.26	NS
Target vessel			
LAD (%)	9.3	6.7	NS
Circumflex (%)	7.7	5.5	NS
RCA (%)	29.1	33.7	NS
LMCA (%)	0.5	0.0	NS
SVG (%)	53.3	54.0	NS
Thrombus (%)	98.9	98.8	NS
ACC/AHA lesion class			
A (%)	0.0	0.6	NS
B1 (%)	25.8	29.4	NS
B2 (or higher grade B) (%)	59.3	55.2	NS
C (%)	14.8	14.7	NS

RVD, reference vessel diameter; MLD, minimum lumen diameter; DS, diameter stenosis; LAD, left anterior descending; RCA, right coronary artery; LMCA, left main coronary artery; SVG, saphenous vein graft.

Table 16.2 VeGAS 2: principal effectiveness and safety results; all randomized patients treated (349 patients; 352 lesions).

Efficacy measures	*AngioJet (N = 180)*	*Urokinase (N = 169)*	*Significant*
Lesion success (%)	87.6	80.1	No
Procedure success (%)	86.3	72.7	Yes
Device success (%)	87.4	75.8	Yes
Post procedure MLD (mm) (%)	2.59 ± 0.82	2.45 ± 1.08	No
Post procedure % DS	22 ± 21	28 ± 29	No
TLR-free at 30 days (%)	96.6	95.8	No
TVR-free at 30 days (%)	94.9	95.2	No
TVF-free at 30 days (%)	84.9	76.9	No
MACE-free at 30 days (%)	84.9	76.9	Yes
Primary endpoint—free at 30 days (%)	70.9	70.8	No
Safety measures and other clinical events			
In-hospital MACE (%)	13.9	32.5	Yes
Out-of-hospital MACE to 30 days (%)	3.9	1.8	No
Abrupt closure (%)	3.3	4.7	No
Subacute closure (%)	2.8	4.1	No
Bleeding complications (%)	5.0	11.8	Yes
Vascular complications (%)	4.4	17.8	Yes
CVA to 30 days (%)	1.7	1.2	No
Length of stay (mean ± SD) days	2.5 ± 2.3	3.5 ± 2.6	Yes

MLD, mimimum lumen diameter; DS, diameter stenosis; TLR, target lesion revascularization; TVR, target vessel revascularization; TVF, target vessel failure; MACE, major adverse cardiovascular events; CVA, cerebro-vascular accident

AngioJet™ catheter has also been tested in 115 patients with acute MI (13% with cardiogenic shock) and angiographic evidence of large thrombus burden.[21] The device was successfully delivered in all lesions. TIMI 3 coronary flow was present in 25% of the patients at baseline, in 74% after rheolytic thrombectomy, and in 89% after definitive treatment ($P < 0.001$). Thrombus burden also decreased significantly, from 63.1 ± 73.3 mm^2 at baseline to 20.3 ± 34.8 mm^2 after rheolytic thrombectomy ($P < 0.001$) (Fig. 16.5). Due to the excellent angiographic resolution of thrombus, 61% of our patients received coronary stents without complications or stent thrombosis. Distal embolization occurred in 12% of the patients. Nine patients died in the hospital (8%), one patient suffered a stroke (1%), and none required emergency bypass surgery. At 1 month follow-up, there were no additional deaths, strokes, or need for bypass surgery. Recurrence of MI occurred in 4% of the patients (3% Q-wave MI and 1% non-Q-wave MI). Repeat target vessel PTCA occurred in 3% of the patients. The 1-month freedom from death or major cardiovascular event was 88%. The Possis AngioJet™ system also appears promising in the treatment of subacute stent thrombosis.[25,26]

The Cordis Hydrolyser

Device description and mechanism of action

The Cordis Hydrolyser consists of a dual lumen catheter with a small injection lumen and a larger exhaust lumen, a power injector, and a collection bag. Like the Possis AngioJet™, the system aspirates fresh thrombus by applying the Venturi–Bernoulli vacuum principle. The device is available in Europe and has been tested successfully in the peripheral circulation (7 French system), particularly in thrombosed lower extremity limb vessels and dialysis grafts and fistulas.[27–29] There is also limited experience with the device in the treatment of thrombotic lesions in saphenous vein grafts and native coronary arteries (6 French system).[30,31]

The 6 French Hydrolyser system[30,31] is a 135-cm long nylon catheter (Fig. 16.6), which accepts a 0.018-inch guidewire and requires a guiding catheter with a minimum inner diameter of 0.086 inch. Using a conventional mechanical contrast injector, a physiologic solution of saline and heparin is injected through the narrow injection lumen at a

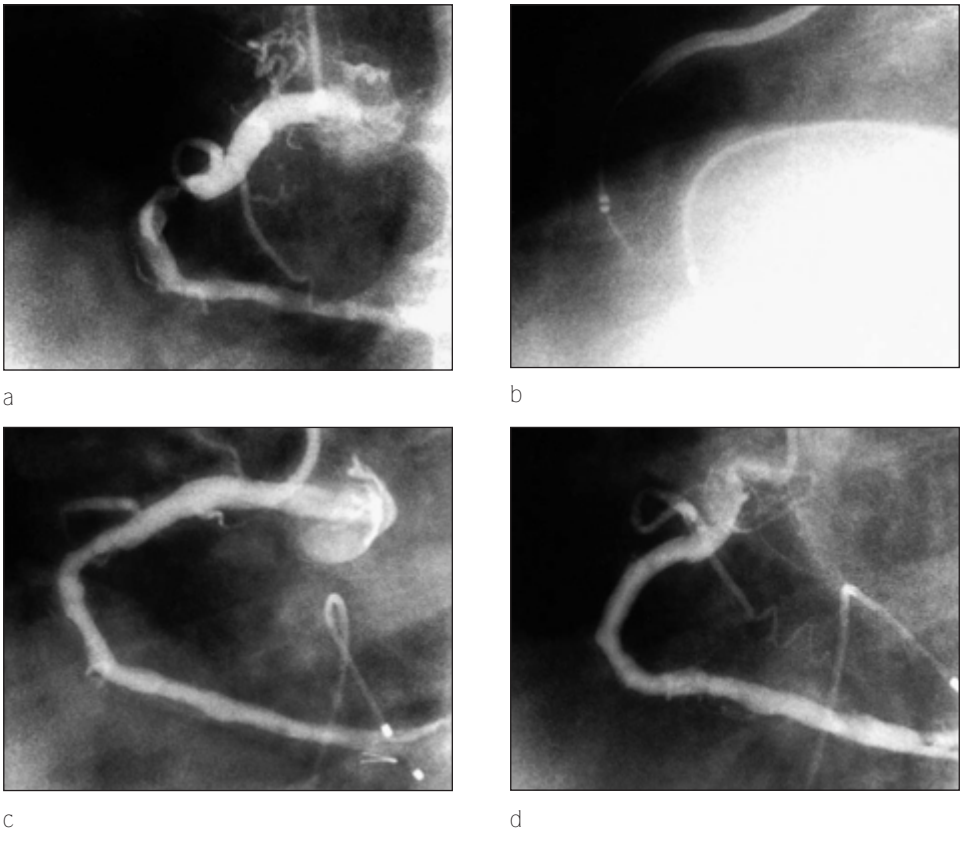

Figure 16.5
(a) Patient with acute inferior myocardial infarction and angiographic evidence of large thrombus burden (TIMI 2 flow). (b) AngioJet™ passed through the thrombotic stenosis. (c) Angiographic results after rheolytic thrombectomy (TIMI 3 flow). (d) Angiographic results after final treatment with stenting.

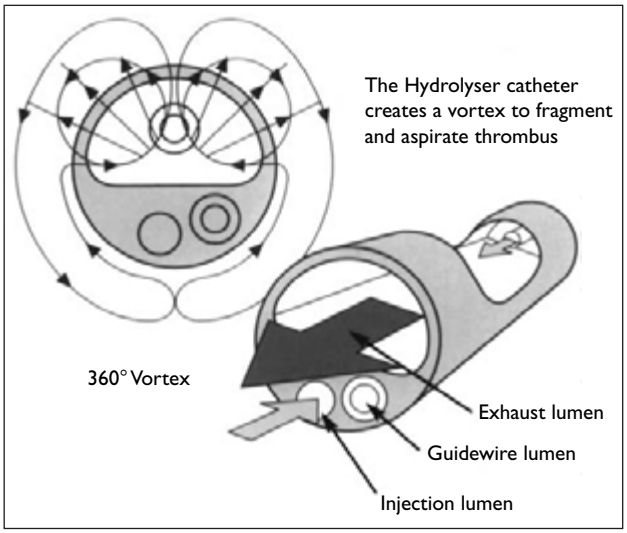

Figure 16.6
The Cordis Hydrolyser catheter design.

flow rate of 9 ml/s and a pressure of 750 psi. This narrow tube makes a 180° bend at the tip of the catheter. The high-velocity saline jet (approximately 150 km/h) is directed toward a side hole near the tip of the catheter, creating a negative pressure gradient at the tip (Venturi–Bernoulli vacuum principle), which aspirates the thrombus into the side hole, where it is fragmented by the saline jet and eventually removed through the larger exhaust lumen as a mixture of thrombotic material, blood and saline to the collection bag.

Indications and contraindications

The Cordis Hydrolyser catheter is indicated for the removal of soft, fresh (preferably less than 5 days old), non-organized thrombus in the peripheral circulation (7 French system), and in saphenous vein grafts (6 French system). The Hydrolyser catheter should not be used in vessels less than 3 mm in diameter and, like the Possis AngioJet™ system, it is contraindicated in vessels with previous dissections, perforations, loose atheromatous flaps, suboptimally deployed or unexpanded stents, or recent anastomosis.

Procedure

Patients are pre treated with aspirin. Heparin is given to maintain an ACT of ≥ 300 seconds during the procedure. After an 8 or 9 French guiding catheter (minimum internal diameter = 0.086 inch) is in position, a guidewire is advanced distal to the treatment site. The device is advanced over the guidewire until it reaches the location of the thrombus. The system is then activated and moved forward and/or backward several times (one to ten passes) until no further improvement of thrombus resolution is observed.

Results of clinical investigations

The Cordis Hydrolyser catheter has been used successfully in the peripheral vascular system for the treatment of arterial thrombosis below the inguinal ligament (native vessels and bypass grafts),[27] as well as for the treatment of thrombosed hemodialysis grafts.[28] There are also reports of the successful use of this device in thrombotic occlusions above the inguinal ligament, pulmonary embolism, and large venous thrombosis (subclavian, iliac, caval).[32]

In the coronary circulation, there are reports of the successful use of this catheter for removal of thrombus in saphenous vein grafts and native coronary arteries. In the largest series, van Ommen et al[31] reported their results of 31 lesions (20 vein grafts and 11 coronary arteries) in 31 patients. In 24 lesions (77%), TIMI coronary flow was 0 or 1 at the beginning of the procedure (the remainder had TIMI 3 flow). Following the use of the Hydrolyser, TIMI flow improved to 2 or 3 in 14 of the 24 cases with initial TIMI 0 or 1 (7 of 15 grafts and 7 of 9 native coronary arteries). Adjunctive balloon angioplasty and/or stenting was performed in 28 of the 31 patients. In four vein grafts, additional pharmacologic thrombolysis was used due to residual thrombus. Complications included mild transient hemolysis, angiographic distal embolization ($N = 3$), non-Q-wave myocardial infarction ($N = 1$), and in-hospital death ($N = 2$).

Mechanical thrombolysis

Ultrasound waves have two main clinical applications: diagnostic applications (low-power class) which use ultrasound frequencies of 20 to 30 MHz, and therapeutic applications (high-power class) which use ultrasound frequencies of 19 to 50 kHz. Anschuetz and Bernard were the first to suggest in 1965 that ultrasound energy has the potential to ablate atherosclerotic plaque.[33] Trubestein showed that high-intensity, low-frequency ultrasound waves cause clot lysis in vitro and in an experimental animal model.[34] In 1994, the initial clinical experience with ultrasound thrombolysis was reported by Siegel et al.[35]

Principle of ultrasound ablation

The principle by which high-power ultrasound waves cause ablation/thrombolysis is thought to be by the generation of transient stable and unstable cavitations, which leads to the formation and subsequent collapse of vapor-filled bubbles in tissue, fluids, and cells.[36,37] The cavitation nuclei are probably the result of consolidation of gas dissolved in the medium or tissue. The bubbles created at the tip of the catheter probe implode. These implosions are capable of generating up to (or

in excess of) 10 atm of pressure. The generation of bubbles as a result of cavitation is one of the mechanisms by which stones in kidneys and gallbladder disintegrate.[38] A similar mechanism of cavitation, bubble generation, and implosion at the tip of the probe is believed to lead to thrombus lysis/disintegration.[39]

Device description and procedural considerations

The device consists of a solid-metal, flexible ultrasound probe which is attached at its proximal end to an ultrasound transducer in the hand-piece. The transducer consists of piezoelectric crystals that convert electrical energy, supplied by a small portable power generator, to high-power, 42 kHz ultrasonic energy. Several devices are available for coronary use. The device used in our catheterization laboratory is the Angiosonics Acolysis™ System (Acolysis, Angiosonics, Morrisville, NC). It consists of a 140 cm long ultrasound probe, with a distal, flexible, multiwire segment connected to a 1.6 mm tip designed to optimize the cavitation effect. The multiwire flexible probe uses solid-metal wire for effective ultrasound transmission but still maintains optimal flexibility. The device is delivered over a 0.014 inch guidewire ('rapid exchange system') and requires a 7 French angioplasty guiding catheter (Fig. 16.7).

Before the procedure, all patients are pretreated with aspirin 325 mg daily and heparin is giving during the procedure to attain an ACT of >300 seconds. Once the target vessel has been cannulated with the guiding catheter and the culprit lesion has been crossed with the guidewire, the ultrasound probe is advanced and the cavitation tip positioned approximately 1 to 2 mm past the proximal end of the thrombotic stenosis/occlusion. Sonication is then performed at 60 second intervals for a total of up to 3 minutes. During sonication, the probe is either stationary or moved slowly back and forth with a small amplitude (≤ 3 mm). To minimize the risk of distal embolization the lesion should not be crossed until effective thrombus ablation has been attained and/or reperfusion has been re-established. Following sonication, treatment of residual plaque is carried out with conventional balloon angioplasty with or without stenting according to the clinical circumstances or operator preferences.

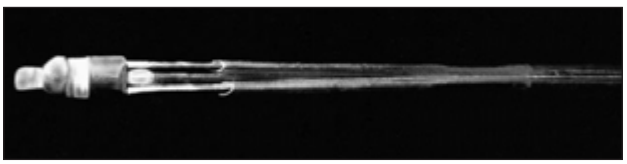

Figure 16.7
Angiosonic Acolysis™ catheter tip.

Experimental studies and clinical applications

Experimental post mortem studies have shown that ultrasound thrombolysis is effective in recanalizing occluded coronary arteries. Siegel et al showed successful recanalization of partially or totally occluded coronary arteries with ultrasound plaque ablation.[40] Trubestein was the first to demonstrate effective thrombolysis with this device in a canine model.[34] Subsequent in vitro studies, confirmed Trubstein's work and also found that the effective dissolution of thrombus occurred irrespective of the thrombus age and did not lead to serum elevation of D-dimers (therefore, there was no activation of the fibrinolytic system).[41]

One of the initial clinical applications of this system was in recanalizing chronically occluded peripheral arteries. Siegel et al treated 45 patients (50 lesions and 35 occluded segments) with disabling limb claudication.[42] The device successfully recanalized 30 of the 35 occluded arteries (86%), with a significant immediate and 6-month clinical improvement. The authors reported four arterial occlusions and four perforations without apparent clinical consequences.

In the CRUSADE trial, a multicenter European study,[43] 163 patients with symptomatic coronary artery disease were treated with ultrasound angioplasty. Fifty-one lesions were thrombotic, 49 occluded, 89 calcified, and 34 lesions were longer than 20 mm. The device successfully crossed 136 of 163 lesions (83%) and 31 of 49 occlusions (63%). The stenosis decreased from 86 ± 14% to 71 ± 19% after the use of mechanical thrombolysis, and to 37 ± 21% after using adjunctive PTCA. Procedural success was obtained in 96% and the 6-month angiographic restenosis was 34%. Procedural complications included 19 dissections (two caused by the device), and three myocardial infarctions. There were no deaths or need for emergency bypass surgery in the first 24 hours.

In the setting of acute myocardial infarction, the ACUTE trial,[44] a small feasibility phase study of 15 patients with acute anterior myocardial infarction (culprit lesion in the LAD with TIMI 0 or 1 at baseline in all patients), showed successful attainment of TIMI 3 coronary flow in 13 of the 15 patients (87%). Abciximab was used in only 3% of the patients. One patient developed asymptomatic reocclusion 10 minutes after successful restoration of TIMI 3 coronary flow. Repeated angiography at 12 to 24 hours post procedure revealed no change in TIMI flow in the remainder of the patients. Adjunctive balloon angioplasty was performed in 14 of the 15 patients. During hospitalization, one patient developed recurrent ischemia requiring repeat balloon angioplasty of the original culprit lesion and another patient required bypass surgery due to diffuse LAD and significant RCA disease. At 6-month follow-up there was one death, one reinfarction, and non-urgent target vessel revascularization in 33% of the patients.[45] The Acolysis Registry[46] tested the device in 100

patients with different clinical presentations (unstable angina 25%, myocardial infarction 23%, post infarction angina 37%, and saphenous vein graft 15%). Baseline TIMI 0 or 1 was present in 87%. Successful recanalization was obtained in 87%, with a residual stenosis of 67 ± 11% after coronary ultrasound thrombolysis. Adjunctive PTCA and/or stenting was performed in 94% and abciximab was used in 14% of the patients. After final treatment, TIMI 3 coronary flow was obtained in 90% and residual diameter stenosis was 13 ± 6%. Device-related complications included angiographic distal embolization ($N = 2$) and non-Q-wave myocardial infarction ($N = 1$). There were no procedural deaths, abrupt occlusion, or perforations.

In a multicenter registry,[47] the same investigators tested the device in 20 saphenous vein grafts (15 grafts had TIMI 0 or 1 before the procedure). Device success (TIMI 2 or 3 after use of the device) was obtained in 70%, and procedural success (TIMI 2 or 3 flow and no device-related clinical or angiographic adverse events) was obtained in 65% of the patients. One patient developed a non-Q-wave myocardial infarction and there was distal embolization in one graft (5%).

The device is at present being actively tested in the ATLAS Study (Acolysis™ during Treatment of Lesions Affecting Saphenous vein bypass grafts), a multicenter US and Canadian prospective randomized trial (25 centers, 540 patients) which will compare ultrasound thrombolysis with abciximab, followed by residual plaque treatment with PTCA/stenting, in thrombotic lesions. The endpoints of the study are cardiac death, Q-wave myocardial infarction, emergent bypass surgery, repeat target vessel revascularization, and disabling stroke. There is a great deal of expectation in this trial as for the first time a mechanical treatment for thrombus-containing lesions is being tested against a GPIIb/IIIa platelet inhibitor, a group of drugs known to 'passivate' complex coronary plaques by mechanisms not well understood as yet. An example of the performance of the device from our cardiac catheterization laboratory is shown in Fig. 16.8.

Conclusion

The treatment of thrombotic lesions is difficult for the interventional cardiologist because percutaneous treatment of these conditions carries an increased complication rate such as abrupt occlusion, emergency bypass surgery, and death. The group of GP IIb/IIIa inhibitors has been shown to be very effective in decreasing the procedural complication rate in the presence of small or clinically suspected thrombus. When approaching a coronary lesion with a large thrombus burden, mechanical thrombectomy or mechanical thrombolysis alone or in combination with a GP IIb/IIIa platelet inhibitor should be strongly considered. The Possis AngioJet™ system has been extensively studied and is safe, easy to use and highly effective for thrombus removal. There is limited experience with the Cordis Hydrolyser catheter in the coronary circulation, but the initial reports are encouraging. Nevertheless, the current device is bulkier and the vacuum generated is weaker than the AngioJet™ system, which will limit its use to large vessels with more fresh thrombus. The ultrasound thrombolysis device appears to be a very effective tool for dissolving thrombus in both native coronary arteries and saphenous

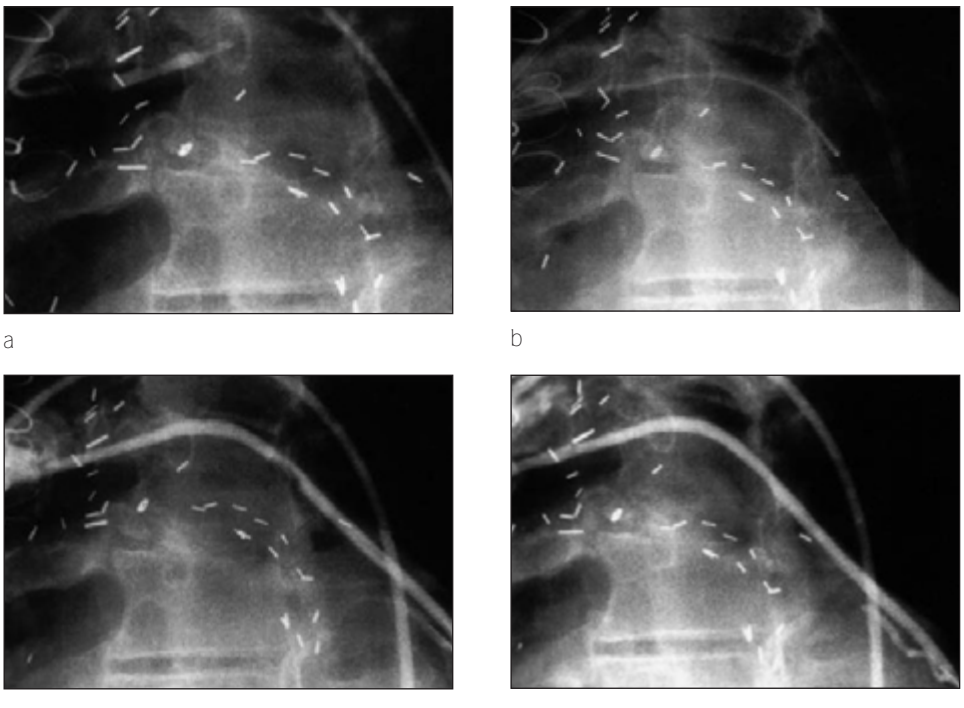

Figure 16.8
(a) Thrombotic occlusion in a saphenous vein graft. (b) Sonication performed within the thrombotic occlusion. (c) Angiographic results after sonication. (d) Final angiographic results after stenting.

vein grafts. Initial clinical reports show that the device is safe and highly effective for lysing/disintegrating thrombus. One particular advantage of the ultrasound thrombolysis device over the two previously mentioned thrombectomy devices is that it appears to be equally effective in dissolving fresh soft and old organized thrombus. These encouraging initial reports will have to be confirmed in large prospective randomized trials.

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17

Intervention after coronary artery bypass surgery

David R Ramsdale

Introduction

Long-term follow-up of patients after coronary artery bypass surgery (CABG) has shown that angina may eventually recur in up to 8% of patients annually[1–3] due to graft stenoses or occlusions[4–6] or progression of disease within the native coronary arteries.[7–9] Approximately 20%, 30% and 50% of saphenous vein grafts have significant disease or are occluded at 1, 5 and 10 years after surgery[4–6,10–15] and although 90% of IMA grafts may be patent at 10 years, stenoses are not infrequently encountered much earlier. As the frequency of CABG surgery has increased, repeat intervention has become necessary more often (perhaps 10–15% of post CABG patients within 10 years)[16] and includes repeat surgery or catheter-based intervention by PTCA, atherectomy or stenting.

The operative risks for repeat CABG are increased especially in the presence of impaired left ventricular function, left main stem and multivessel disease, functional class III or IV, advanced age and incomplete revascularization. A 3.4% to 9.2% mortality rate and up to a 15% incidence of perioperative Q-wave myocardial infarction has been reported[17–25] and the risks are even higher for a second reoperation.[23] Repeat surgery is technically more difficult and also less effective in relieving symptoms. Good quality conduits may not be available and graft patency rates are lower. Adverse features for repeat CABG are shown in Table 17.1. Therefore, in many interventional centres cardiologists consider percutaneous coronary intervention (PCI) to improve myocardial blood supply by addressing graft stenoses and/or lesions in the native vessels.

Saphenous vein graft (SVG) PTCA was first performed in 1980 with a high primary success rate. The progressive improvement in guide catheter, guidewire and balloon technology has enabled more difficult cases to be performed successfully with low complication rates.[26–48] Such cases include stenoses in the ostia, body and distal portions of SVGs as well as in the distal coronary artery beyond the graft's distal anastomosis and in LIMA, RIMA[49,50] and gastroepiploic arterial[51,52] coronary grafts; even totally occluded SVGs and LIMAs can be recanalized by PTCA.[53–55] Certain disease in SVGs may be best dealt with by atherectomy techniques and coronary stenting is frequently indicated to produce optimal results.[56] However, special expertise is necessary for these procedures, all add significantly to the cost and at present there are few randomized trials to support a more than short-term advantage for these more sophisticated techniques.

Table 17.1 Less than ideal candidates for repeat CABG.

Lack of venous or arterial conduits
Advanced age
Poor LV function
Poor distal vessels
Patent grafts at risk of damage during reoperation
Previous CABG surgery, i.e. two previous operations
Coexisting medical problems, e.g. stroke, malignancy, renal or respiratory failure, immunosuppressive therapy

Intervention in patients with previous CABG surgery is challenging, but remains a very useful treatment for what are frequently difficult cases including patients who have undergone CABG surgery on more than one previous occasion.[57]

Indications

Patients with recurrent angina pectoris after CABG surgery may be suitable for PTCA to their grafts or native coronary arteries as an alternative to medical treatment or repeat CABG surgery. The choice depends on many factors includ-

ing age, coexisting medical conditions, left ventricular function, availability of conduits, the risk of damaging functioning grafts and the likelihood of a successful reoperation. The major factor which determines the suitability for PTCA is the coronary anatomy defined by coronary arteriography.

Short, discrete stenoses in easily accessible grafts are an easier proposition than long diffuse segments of disease associated with thrombus in aged grafts which are difficult to access with a guiding catheter. Recently-occluded grafts can be reopened although chronically blocked grafts may be impossible to recanalize and have poor prospects for long term patency.

Contraindications

There are few absolute contraindications to PTCA. However, unprotected left main coronary artery stenoses, long ectatic tortuous grafts with much intraluminal material and thrombus and chronically occluded grafts are usually regarded as such (Fig. 17.1). Relative contraindications include heavy calcification of the stenosis, grafts with poor distal run-off into the native coronary circulation and long diffuse lesions.

Relation of graft age to problem encountered

After CABG surgery, the problems encountered are related to the time interval from surgery to the onset of recurrent angina and the associated pathology that has developed. Prospects for successful treatment can be maximized by prompt repeat arteriography.

Early

Up to 15% of SVGs may close in the first month after surgery due to technical factors and acute thrombosis. Approximately half of these occur within the first 10 days. If the graft is thrombosed an attempt should be made to re-establish flow by passing a guidewire and balloon catheter and intragraft rtPA or urokinase infused in boluses or via an infusion catheter placed within the graft in order to lyse visible thrombus. In the first few days postoperatively, thrombolytic therapy should be avoided. If a discrete focal stenosis is present at a graft anastomosis site, PTCA should be performed, taking care not to oversize the balloon.

Angiography may also indicate incomplete revascularization due to diffuse disease, incorrect vessel being grafted, intramyocardial vessel stenoses or a discrete lesion beyond the graft's insertion site which may be suitable for PTCA. Recurrent episodes of pain without ECG changes may be due to occlusion of the native vessel (previously subtotally occluded) above the graft's distal anastomosis site. This should be left untreated as long as the graft is functioning satisfactorily.

Early–mid term

Although graft thrombosis may still occur within twelve months after CABG, recurrent angina may be due to discrete

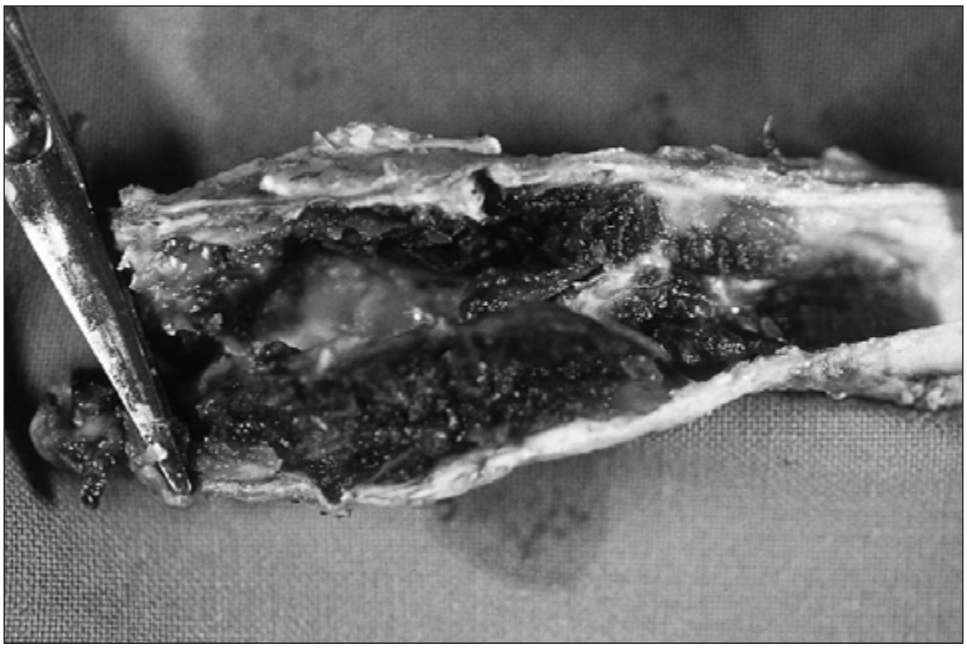


Figure 17.1
A 17-year-old SVG opened longitudinally. Although patent, the SVG contains a large amount of necrotic, grummous debris, friable, laminated thrombus and ulcerated atheromatous plaque. Such diffusely diseased, old SVGs are contraindications to PTCA.

fibroproliferative stenoses at the ostium, in the body or at the distal anastomosis of the SVG.

Mid-term

Between 1 and 5 years, a recurrence of angina is likely to be due to atherosclerotic stenoses in the SVGs or native vessels. As above, PTCA or other interventional techniques can be performed with little risk of distal embolization as long as there are no large intraluminal opacities or visible thrombus. Thrombotic occlusion of the SVG may be responsible for acute myocardial infarction.

Late

Beyond 5 years, complex vein graft lesions with eccentric, ulcerated atheromatous stenoses and friable thrombotic material are more frequently encountered. Diffuse disease and graft occlusion are more likely too. Distal embolization of material may occur in more than 20% of cases and restenosis rates are high.[58] Nevertheless, PTCA and stenting may be worthwhile especially in patients in whom reoperation is better avoided or contraindicated.

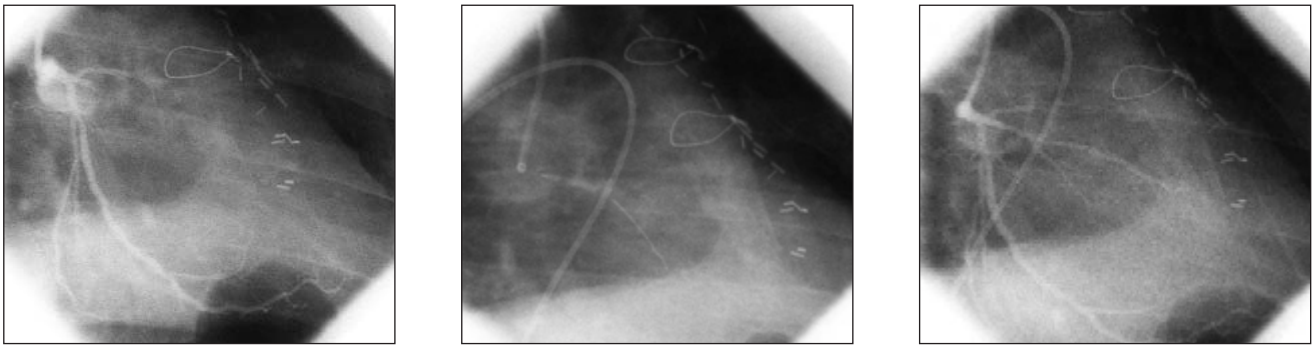
Unstable angina and acute myocardial infarction occurring in patients after CABG surgery

Patients presenting with unstable angina or acute myocardial infarction after CABG surgery should undergo angiography as soon as possible. PTCA has been shown to have a high success rate in SVGs in patients with unstable angina.[59] Acute native vessel or SVG occlusion can be reopened by direct PTCA (Fig. 17.2), together with intracoronary thrombolytic therapy if necessary (Fig. 17.3), but it may be impossible several weeks after 'stabilizing' the individual with medical therapy. Data from the Myocardial Infarction Triage and Intervention trial suggest an increased risk after reperfusion in patients with previous CABG, especially those with multivessel coronary disease, previous myocardial infarction and impaired LV function.[60,61] In approximately two thirds of cases the infarct related vessel is an occluded graft and extensive thrombus formation is common, providing a major challenge for the interventional cardiologist.[62–64] Other techniques besides PTCA may have a role in treating such patients.

Strategy

The strategy for intervention should be clear to the patient and relatives before the procedure and the case should have been discussed with surgical colleagues and the therapeutic options agreed upon, especially when the graft supplies much of the remaining viable myocardium.[65] Multiple grafts may need to be dilated and the procedure staged. If myocardium is supplied by a stenotic SVG and a stenosed native vessel, PTCA to both should be considered,[66] but if a choice has to be made then PTCA to the native vessel should be preferred because of the lower restenosis and late complication rates.[67]

Emergency surgery in patients who have previously undergone CABG surgery is difficult and the time to revascularization is often prolonged.[68,69] High-risk patients including those with poor left ventricular function, last remaining graft/vessel or unstable angina associated with thrombotic



a b c

Figure 17.2
50-year-old man presented with sudden onset severe prolonged chest pain 5 years after undergoing CABG surgery. Angiograms (RAO view) show: (a) on presentation—acute occlusion of intermediate coronary artery. (b) After crossing occlusion with a 2.5 mm fixed-wire balloon catheter, balloon inflation shows indentation due to stenosis present. (c) Post PTCA result with full recanalization of intermediate artery.

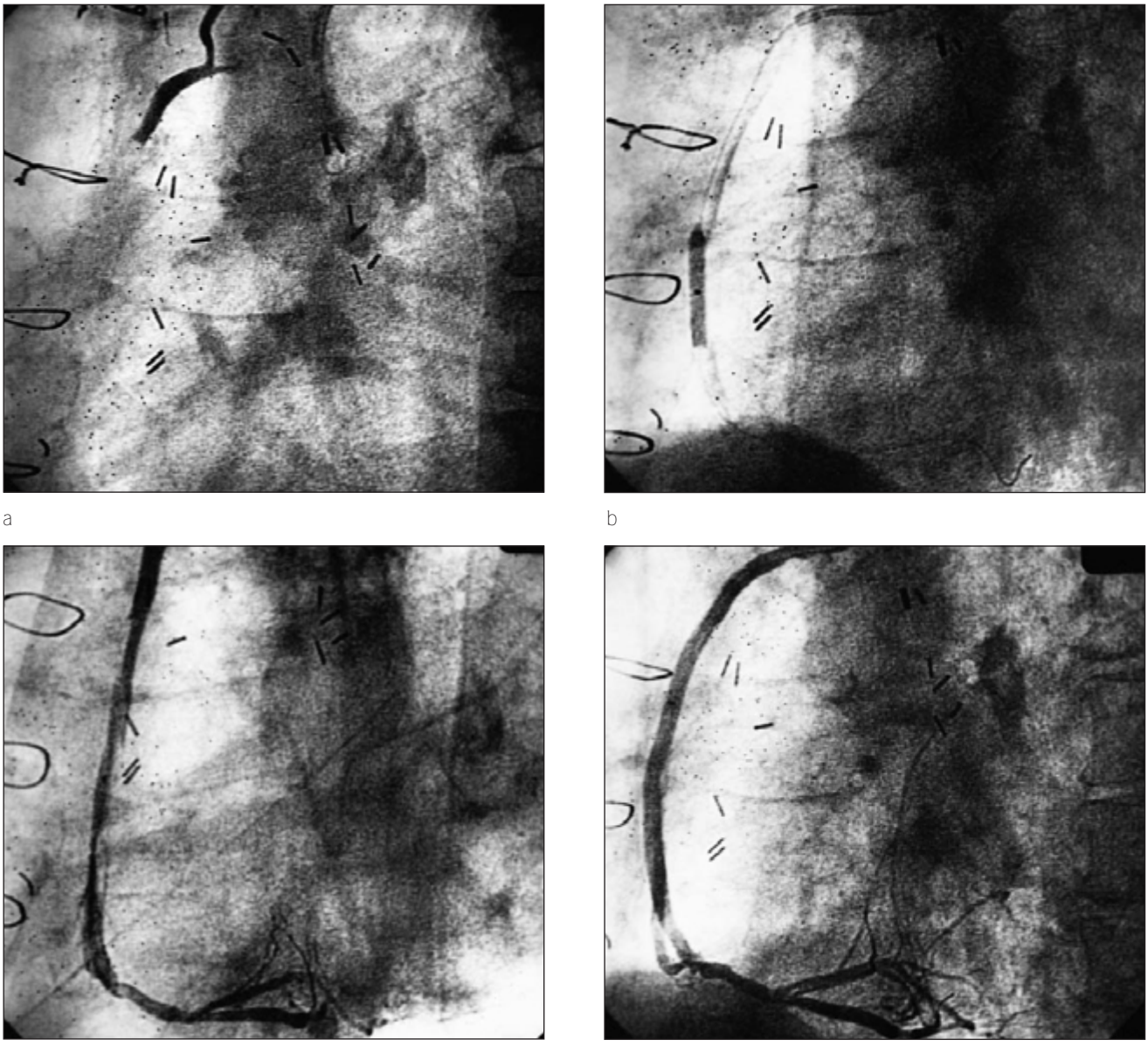


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Figure 17.3
(a) Occluded SVG RCA. (b) PTCA—one of several balloon inflations along length of SVG RCA. (c) Flow re-established, but filling defects due to thrombus are clearly apparent. (d) Improved angiographic appearance after IC rtPA and PTCA.

occlusion of a graft should be considered for intraaortic balloon counterpulsation or other support prior to PTCA.

Technique

All patients should be on aspirin, and should receive 10 000 units of heparin at the start of the procedure, and the ACT should be kept at twice normal during the procedure. Long-term anticoagulation with warfarin and aspirin should be seriously considered.

Native vessel PTCA

PTCA to suitable lesions in the native vessels should be performed with standard guide catheters, balloons and guidewires chosen according to the specific anatomical problem present (Figs. 17.4–17.6). It may be useful to attempt branch vessel stenoses, for example septal, intermediate or diagonals, in order to improve the blood supply to as much myocardium as possible. It is not unusual to perform PTCA to distal native vessel stenoses through patent SVGs (Fig. 17.7) and IMAs and even stenoses proximal to the distal

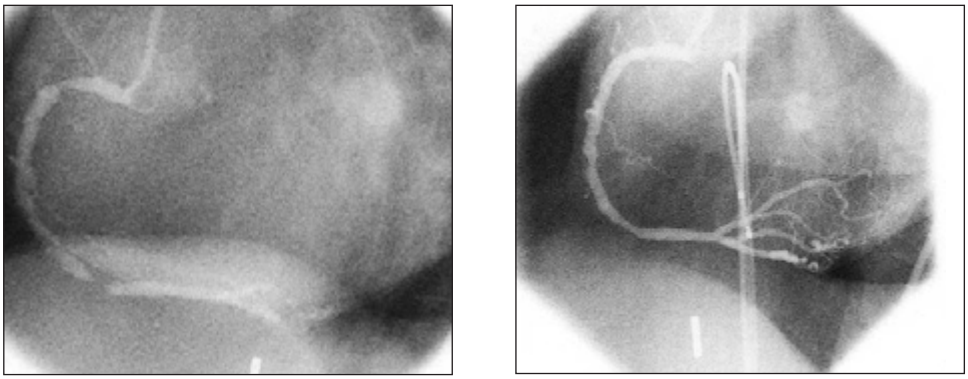

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Figure 17.4
PTCA to proximal and distal RCA stenoses 8 years post RCA SVG. RCA SVG occluded. (a) Pre PTCA. (b) Post PTCA.

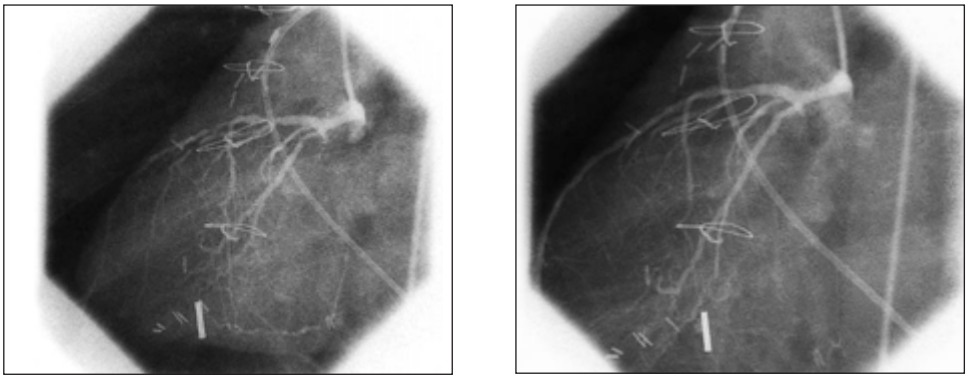

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Figure 17.5
PTCA to LAD and intermediate coronary arteries 5 years post CABG. (a) Pre PTCA. (b) Post PTCA.

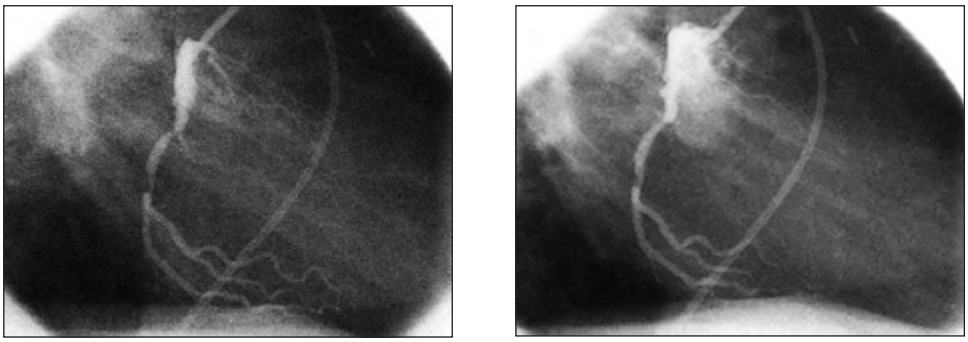

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Figure 17.6
PTCA to left circumflex artery (LCX) stenoses 4 years post CABG. (a) Pre PTCA. (b) Post PTCA.

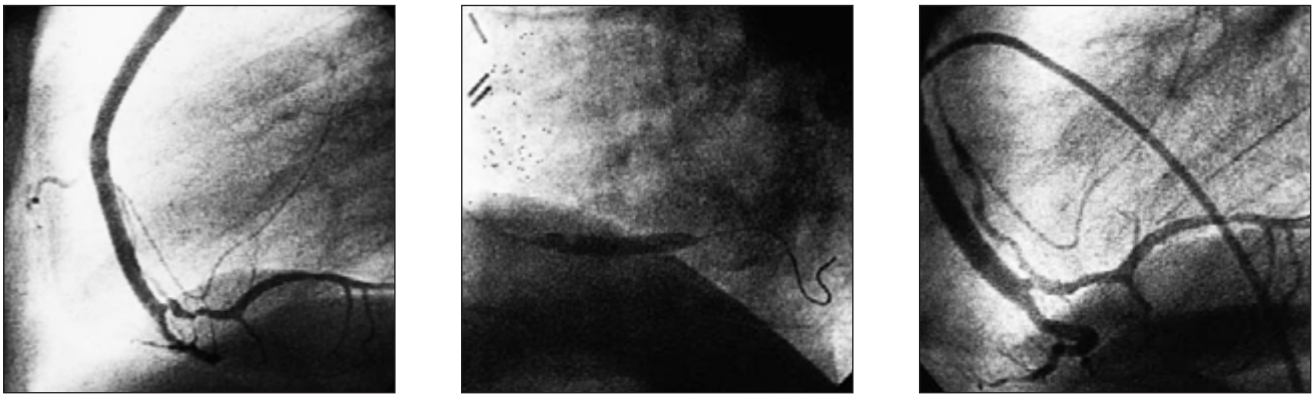

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Figure 17.7
8 years after CABG, PTCA was performed to the severe stenoses in the distal RCA through the patent SVG RCA. (a) Pre PTCA. (b) PTCA using 0.014 intermediate guidewire and 2.5 mm Express (SCIMED) balloon catheter. (c) Post PTCA angiographic result.

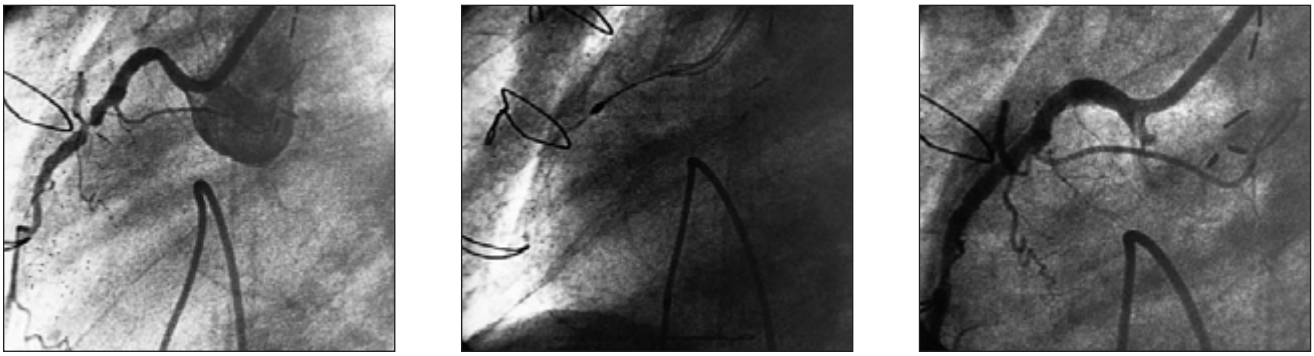

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Figure 17.8
(a) Severe, hard, discrete stenosis in RCA (arrow) in patient with residual angina 2 years after CABG, (b) is ablated by Rotablator atherectomy. (c) A good angiographic result after adjunctive PTCA was associated with relief of symptoms.

anastomosis site by retrograde passage of the guidewire and balloon catheter.[70,71] Rotablator atherectomy (Fig. 17.8), DCA (Fig. 17.9), ELCA and stenting may be appropriate depending on the coronary anatomy and/or on the presence of calcification. Intracoronary ultrasound may help in the decision making.

Saphenous vein graft intervention

Guide catheter

8F guide catheters are ideal, although 6F and 7F catheters with large internal lumens are available for smaller grafts. Larger guide catheters are necessary for atherectomy and side-hole catheters are useful if damping is problematic.

For RCA SVGs and horizontal or inferiorly directed LAD SVGs a right Judkins, right or left Amplatz, multipurpose or saphenous vein by-pass guide catheters are helpful. For superiorly directed LAD SVGs, diagonal and LCx SVGs, a left Amplatz guide catheter may be best.

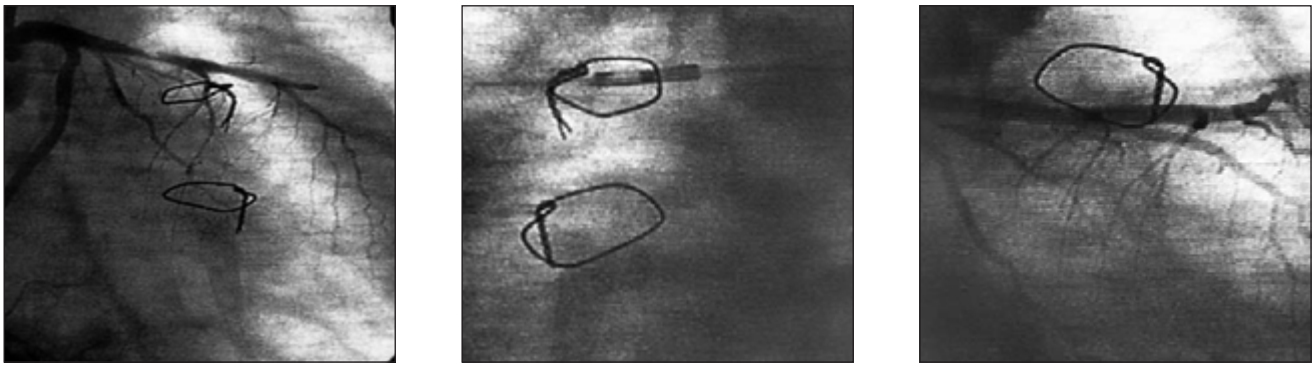
Balloon catheters and guidewires

Long balloons may be necessary to prevent movement off the lesion during inflation and balloon catheters with extended shafts may be required for long snake grafts or IMAs in very posterior locations. Tortuous IMAs and long, tortuous SVGs require flexible, steerable and low-profile devices.

Lesion site

Proximal/aorta-ostial stenoses

Proximal or aorta-ostial lesions are difficult since the guide catheter has to be backed out into the aorta and the balloon



a b c

Figure 17.9
(a) RAO view showing bulky eccentric stenosis in proximal LAD in patient with angina 4 years after CABG. (b) 7F Simpson AtheroCath® excising atheromatous lesion (9 specimens). (c) Post DCA angiographic result.

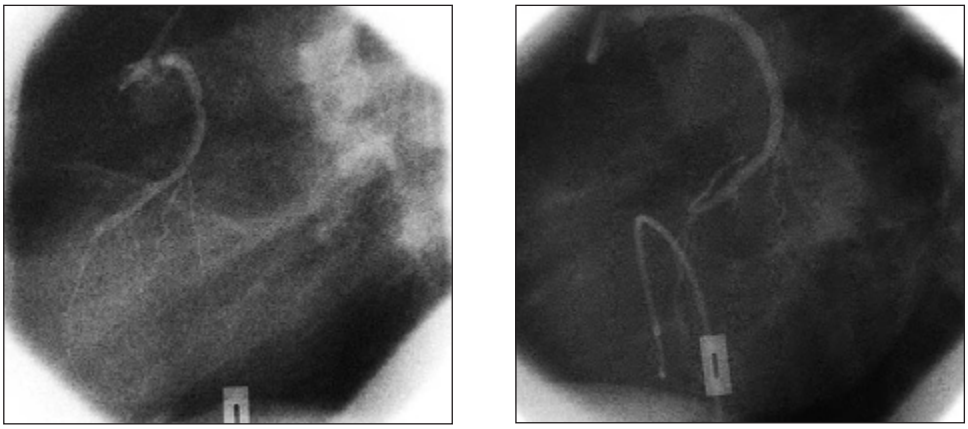


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Figure 17.10
Severe ostial stenosis in an SVG LAD (LAO view). (a) Pre PTCA. (b) Post PTCA (up to 10 atm).

or other device balanced at the ostium (Fig. 17.10). Rigid ostial stenoses often require high pressure inflations, with relatively young (<3 years) SVGs responding best. Although technically more demanding, atherectomy and stenting may be most appropriate for ostial lesions because of the often suboptimal acute angiographic appearance and the high recurrence rate after PTCA.[72]

Body stenoses

Lesions in the body of SVGs are often tough and require high inflation pressures to respond to PTCA (Figs. 17.11–17.13). Oversizing of the balloon and stenting can be performed for a suboptimal result but because of high restenosis rates, stenting (primary or after predilatation) is

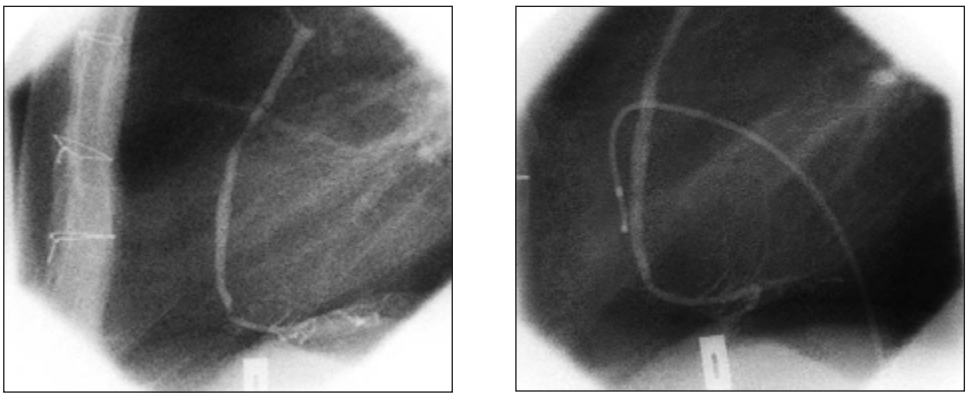

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Figure 17.11
Two stenoses in body (proximal and distal) of 5-year-old SVG RCA. (a) Pre PTCA. (b) Post PTCA.

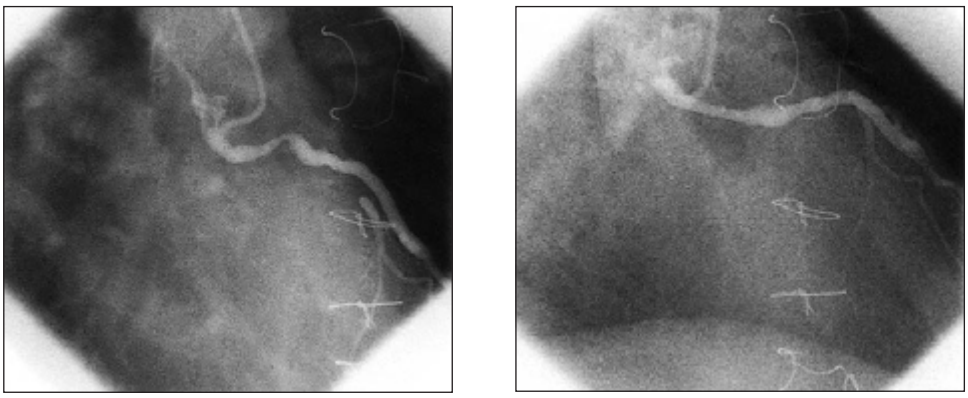

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Figure 17.12
Stenosis in body of 6 year old SVG LCX. (a) Pre PTCA. (b) Post PTCA.

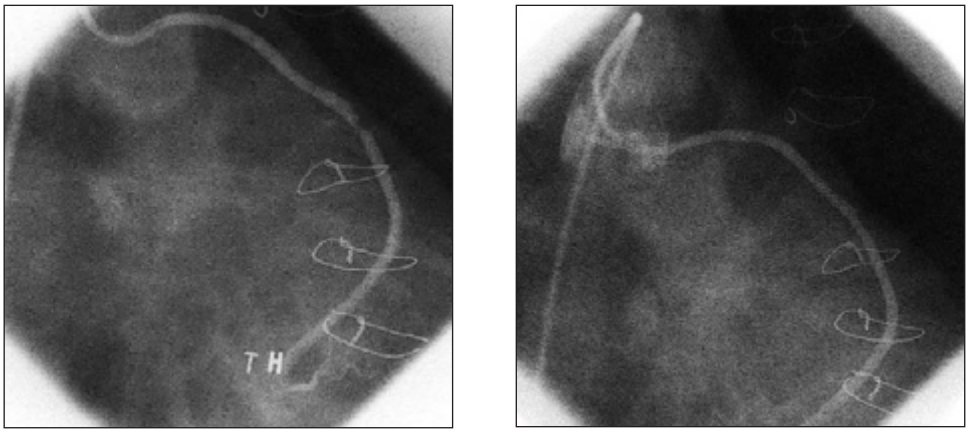

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Figure 17.13
Hard stenosis in body of 9 year old SVG LCX required balloon pressure of 14 atm. (a) Pre PTCA. (b) Post PTCA.

probably appropriate for all such lesions. DCA or TEC prior to stenting should be considered for eccentric, ulcerated or web-like focal lesions and those with associated thrombus (Fig. 17.14).

Distal stenoses

Distal anastomotic stenoses which occur within one year of CABG usually respond well to low pressure PTCA and are associated with a low complication and restenosis rate (Fig. 17.15).

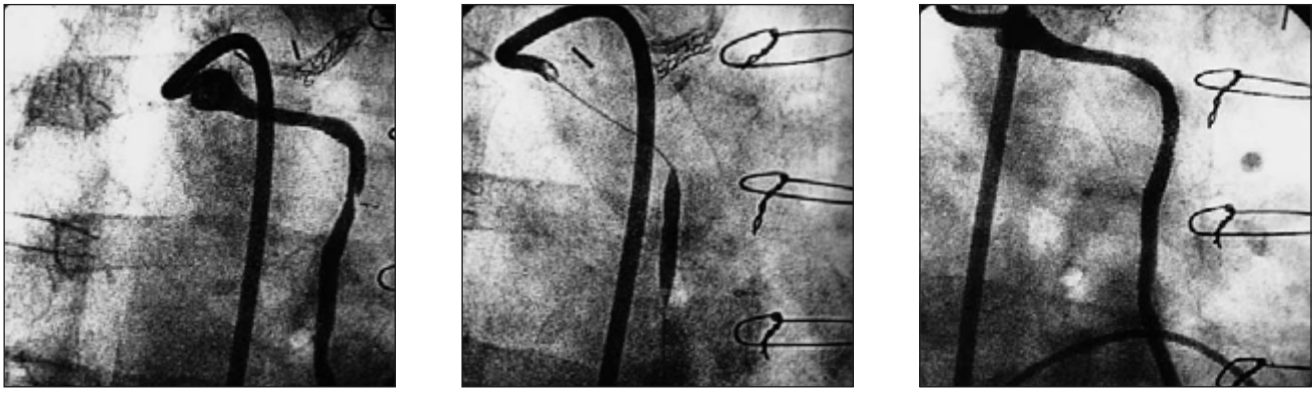

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Figure 17.14
Eccentric stenosis in mid third of 6-year-old SVG RCA (arrow). (a) Pre PTCA. (b) During PTCA with a 3.5 mm Samba balloon (BARD). (c) Post Wiktor stent deployment.

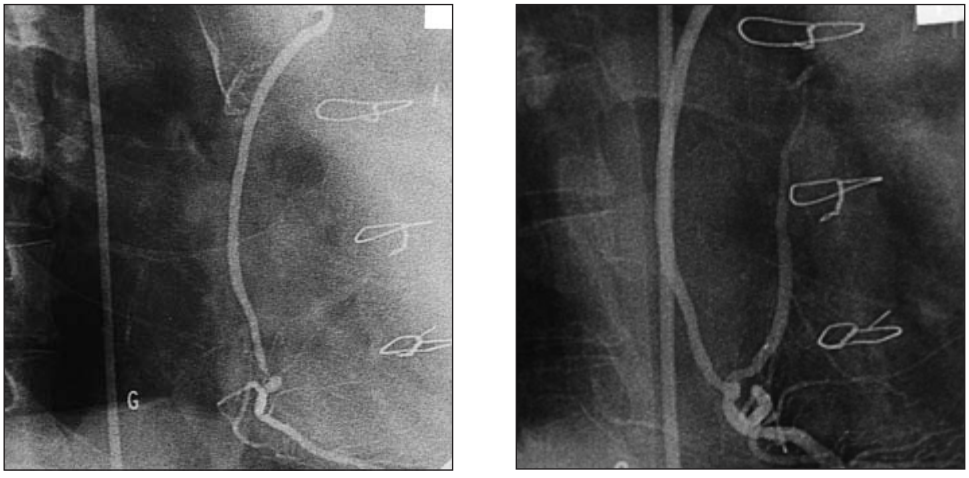

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Figure 17.15
Severe distal stenosis in a 9-year-old SVG RCA (arrow). (a) Pre PTCA. (b) Post PTCA.

Stenoses which occur later behave like lesions in the body of the graft and probably require stenting. Correct balloon sizing is essential to avoid rupture and dissection of the graft and distal vessel.

Acute/subacute occlusions

Acutely or subacutely thrombosed SVGs may be recanalized by PTCA, but initial and long-term success may be limited and myocardial infarction due to embolization is a real risk[15,73–75] (Fig. 17.16). We initially use a 0.014 inch high torque floppy, intermediate or standard guidewire to reach the native vessel beyond the distal anastomosis (Fig. 17.17). A balloon catheter can then be passed to re-establish flow down the graft by serial inflations along its length and intragraft thrombolytic therapy given to remove any fresh thrombus present. Thrombolytic therapy may be used in boluses but is only likely to be effective once some flow has been established[73,76] and is unfortunately associated with distal embolization and MI.[77] Thrombolytic therapy can be infused through a Tracker™ catheter left in situ in the SVG, although several hours may be required — often an ordeal for the patient and operator, and bleeding and stroke are realistic complications.[78–81]

TEC™ atherectomy,[82,83] perhaps with adjunctive abciximab,[84] may optimize outcomes during recanalization of totally occluded SVGs (Fig. 17.18). AngioJet™ thrombectomy[85–88] may also be useful, but whether these techniques, Acolysis™[89] or the X-sizer™ device[90,91] are more effective in this situation than PTCA remains to be established by randomized trials.

Chronic occlusions

Chronically occluded SVGs cannot usually be entered let alone be recanalized by PTCA and should be left alone. Long-term patency is low even if one is successful.

Restenosis lesions

PTCA for restenosis lesions in grafts is usually effective but recurrence is high. DCA, TEC and ELCA have not been able

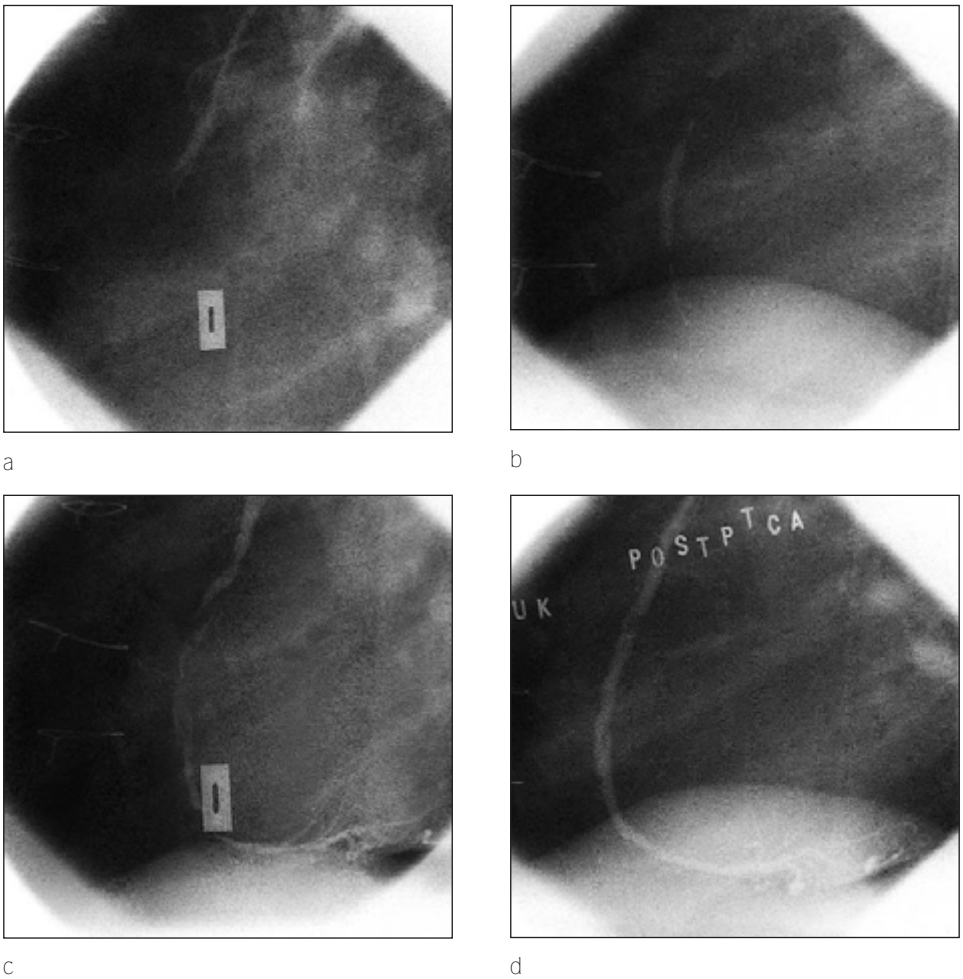

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Figure 17.16
8-week history of unstable angina. (a) Angiogram shows occluded 12-year-old SVG RCA. (b) In this case a fixed wire balloon catheter is sequentially inflated along length of SVG (c) recanalizing the graft but leaving significant filling defects due to organized thrombus. (d) Filling defects persist but are less voluminous after PTCA and intragraft infusion of urokinase.

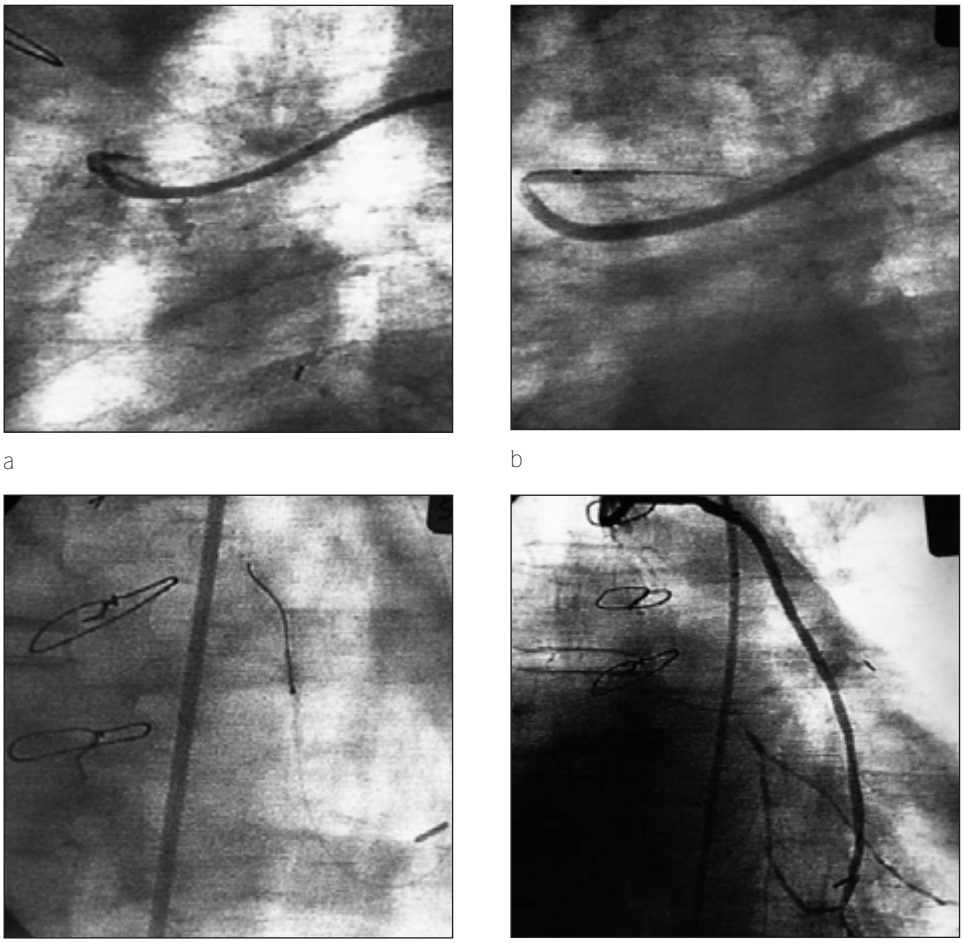

Figure 17.17
(a) 7-year-old occluded SVG OMCX. (b) 0.018 inch High Torque Intermediate guidewire is passed through SVG and its distal anastomosis and a 2.5 mm Express (SCIMED) balloon dilatation catheter serially inflated (proximal to distal) along length of SVG to re-establish flow. After a 3.0 mm 30 mm long Rx perfusion (GUIDANT) balloon is similarly dilated along length of SVG (c) a 2.5 mm balloon is passed retrogradely up LCX to OMCX/LCX bifurcation to dilate disease in native vessel. (d) Final post PTCA/rtPA angiographic result.

to reduce the restenosis rates. Stent implantation offers the best hope using high pressure inflations with an appropriate size balloon dilatation catheter. Even biliary stents may be required for the large diameter grafts.

Internal mammary artery PTCA

IMAs seem less susceptible than SVGs to atherosclerosis, yield superior clinical results over SVGs during 20 years of follow-

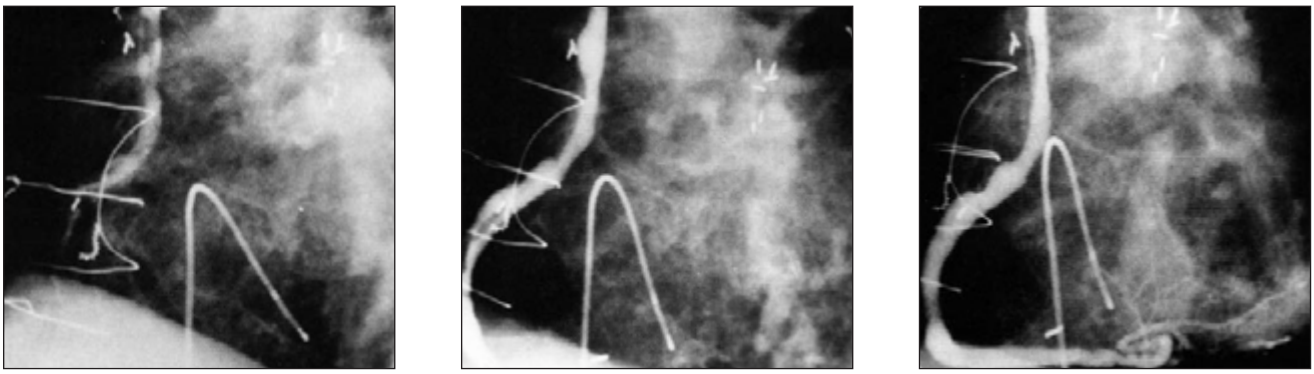

Figure 17.18
(a) A 3-year-old SVG RCA is totally occluded in its mid third and has visible thrombus within it. (b) After direct infusion of urokinase, intraluminal thrombus is still visible. (c) Post TEC atherectomy (2.5 mm TEC device) and after adjunct PTCA with a 3.0 mm balloon catheter, only residual irregularities are visible. (Acknowledgement: Drs R Cain, J Work and J Fleisher, Encino-Tarzana Medical Center, Encino, California.)

up[92–96] and 95% are patent at 10 years. However, problems do occur and up to 9% of IMAs have been reported to be stenosed or occluded within 2 years of surgery. The most common stenosis encountered is at the distal anastomosis of the IMA and the results of PTCA are usually good[48,49,97–103] (Figs. 17.19 and 17.20). IMAs are prone to vasospasm and patients should be pretreated with nitrates and calcium channel blockers before PTCA. Stenoses in IMA grafts are generally unsuitable for techniques other than PTCA although stenting has been performed successfully[104,105] and shown to have a good long-term outcome.[106] Occlusion of the IMA in its proximal or mid course has been attributed to trauma to the pedicle during mobilization at the time of surgery[107,108] and cannot usually be rescued by PTCA—but it is feasible.[55] The Magnum wire may be useful in this situation (Fig. 17.21).

8F IMA guide catheters provide the best back-up support, however they should be handled carefully to avoid dissecting the friable ostium. 6F and 7F large lumen guide catheters may be preferred if the IMA is small but visualization of the distal vessel and the stenosis is of paramount importance during PTCA. Low profile balloon catheters are essential.

The brachial[109,110] or even radial[111] approach may be useful if the femoral route fails to provide sufficient back-up support or if a proximal subclavian stenosis or occlusion interferes with access to the IMA.

The RIMA is best approached from the right brachial artery using a IMA guide catheter (Fig. 17.20).

Other conduits

PTCA can be successfully performed in gastroepiploic arterial grafts and this requires cannulation of the coeliac, common hepatic, gastroduodenal and gastroepiploic arteries[51,52] (Fig. 17.22). A 7F JR4 guide catheter may be used but special

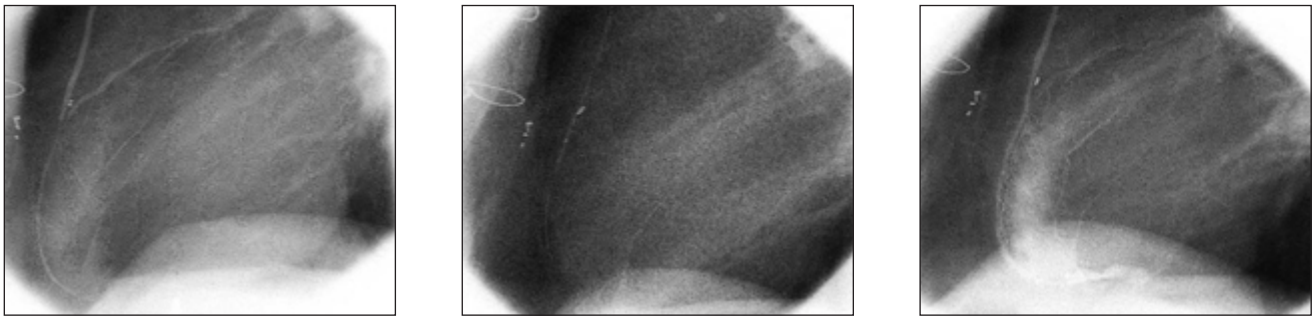

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Figure 17.19
Severe stenosis at the distal anastomosis of LIMA and LAD coronary artery 10 months after CABG (LLAT view). (a) Pre PTCA. (b) During balloon inflation with a 2.0 mm fixed-wire ACE balloon catheter (SCIMED). (c) Post PTCA shows good result with blushing of anterior wall and apex. This appearance was still present 5 years later.

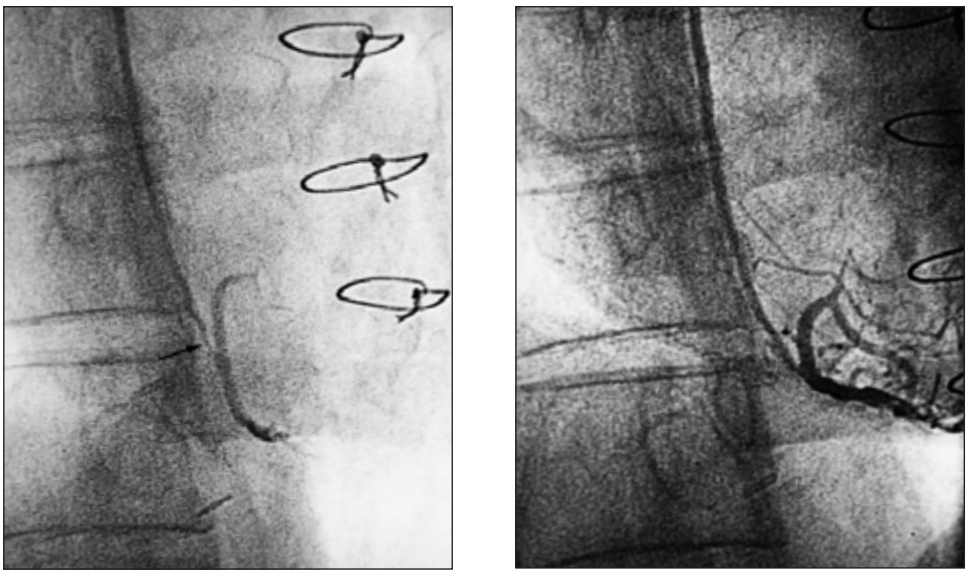

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Figure 17.20
(a) Severe stenosis at the distal anastomosis of RIMA and RCA (arrow). (b) Post PTCA result (2.5 mm balloon).

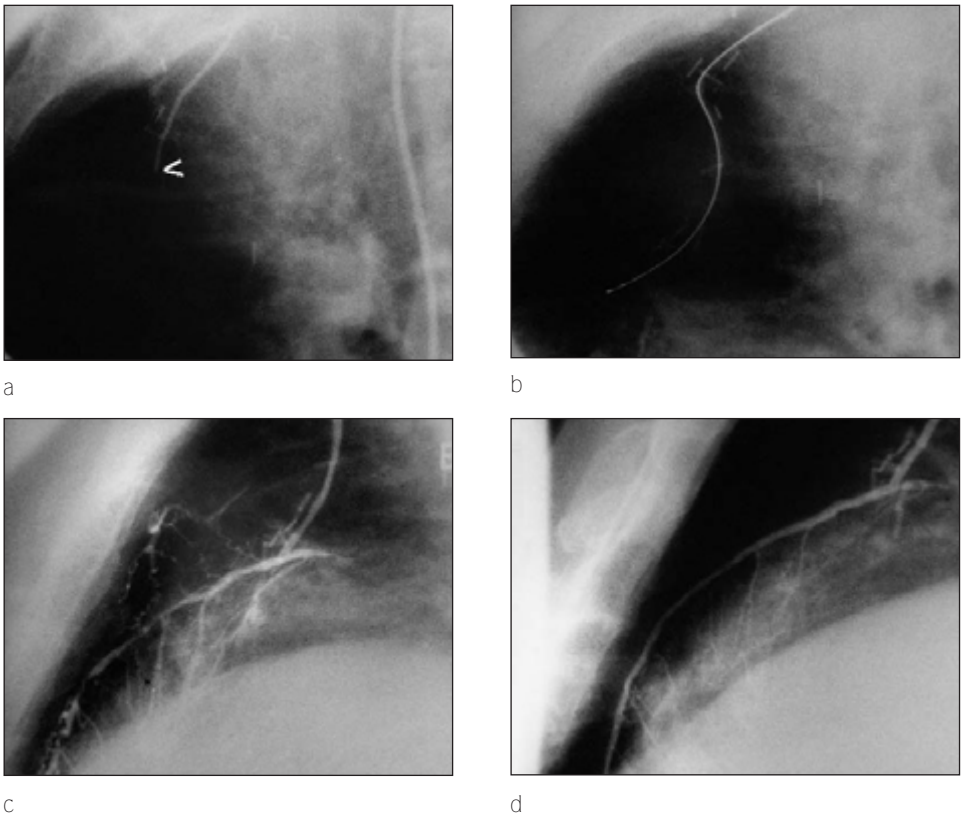


Figure 17.21
(a) LIMA occluded in mid segment (arrow) (lateral view). (b) Recanalization with Magnum guidewire supported by a 2.5 mm Magnarail balloon (SCHNEIDER). (c) Angiogram after first passage of Magnum wire showing a recanalized LIMA with distal stenoses in LAD. (d) Final angiogram after PTCA with Magnarail balloon catheter, showing a recanalized LIMA with good run-off into a widely patent LAD. (Illustrations provided by B Meier and published with permission of Mehan VK et al, *Br Heart J* 1993; **70**: 195–7.)

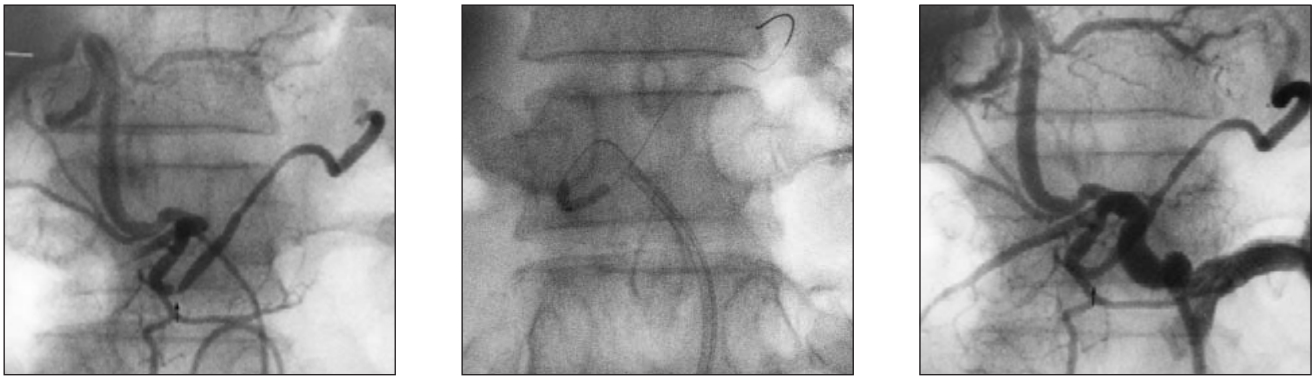


Figure 17.22
(a) A severe stenosis in a gastroepiploic artery inserted into the RCA (arrow) of a 51 year old man. (b) The lesion was dilated with a 2.5 mm Viva™ balloon through an 8F Multipurpose guide catheter. (c) The final result was excellent (arrow). (Courtesy of Dr N Komiyama, Department of Cardiovascular Medicine, Toranomon Hospital, Tokyo, Japan).

guide catheters (COBRA) are available to selectively engage the gastroduodenal artery. If the gastroepiploic artery originates from the superior mesenteric artery (10–20%) the route to the graft is very tortuous and the distance to the anastomosis is longer and more challenging. Vasospasm is frequent and requires direct nitrate administration.

Large unligated side branches of IMAs may cause a coronary steal phenomenon but it may be possible to close them by coil embolization.[112]

Results of intervention in saphenous vein grafts and internal mammary artery grafts

Despite taking on patients with more adverse characteristics for percutaneous coronary intervention, success rates are now higher than a decade ago as a result of improved technology.[56]

PTCA

PTCA in patients with previous CABG surgery generally produces high (>90%) success rates[113] and low major complication rates (Table 17.2). In a large series, Douglas et al[43] reported a success rate of 90% with a Q-wave MI rate of 2.3%, emergency CABG rate of 3.5% and a death rate of 1.2%.

The results depend on the site of the stenosis, age of the graft, morphology of the lesion and the presence of intraluminal thrombus. Aorta-ostial lesions are tough and prone to recoil and have a lower success rate with PTCA compared to lesions in the body or distal anastomosis site. Moreover, severe stenoses (>70% diameter stenosis), lesions with thrombus, complex and/or ulcerated morphology and lesions in old SVGs tend to have a lower success rate and a higher complication rate than less severe and less complex lesions. Angioscopy has shown that angiography underestimates the incidence of intraluminal thrombus and friable plaque and this may account for the unpredictability of complications in SVG PTCA.[114]

Angiographic restenosis occurs frequently and is often more difficult to recognize clinically in patients with multivessel disease and incomplete revascularization. Douglas et al.[43] reported a restenosis rate of 32% in SVGs <6 months old, 43% for SVGs 6–12 months old, 61% for SVGs 1–5 years old and 64% for SVGs >5 years of age. Restenosis rates average 24% for distal anastomotic lesions but 45% and 62%, respectively, for body and aorta-ostial lesions.[115] Short lesions were reported to have restenosis rates of 38% compared to virtually 100% for diffuse disease and total occlusions.[44]

During clinical follow-up, Plokker et al.[42] reported that 5-year survival was 78% after successful PTCA but that event-free survival was only 26%. However, in those in whom PTCA failed, event-free survival was only 3%. Freedom from cardiac events was better in SVGs <1 year old compared to those 1–5 years and >5 years old (45% vs 25% vs 19%) or in those undergoing PTCA for total SVG occlusion (38%).

Internal mammary artery PTCA has a high procedural success rate (83–94%) and a low complication rate. Shimshak et al.[116] reported a 94.3% success rate in 86 patients, no deaths and only a 1% Q-wave MI rate despite multilesion PTCA in 74% and 3 vessel PTCA in 18%.

Angiographic restenosis in LIMAs occurs in 0–31% of successfully treated patients, although the exact incidence is unknown because follow-up angiography is infrequent in

Table 17.2 Results of PTCA in patients after CABG surgery.

Author/year	*Patients*	*Stenoses*	*Success (%)*	*Q-wave MI (%)*	*Emergency CABG (%)*	*Death (%)*	*Restenosis (%)*
Douglas et al (1983)[26]	116	62	94	1.7	2.6	0	34
El Gamal et al (1984)[27]	31	44	93	6.5	0	0	50
Dorros et al (1984)[28]	61	33	79	4.9	1.6	3.3	46
Block et al (1984)[29]	40	40	78	0	2.5	–	–
Corbelli et al (1985)[30]	35	47	92	–	2	0	29
Dorros et al (1985)[31]	–	82	90	–	–	–	20
Reeder et al (1986)[32]	19	19	84	5.3	0	5.3	38
Ernst et al (1987)[33]	83	33	97	2.4	0	0	31
Cote et al (1987)[34]	82	101	85	3.6	1.2	0	23
Pinkerton et al (1987)[35]	236	100	93	3	3	0.4	43
Cooper et al (1989)[36]	59	24	75	5.1	0	1.7	–
Platko et al (1989)[37]	101	107	91.8	5.9	2	2	61
Tabbalat et al (1990)[38]	19	24	92	–	–	0	–
Webb et al (1990)[39]	140	148	85	4	1.4	0	–
Jost et al (1991)[40]	41	49	94	0	0	0	21
Meester et al (1991)[41]	84	93	84	8.3	2.4	1.2	–
Plokker et al (1991)[42]	454	–	90	2.8	1.3	0.7	–
Douglas et al (1991)[43]	599	672	90	2.3	3.5	1.2	–
Reeves et al (1991)[44a]	57	64	95.3	3.5	1.8	1.8	56
Miranda et al (1992)[45b]	351	–	94	–	–	–	–
Morrison et al (1994)[47]	75	89	94	3	1	3	–

[a]Reeves et al reported a clinical success of 82.5%.
[b]Miranda et al reported a 'major complication rate' of 5%.

most studies.[50,98,99,103] Restenosis is especially infrequent in distal anastomotic lesions.

During clinical follow-up, 73.3% had class I–III angina, after 20.5 months (mean). Actuarial survival at 1 and 5 years was 95% and 92.3% and event-free survival was 88% and 82%, respectively.[116] Dimas et al[50] reported similar results.

Directional atherectomy (DCA)

SVGs are suited for DCA because of their relatively large size and their often complex, bulky or highly eccentric lesions[117] (see Chapter 9).

The initial multicentre investigational experience and several individual reports on DCA for SVG lesions indicate high success rates (86–97%) and low major complication rates (1.0–3.8%) in selected patients.[118–123] Major complications occurred in 2.5% of patients (Q-wave MI in 1.3%; emergency CABG in 0.9% and death in 0.9%). Other complications included non-Q-wave MI (4.4%), distal embolization (7.2%), coronary occlusion (1.9%) and vessel perforation (0.6%).[119] As with PTCA, the results and technique of DCA for SVG disease vary according to the graft location as well as lesion location and morphology.

Aorta-ostial lesions are perhaps the most difficult for DCA, especially in left coronary grafts, due to difficult guide catheter engagement and coaxial alignment.

Predilatation with a 2.0 mm balloon catheter may be helpful and the Extra-Support™ guidewire (GUIDANT) helps the atherectomy device to track more easily.

The 7F atherectomy device is often necessary to debulk tough ostial lesions and higher balloon pressures or a 7F graft device may be needed for grafts 4.0–4.5 mm in diameter. The 7F graft device has an extra large support balloon giving it a larger working diameter. High success and low complication rates with ostial SVG lesions have been reported.[124–126]

SVG body lesions are a little easier to address, especially if focal (Fig. 17.23). The incidence of distal embolization is approximately 10% but diffusely diseased old SVGs should be avoided.[127–129]

Studies suggest an overall restenosis rate of 57–59% for DCA[118]—lower in de novo (36–38%) than in restenotic SVG lesions (75–81%).

In the CAVEAT II study,[130] DCA resulted in a higher angiographic success rate than PTCA (89.2% vs 79.0%). This achievement was partially offset by the initial increase in distal embolization (13.4% vs 5.1%) and non-Q-wave MI rates—due to the large device, active debulking and manipulation of the lesion in the presence of thrombus.[131] Q-wave MI (1.3%

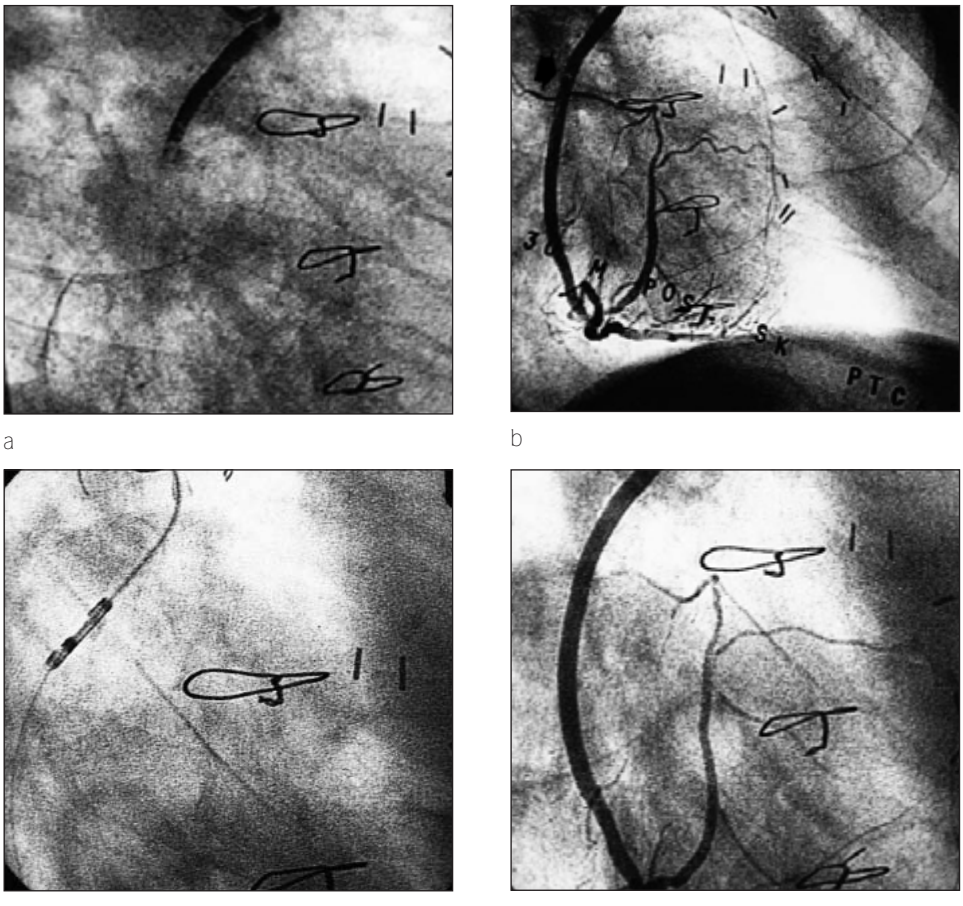


Figure 17.23
(a) SVG RCA occluded for the second time. (b) After recanalization by a combination of PTCA and intracoronary streptokinase therapy, a focal filling defect was evident at the point of occlusion (arrow). (c) DCA was used to remove the lesion and shown to be an organized coronary thrombosis. (d) SVG RCA is patent with normal angiographic appearance.

vs 1.0%) and death (2.0% vs 1.9%) occurred with similar frequencies. At 6 months, the restenosis (45.6% vs 50.5%) and TVR (18.6% vs 26.2%) rates were similar.

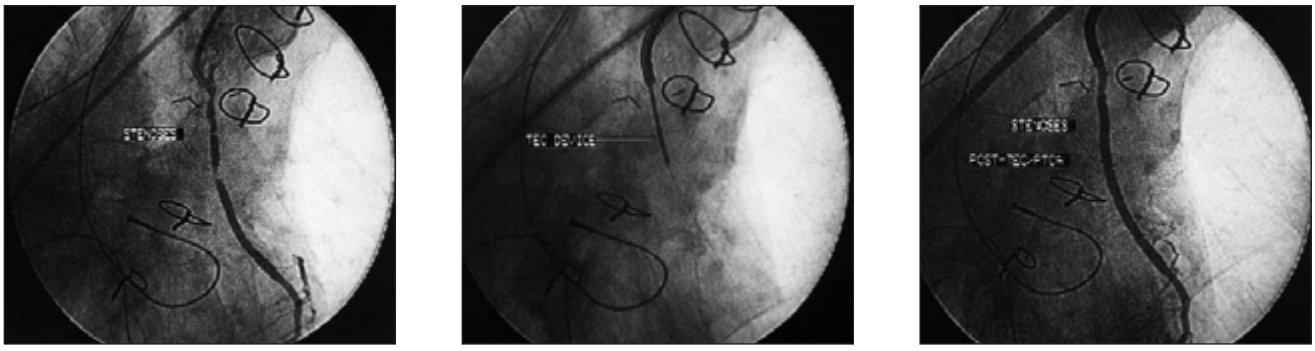
Stenting should optimize both the acute and long-term results.

Transluminal extraction coronary (TEC) atherectomy

The TEC atherectomy device (IVT) excises and aspirates plaque simultaneously (Fig. 17.24) (see Chapter 12). It may have its foremost indication in SVGs, particularly in old degenerated SVGs containing friable atheromatous material and thrombus where aspiration might reduce the incidence of distal embolization (Figs. 17.25 and 17.26). However, the cutter is limited by a maximum catheter size of only 7.5F (2.5 mm) and a significant residual stenosis often persists requiring adjunctive PTCA/stenting.

In the original FDA Pre Market Approval Study, 278 patients (348 lesions) had SVG disease with a mean graft age of 8.8 years (0.3–20 years) and 85% were >3 years old.[132] Adjunctive PTCA was used in 71% of the cases. The lesion and patient success rates were 95% and 89%, respectively. Major complications occurred in 3.9% (Q-wave MI 0.4%; CABG 0.7%; in hospital mortality 2.9%). Distal embolization occurred in 3.4% mostly after adjunctive PTCA and perforation in one case. Clinical and angiographic restenosis occurred in 43% and 53% of patients, respectively.

O'Neill et al reported a 93% success rate in SVGs >3 years old. Major complications included death (3.2%), Q-wave MI (0.9%) and emergency CABG (0.4%).[133,134] Hong et al reported that TEC in SVGs containing thrombi resulted in frequent distal embolization (14%), being largely attributed to adjunctive PTCA.[135] Distal embolization was frequently associated with complications including no reflow, MI and death.[136] Other workers have reported similar problems in old SVGs containing thrombus[127,137] and in totally occluded SVGs, even concomitant intragraft thrombolytic therapy is associated with a distal embolization rate of 17% and



a b c

Figure 17.24
(a) Two stenoses in LAD SVG—the more distal lesion is associated with a filling defect. (b) TEC device (IVT) activated and catheter passed slowly while maintaining continuous rotation and aspiration. (c) Post adjunctive PTCA (4.0 mm balloon catheter) shows no residual stenosis. (Acknowledgement: Dr RS Gottlieb, The Graduate Hospital, Philadelphia, Pennsylvania, USA.)

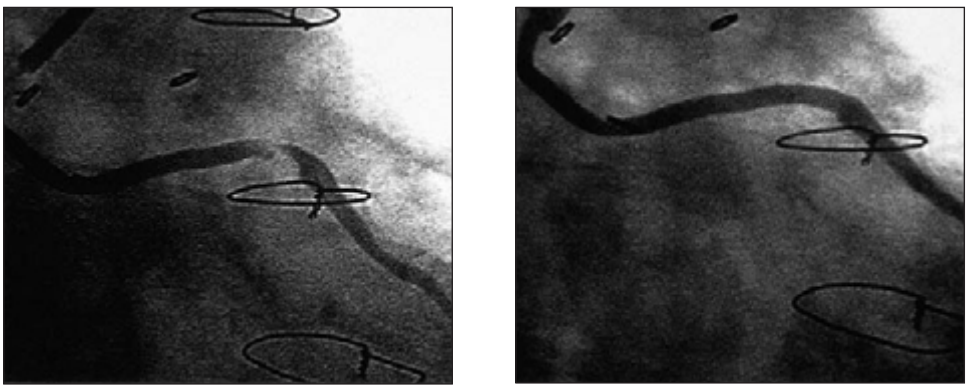


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Figure 17.25
(a) 11-year-old SVG OMCX showing an eccentric 95% stenosis in its mid third. The associated angiographic lucency suggests intraluminal thrombus. (b) Appearance after two passes with a 2.5 mm (7.5F) TEC device (IVT) and post adjunctive PTCA (3.5 mm balloon catheter) shows no residual stenosis. (Acknowledgement: Drs TC Trageser and CM Furr, Hamot Medical Center, Erie, Pennsylvania, USA.)

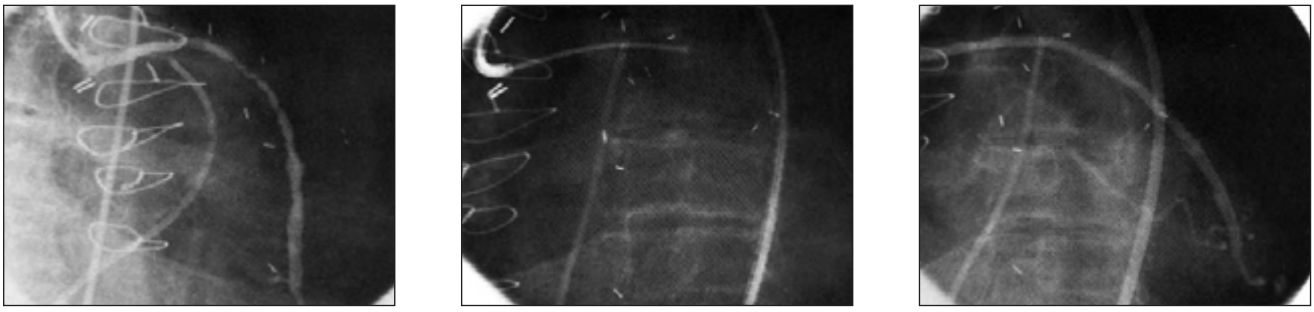

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Figure 17.26
(a) SVG OMCX shows diffuse disease with intraluminal filling defect suggestive of thrombus. (b) A 2.5 mm TEC device (IVT) is advanced whilst rotating and aspirating through the diseased SVG. (c) Post TEC atherectomy and adjunctive PTCA (3.5 mm balloon) angiogram shows overall improved appearance. (Acknowledgement: Dr RD Safian, William Beaumont Hospital, Royal Oak, Michigan, USA.)

detectable MI. In this latter series, Margolis et al reported an 82% success rate in patients with recent (3 days to 4 weeks) SVG occlusions.[138] The SVGs were 10 ± 3 years old and occlusions were estimated to be >6 cm in length.

Safian et al reported their results in SVGs aged 8.3 ± 3 years.[139] 17% were diffusely diseased or degenerated, TEC was advanced successfully in 91% and the failures underwent PTCA. The diameter stenosis was 75% ± 14% pre, 58% ± 20% post TEC and 36% ± 22% post PTCA, 20.7% had angiographic complications immediately after TEC and 5% after PTCA including distal embolization in 11.9%, no reflow in 8.8% and abrupt closure in 5%. Adjunctive PTCA managed 61% of angiographic complications and there were no perforations. Serious clinical complications included three in-hospital deaths (2.0%), one emergency CABG (0.7%), three Q-wave MI (2.0%), four non-Q-wave MI (2.7%), nine vascular injuries requiring surgery (6.1%) and four haemorrhagic cerebral infarcts (2.7%). At 6 months, angina requiring medical treatment was present in 18%, repeat intervention required in 26%, repeat CABG in 5%, Q-wave MI in 4% and late cardiac death in 7%. Angiographic follow-up revealed restenosis rates of 69% including 30 lesions with total occlusion of the original lesion.

Excimer laser coronary (ELCA) angioplasty

Excimer laser can ablate plaque in SVGs (see Chapter 11). However, the amount of material that can be removed is limited by the small size of the largest laser catheter currently available and adjunctive PTCA is usually necessary.

In 1992, a multicentre ELCA Registry reported a 91% procedural success rate (adjunctive PTCA in 80%) and 87% laser success in 514 SVG lesions in 434 patients, 80% of the SVGs were >3 years old.[140] Complications included perforation (1.1%), MI (2.3%), distal embolization (4.1%), dissection (4.6%), acute closure (5%), death (0.9%) and emergency CABG surgery (0.7%). Restenosis occurred in 57% at 6 months. Other workers have also reported 92–94% success rates and similar restenosis rates.[141,142] Complications are higher in lesions containing thrombus (embolization 25% vs 1%; MI 33% vs 2%; abrupt closure 17% vs 4%; restenosis 70% vs 51%).[143,144]

Rigid, aorta-ostial lesions may be ideal for ELCA.[145] Eigler et al reported a 90% procedural success and a 6 month restenosis rate of 47%.[146]

Rotablator atherectomy

Rotablator atherectomy is contraindicated in degenerated SVGs or grafts with thrombus and the technique has been used infrequently.[147–149] It may be used for rigid, balloon-resistant aorta-ostial stenoses (Fig. 17.27). Few data are available in the literature on restenosis rates.[150,151]

Stenting

PTCA in SVGs >3 years old can be accompanied by a procedural complication rate of up to 15% reflecting the friable nature of late graft atherosclerosis.[34,37,39,44] Even successful PTCA often leaves a residual stenosis of almost 30% and is followed by angiographic restenosis rates of between 40 and 70% - resulting in a high incidence of late cardiac events.[26,29,30,34,44,46,57,152] Endovascular stenting has therefore been proposed as an adjunctive procedure to PTCA for the management of SVG stenoses because of its ability to maximize the lumen's diameter and prevent elastic recoil after balloon dilatation,[121,153,154] making stents effective bail-out devices following acute failure of PTCA or atherectomy and for reducing late restenosis and reocclusion.

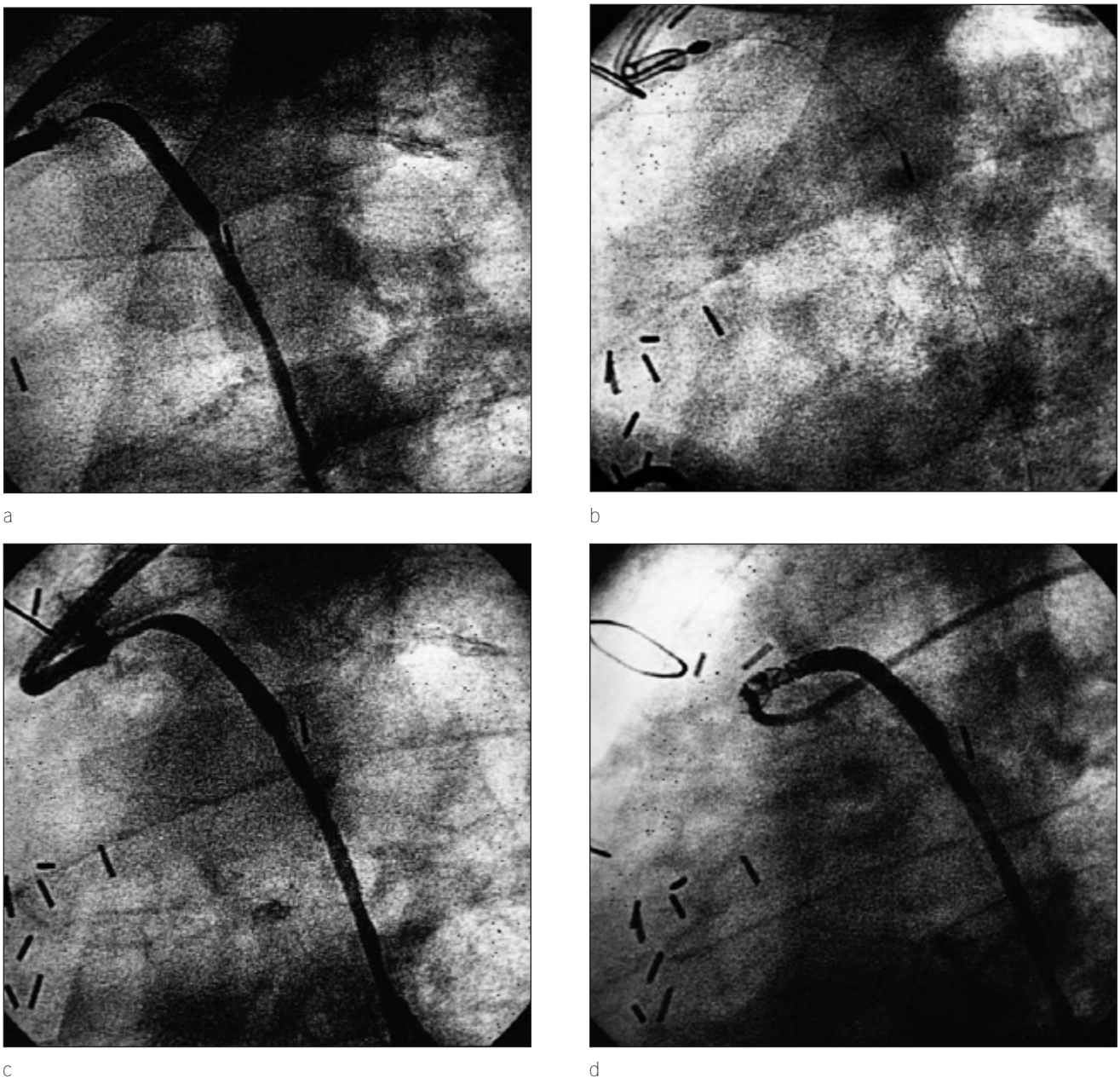

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Figure 17.27
Angiograms in left lateral projection. (a) Severe balloon resistant aorta-ostial stenosis in 10 year old SVG LCX causing unstable angina. (b) Rotablator atherectomy using 1.75 mm Rotablator burr and C wire (Boston Scientific/SCMED). (c) Post Rotablator atherectomy. (d) Wiktor stent deployed by balloon inflation (3.5 mm balloon) up to 16 atm. results in improved angiographic appearance.

Several studies have shown that stents can be successfully deployed (98–100%) in SVGs with low complication rates (Table 17.3).[72,121,153,155–164] Preliminary data from the randomized trial of PTCA versus elective Palmaz–Schatz coronary stent placement for de novo SVG lesions (SAVED) showed a higher procedural success rate (96% vs 85%), a bigger final MLD (2.85 mm vs 2.12 mm), fewer clinical events (5.9% vs 11.7%) and a reduced need for CABG (0% vs 6.7%), respectively.[165] Moreover unlike PTCA, the favourable early (97% vs 97% procedural success) and 1 year clinical outcome (73% vs 77% event free survival) after stent implantation are not diminished by advancing SVG age (<4 years vs >4 years).[166] Early complications in the JJIS Registry included subacute thrombotic closure (1.4%), in-hospital death (1.7%), urgent CABG (2.9%) and Q-wave MI (0.3%).[155] The early regimens of aggressive anticoagulation with coumadin after stenting have been replaced by a combination of aspirin and clopidogrel, as well as high pressure balloon inflation to ensure maximal MLDs, full stent expansion and complete wall apposition. Bleeding complications

Table 17.3 Results of stent implantation for SVG disease.

Author/year	Stent	Patients	Success (%)	Reference MLD mm	Stenosis MLD mm	Thrombosis (%)	Haemorrhage complications (%)	MI (%)	CABG (%)	Death (%)	Restenosis (%)	Peripheral vascular complications
Urban et al (1989)[153]	Wallstent	13	100	—	—	0	8	0	—	0	38	—
Leon et al (1991)[155]	P-S	192	98	—	—	—	—	1	1.6	1.6	26	—
Pomerantz et al (1992)[121]	P-S	69	99	3.6	3.6	0	7	13	—	0	25	—
Bilodeau et al (1992)[156]	G-R	37	100	—	—	—	21	13[c]	—	0	35	—
de Schreeder et al (1992)[157]	Wallstent	69	100	3.3	2.7	10	33	6	—	4.3	47	—
White et al (1993)[158]	P-S[a]	67	100	3.6	3.7	3.2	10	6.4	—	3.2	32	—
Leon et al (1993)[159]	P-S	589	99[e]	3.2	3.4	1.4	15	0.3	2.9	1.7	30	14.3
Piana et al (1994)[160]	P-S[b]	150	98	3.7	3.65	0.6	16	7[c]	0	0.6	17	8.5
Rechavia et al (1995)[72d]	P-S	29	100	3.2	3.3	0	——	7[c]	0	0	—	3
Wong et al (1995)[162]	P-S[b]	231	99[f]	3.3	2.95	0.9	25	13[c]	0.4	1.3	—	8.4
Savage et al (1995)[165] (1997)[175]	P-S	110[g]	95									

[a]Palmaz-Schatz peripheral
[b]Palmaz-Schatz coronary and biliary stents
[c]Most non-Q wave MI
[d]Aorta-ostial SVG lesions
[e]Clinical success = 97%
[f]Procedural success = 95.3%; clinical success = 93.6%
[g]Randomized SAVED Trial 110 Pts stented vs 110 Pts PTCA

and their sequelae have diminished without any increase in acute thrombotic closures.[167]

Multivessel stenting has been shown to have lower overall in-hospital complications than redo CABG (death: 0% vs 5.4%; Q-wave-MI: 1.1% vs 2.0%; stroke 0% vs 2.6%) and a shorter in-hospital stay (4 vs 9 days).[168] Although multiple SVG stenting has a similar in-hospital procedural success (97%) and major complication rate after 18 months as single SVG stenting (death/MI: 5.3%/2.9% vs 5.6%/4.3%), periprocedural non-Q-wave-MI was higher (27.9% vs 15.5%).[169] Stenting the native coronary vessels in post-CABG patients has a better 1 year outcome than stenting SVGs (death: 4.3% vs 9.1%; MI: 2.3% vs 4.5%) and a lower rate of post procedural MI (13% vs 18%).[170]

A lower restenosis rate after stent implantation is almost certainly due to the greater gains in acute luminal improvement (0–5% residual stenosis after stenting compared to 20–30% after PTCA alone) since late intimal proliferation (late loss) after stenting may exceed that of PTCA (0.5–1.1 mm vs 0.4–0.7 mm).[171–173] Six month follow-up data from the SAVED trial also showed an improved clinical outcome for stenting in SVGs compared to PTCA even though restenosis rates were similar (37% vs 46%) in the two groups.[174,175] In the JJIS Graft Registry of patients with symptomatic focal SVG stenoses, 6 month follow-up revealed an overall restenosis rate of 29.7% but lower (18.3%) in patients with de novo lesions and in patients with MLD >3 mm after final stent expansion (26%) than restenotic lesions.[159] A history of diabetes, previous restenosis and reference vessel size independently predicted restenosis. Other studies have reported low restenosis rates,[176,177] but there is significant variation relating to the site of the stenosis and the length of time to follow-up. For example, the restenosis rate after stenting non-ostial lesions (29%) has been shown to be lower than that for ostial lesions (60–62%).[178,179]

Unfortunately, the longer-term results are less good. In the JJIS Graft Registry the 12 month event-free survival for the entire cohort was 76.3% and target vessel revascularization was 13.3% (5.4% CABG and 7.9% repeat PTCA). Similarly Le May et al[180] showed a 98% in-hospital success rate with no intraoperative deaths, but follow-up at 18 months showed a 15% death rate, 17% had MI, 20% required repeat CABG and 37% repeat PTCA. Event-free survival occurred in only 44% of cases and cumulative survival at 2.5 years was 78.7%. Sketch et al[181] have indicated that late (2 year) clinical outcomes after stent implantation in SVGs progressively deteriorate such that event-free survival was only 75%, 67% and 55% at 6, 12 and 24 months, respectively, and that death (5% vs 8% vs 14%), CABG (7% vs 9% vs 12%) and PTCA (6% vs 8% vs 12%) increased steadily. Further deterioration at the stent site (late restenosis), increasing target lesion revascularization events, less favourable baseline characteristics and progression of disease at other sites[182] are responsible.

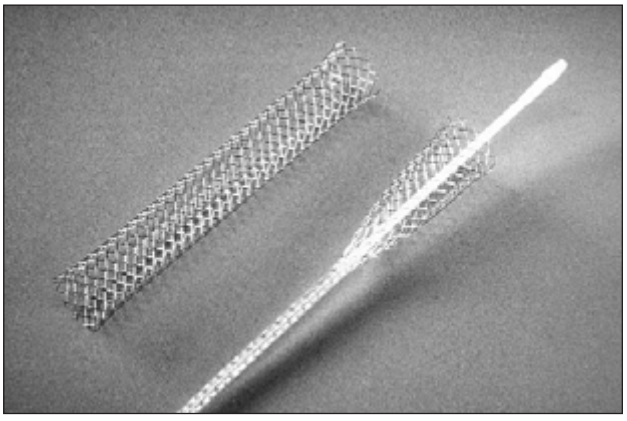
Overall survival at 5 years was reported in one observational study to be 83% but event-free survival only 30%. Pooled data analysis from the literature showed similar results with 5 year survival being 26% after PTCA, 30% after stenting and 63–76% after repeat CABG.[183]

Most stents can be used in SVGs but because of the volume of friable atherothrombotic material often present, stents with a higher metal:artery ratio or covered stents may be most appropriate, especially since there are no side branches in SVGs. The self-expanding Wallstent®

(Schneider/Boston Scientific) and the balloon-expandable Ultra™ stent (Guidant) are two stents appropriate for SVGs and are available in large diameters (2.5–6.0 mm) and a range of lengths (15–30 mm) (Fig. 17.28). The WINS Registry showed that the Wallstent produces good results in large (up to 5.5 mm) SVGs with 8.6% TLR and 30% angiographic restenosis rates at 6 months,[184] although the WINS randomized trial showed similar in-hospital and 6 month outcome from the Wallstent® and the Palmaz–Schatz® stents.[185]

For very large SVGs and those with complex disease[186,187] the Palmaz–Schatz® Biliary Stent (4–9 mm) is also of use but can be a technically demanding implant procedure.[188] The greater radial strength comes from its thicker struts and is of value for treating tough aorta-ostial lesions. In the study reported by Piana et al, the lesion MLD increased from 0.98 mm to 3.7 mm, the diameter stenosis fell from 74% to 1%[160] and restenosis occurred in only 17%. Wong et al reported a high angiographic (100% vs 98%) and procedural success (97% vs 96%) and a low subacute thrombosis rate (0% vs 1.7%) in groups receiving coronary and biliary stents.[162] Major complications were infrequent—2.9% and 1.4% for the coronary and biliary groups, respectively. Six month event-free survival was favourable (80%) in both groups.

Occasionally procedures can be combined. Severe aorta-ostial lesions or bulky eccentric stenoses in the proximal or body of SVGs can be excised by DCA or ELCA and then stented to improve the acute result although the long-term result may not be any different than lesions treated only by stenting.[189] Rigid aorta-ostial lesions may also be ablated by Rotablator atherectomy before stent implantation (Fig. 17.27). TEC atherectomy prior to stenting may optimize the angiographic results in complex SVGs, but distal embolization and CK-MB release remains a problem.[190–192] DCA has also been shown to be useful for debulking severe restenotic lesions within stents in SVGs.[193]



a

b

Figure 17.28
(a) The self-expanding Magic Wallstent™. (b) The Ultra™ stent.

Covered stents

The Jostent® coronary stent graft is characterized by an expandable PTFE membrane placed between two layers of stainless steel stent struts (Fig. 17.29). This may prevent friable material being forced through the stent struts and into the lumen and hence reduce in-stent restenosis. Stent lengths of 9 mm, 12 mm, 19 mm and 26 mm are available and come ready mounted on a rapid-exchange balloon catheter (2.5–5.0 mm). High-pressure (>16 atmospheres) is necessary for deployment. They can be successfully deployed and may reduce restenosis in SVGs.[194–196] It should be remembered that re-endothelialization, which can only start at either end of the stent due to the PTFE covering, is significantly delayed and in-stent thrombosis may be a problem unless clopidogrel is continued for 3–4 months.

Complications

The complications which occur after intervention in SVGs are shown in Table 17.4.

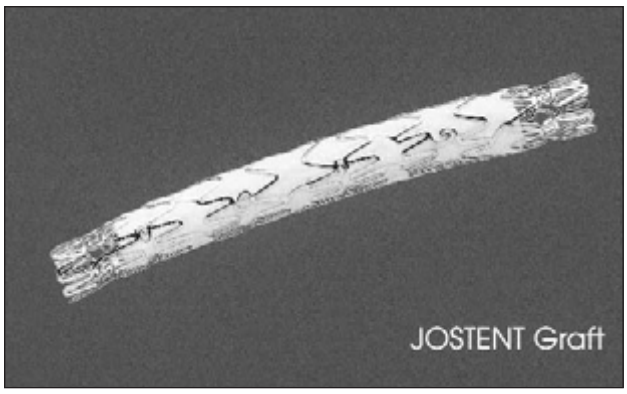


Figure 17.29
The JoMed® Covered Stent Graft is now available premounted on a balloon.

Table 17.4 Complications of intervention after CABG surgery.

Acute occlusion
Acute dissection
Distal embolization
Acute myocardial infarction
Perforation
Death
Restenosis

Acute occlusion

Abrupt closure is less common after PTCA in grafts than in the native coronary arteries (1.5% vs 6%) and may be due to localized occlusive thrombus, dissection flaps or even embolic phenomenon in older grafts. Prolonged inflation with a perfusion balloon and/or thrombolytic therapy, DCA or stenting may rectify the situation.

Non-Q-wave and Q-wave MI (0–8.3%) may result. CABG is necessary in 0–3.5% and death may occur in 0–5.3%. Emergency CABG for occlusion of SVG or native vessel has a high mortality (up to 15%) if the patient is ischaemic prior to surgery.[68,197]

Coronary embolism

Coronary embolism (3–15%) is commoner after intervention in SVGs than in native vessels due to the presence of larger volumes of friable atheromatous material and thrombus (Fig. 17.30). Bulky lesions in grafts greater than 3 years old, totally occluded and diffusely diseased SVGs have a higher risk of embolism (up to 15%)[198] which may give rise to MI[199] and the 'no-reflow' phenomenon.[200] Cardiogenic shock and death may occur if important distal coronary circulation is lost or temporarily occluded by extensive embolization. Emergency CABG is unlikely to prevent myocardial infarction.[201] Major CK-MB elevations may occur after 15% of otherwise successful SVG interventions and is associated with increased late mortality.[202]

Treatment includes continued heparinization, glyceryl trinitrate infusion, intragraft verapamil, intragraft thrombolytic therapy and intra-aortic balloon counterpulsation. TEC atherectomy may reduce the amount of distal embolization but will not prevent it. The administration of abciximab periprocedurally does not appear to reduce major adverse clinical events.[203]

The SAFE study demonstrated the use of the PercuSurge Guardwire™ (PercuSurge Inc, California) emboli-containment system which consists of a hollow 0.014 inch PTCA wire incorporating a compliant inflatable distal occlusion balloon (Fig. 17.31). During occlusion of the distal graft, PTCA and stent

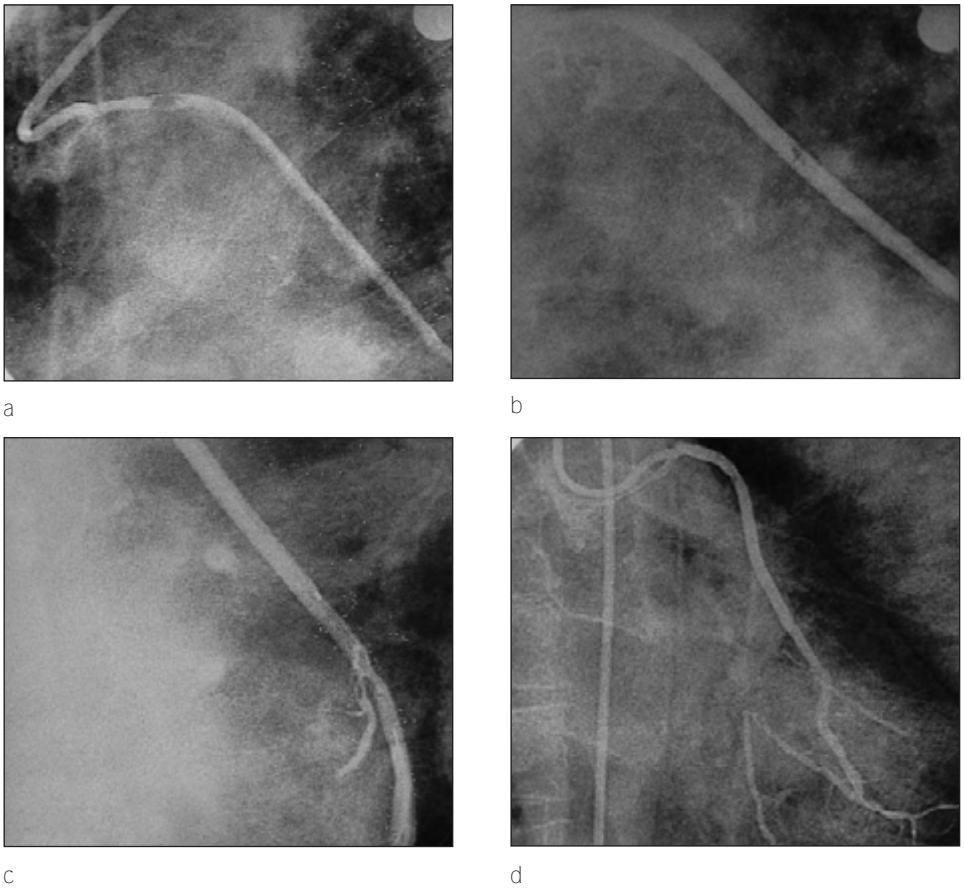


Figure 17.30
(a) 10-year-old sequential SVG to first and second obtuse marginal branches of left circumflex coronary artery (OMCX 1 and 2) has a bulky, eccentric proximal stenosis virtually occluding the SVG. The angiographic appearance suggests associated thrombus. The patient was a 67-year-old man with recent onset unstable angina. (b) Angiogram shortly after PTCA with a 3.5 mm balloon showed distal embolization of thrombus into the body of the SVG, (c) which quickly moved into the smaller OMCX 1. (d) Excellent final angiographic appearance after PTCA to thrombus, intragraft rtPA (15 mg) and 3.5 mm Wiktor stent placed proximally.

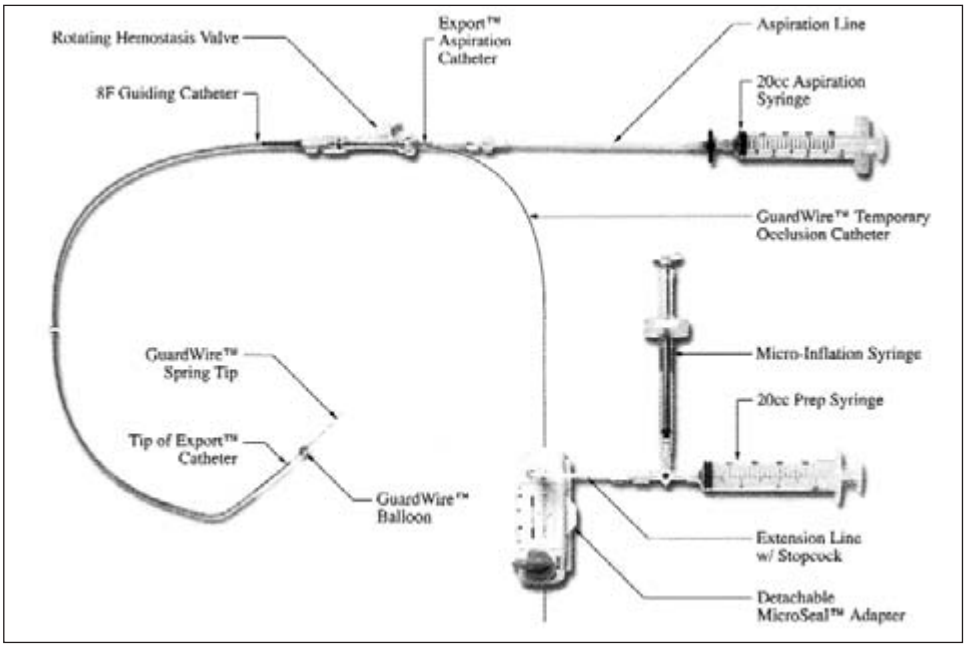


Figure 17.31
The Percusurge™/Guardwire™ device.

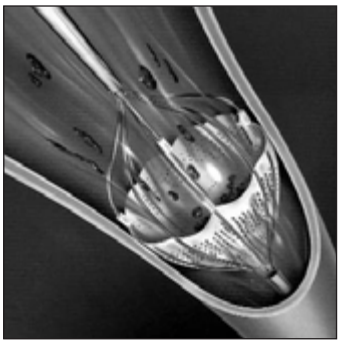
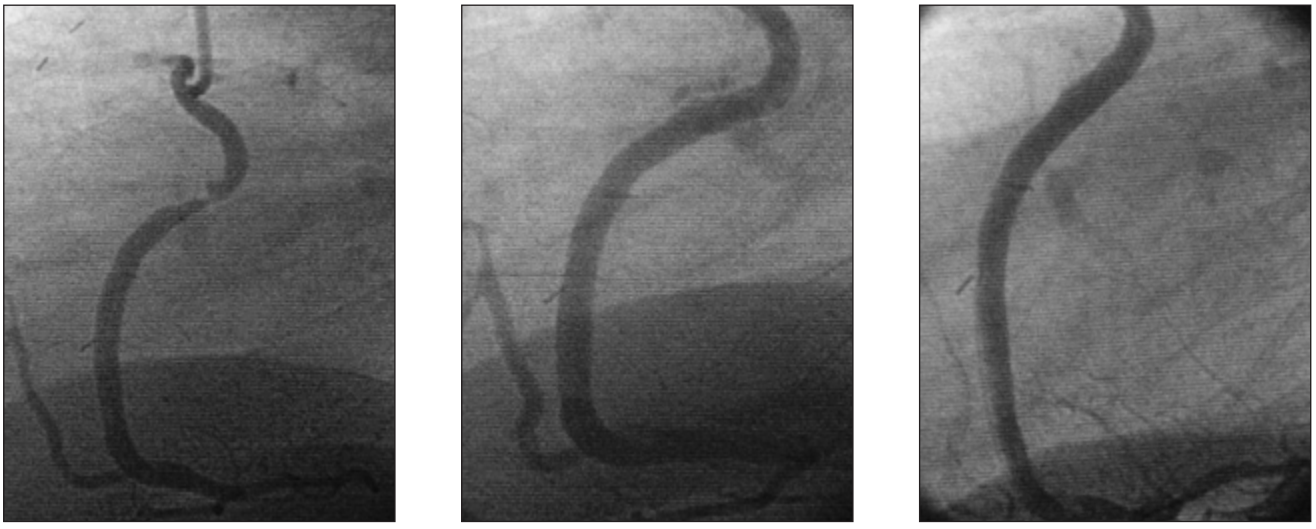


Figure 17.32
The AngioGuard™ device.



a b c

Figure 17.33
Unusual complication following primary Palmaz–Schatz stent (Johnson & Johnson) deployment in a complex SVG RCA lesion. (a) Pre PTCA. (b) During inflation to 15 atm, rupture of the 4.5 mm balloon resulted in a pinhole perforation of the VG with visible contrast extravasation. (c) Prolonged inflation with a 4.0 mm perfusion balloon resulted in an improved angiographic appearance with closure of the perforation. The patient was asymptomatic throughout. (Case provided by Drs U Sigwart and ED Grech.)

placement can be performed and then the Export™ monorail aspiration catheter is used to remove potentially embolic debris prior to deflation of the occlusion balloon.[204–206]

The AngioGuard™ device (Boston-Scientific) employs a PVC net/filter which can be deployed in the distal SVG prior to intervention to catch embolizing debris and prevent it from going distally (Fig. 17.32). The umbrella-shaped net behaves like a sieve with 100 micron pores which allows distal perfusion. The net can be closed once the intervention is completed and the material is then retrieved.

Perforation

Perforation due to a stiff guidewire, atherectomy device or balloon dilatation with an oversized balloon catheter is a rare occurrence. Pericardial and mediastinal fibrosis often protects against free rupture and cardiac tamponade, although this can occur.[207] SVGs may rupture with only slight balloon oversizing in older grafts.[208] Prolonged inflation with a perfusion balloon, reversal of heparinization or stenting with a covered stent may all be effective (Fig. 17.33).

Restenosis

Restenosis rates after intervention in SVGs are higher than in native vessels (45–65%) and depend on the age of the graft and the site of the lesion.

Age of graft

Douglas et al[43] have reported 32%, 43%, 61% and 64% restenosis rates for lesions dilated in SVGs < 6 months, 6–12 months, 1–5 years and >5 years old, respectively.

Site of graft stenosis

Ostial (aorta-saphenous) stenoses have the highest restenosis rates (68%) and distal anastomosis stenoses the lowest (24%). Lesions in the body of the graft have an approximately 45% restenosis rate.

DCA in SVGs has similar restenosis rates to PTCA but atherectomy to restenotic lesions may be associated with an even higher restenosis rate than PTCA (see above).

ELCA has similar restenosis rates to PTCA (see above).

Coronary graft stenting may have lower restenosis rates than other techniques. A 19% incidence has been reported for de novo lesions and 33% for restenotic lesions.[151] Randomized trials are necessary to confirm the superiority of stenting in SVGs.

Restenosis following IMA PTCA is uncommon and in the distal anastomotic site the restenosis rates tend to be about 15%.[209]

Conclusions

Coronary intervention after CABG surgery can be an extremely useful means of alleviating angina pectoris in patients who have developed recurrent symptoms due to advancing native coronary artery disease or disease within the grafts themselves. This may delay the need for further surgical intervention or be the only alternative to medical therapy when repeat CABG is contraindicated. Wherever possible, PTCA to amenable lesions in the native coronary circulation should be considered since restenosis rates may be lower than in the SVGs. Nevertheless, maximum myocardial revascularization should be sought at the least risk to the patient by formulating a strategy prior to the procedure after due discussion with surgical colleagues, the patient and the patient's relatives. DCA, ELCA, Rotablator and TEC atherectomy may be particularly helpful for specific problems in grafts such as bulky, eccentric lesions in large, non-tortuous grafts, tough, balloon-resistant aorta-ostial lesions and SVGs with much intraluminal material respectively although special expertise is required. Stent implantation is useful for improving suboptimal PTCA results and for reducing restenosis rates after balloon dilatation. However, little can be done for chronically-occluded SVGs or those with marked tortuosity and diffuse disease where there is a real risk of distal embolization and myocardial infarction.

Unfortunately the progressive development of atherosclerosis in SVGs with age seems unavoidable at present, but catheter-based intervention may minimize the associated clinical sequelae on the way and hopefully delay the need for repeat CABG.

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18

Overview of randomized trials of percutaneous coronary intervention: comparison with medical and surgical therapy for chronic coronary artery disease

Dominic L Raco and Salim Yusuf

Soon after the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1979, Andreas Gruentzig stated that randomized trials are 'clearly needed if we are to evaluate the efficacy of this new technique as compared with current medical and surgical treatments'.[1] Despite repeated calls for such studies throughout the 1980s, it was not until 1992 that the first randomized study comparing PTCA to more traditional treatment was published.[2] Over the last 30 years an explosive proliferation in the number of PTCA procedures has occurred. In 1997, 459 000 percutaneous coronary interventions (PCIs) were performed in the US alone.[3] In this same year over 12 million Americans were medically treated for coronary artery disease and 607 000 underwent CABG.[3] As technological advances have occurred, and operator experience has increased, the application of PCI has expanded from balloon dilatation of simple, concentric, single-vessel stenotic lesions to multi-device, stent-facilitated intervention of multiple complex lesions. This growth in PCI has had an enormous impact on the management of patients with coronary artery disease, as well as on the utilization of health care resources and cost. However, despite its rapid proliferation, randomized studies providing data defining and substantiating the role of PCI have only been published in the past 5 years. This chapter will review the published and ongoing studies comparing medical and surgical therapies. The limitations of the studies, their interpretation and application to clinical practice will also be discussed.

Background

Before comparing PCI to medical and surgical therapy, it is useful to review briefly the lessons of the pioneering randomized studies comparing medical to surgical therapy. Three major studies provide the bulk of the data: the European Coronary Surgery Study, the Veteran's Administration Coronary Artery Bypass Surgery Cooperative Study Group and the Coronary Artery Surgery Study.[4–6] In general, these studies demonstrated that the absolute benefit (mortality) of CABG surgery is proportional to the long-term risk of medical therapy. Various anatomical markers, such as number of diseased vessels, involvement of the proximal left anterior descending (LAD) artery and lower ejection fraction, are the major determinants of long-term risk. In a meta-analysis of the CABG surgery versus medical management studies, a survival advantage for CABG over medical therapy was demonstrated for patients with left main coronary artery disease, left main 'equivalents' and three-vessel disease (irrespective of left ventricular dysfunction), and for proximal LAD disease (even if one- or two-vessel).[7] After taking multiple clinical and angiographic factors into account, this meta-analysis indicated that only those at high (4.8% annual mortality) risk or moderate (2.5% annual mortality) risk experienced a clinically and statistically significant improvement in survival. By contrast, there was no evidence of survival benefit among those at low risk (1.2% annual mortality). Among patients without involvement of the proximal LAD, only in those with three-vessel disease was mortality lowered with surgical therapy. Among those with one- and two-vessel disease without involvement of the proximal LAD, the results were equivalent. Figure 18.1 summarizes the overall survival advantage associated with surgical over medical therapy.

Among patients in whom a survival benefit cannot be expected, CABG surgery is potentially indicated for only two indications: to improve functional capacity and quality of life (if not accomplished by maximally tolerated medical therapy) or to reduce the incidence of non-fatal end-points, such as myocardial infarction. Although surgical revascularization is generally considered to improve or relieve angina pectoris in a much broader group of patients than the subgroups in

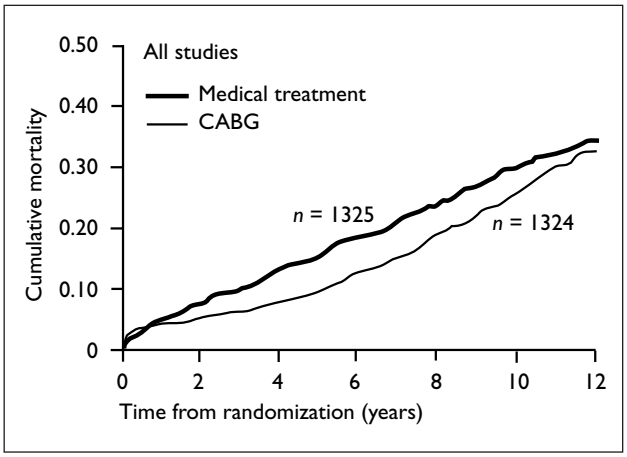

Figure 18.1
Overall survival advantage of CABG over medical treatment from a meta-analysis of all CABG versus medical management trials. Reproduced with permission from Yusuf et al. *Lancet* 1994; **344**: 563–70.

which it has been found to be superior in extending survival, no overall impact of CABG surgery on subsequent infarction can be demonstrated. This is due to an excess of infarction in the perioperative period among those assigned to surgery, even though the subsequent risk is lower during extended follow-up.

Considerations for comparison of CABG surgery versus PCI, versus medical therapy

In comparing PCI with CABG surgery, several outcomes could be assessed: mortality, myocardial infarction, contractile function, or symptoms. With respect to mortality, inclusion of low-risk subgroups in whom CABG surgery has not been shown to improve survival (as compared to medical therapy) decreases the ability to show a difference on mortality. An exception to this rule would occur if PCI were significantly worse than medical therapy or PCI were substantially superior to surgery, both of which can be considered unlikely. Therefore, several plausible hypotheses could be suggested with regard to a comparison of PCI and CABG surgery, at least with respect to survival.

In comparison to medical therapy, CABG surgery in moderate-risk patients is associated with an approximate 40% relative risk reduction at 5 years, and an approximate 50% risk reduction in high-risk subgroups at 5 years. Therefore, detection of a difference in relative risk of about 10% or 20% in a comparison between CABG surgery and PCI among high-risk patients would be clinically relevant. If such a comparison indicated superiority of PCI over CABG surgery, one could reasonably conclude that PCI was superior to both medical therapy (indirect extrapolation) and CABG surgery (direct inference). If, on the other hand, a 20% difference in the relative risk of mortality in favour of CABG surgery existed, then one would generally prefer surgical revascularization to PCI in such patients. If the available data from such a comparison were large, then the confidence interval of any observed difference (e.g. 20%) would be narrow (e.g. ±10%) and one might also reasonably conclude that PCI was superior to medical therapy to a clinically worthwhile extent (for example, 20–30% relative risk). If no difference between CABG surgery and PCI were observed, one could not conclude that PCI was equivalent to CABG surgery if the trials were too small to detect or exclude relative differences in mortality of about 20%. Moreover, if the confidence limits of any difference included the possibility that PCI was worse than CABG surgery by 50% (relative risk), then one could not conclude that PCI had any favourable impact on survival compared to medical therapy. These considerations indicate that to reliably compare the relative impact of PCI and CABG surgery and to avoid missing clinically important differences (such as 20%) the following conditions would need to be met:

- Inclusion of subgroups in whom surgery has been shown to be superior to medical therapy.
- Inclusion of sufficient numbers of patients (eg 4000 in each of the two groups). A total of 600 end-points would be needed in the 'control' group to exclude a relative risk reduction of 20% with 90% power. On the other hand, if a 30% risk reduction were observed, then trials of about 2000 patients in each group would suffice.
- Follow-up of patients for at least 3–4 years would be required, not only to accrue a sufficient number of end-points but also to obtain data well beyond the early period when periprocedural mortality rates have a substantial influence. Ideally, follow-up would be extended to 10 years to assess the late effects of both procedures.
- Compliance to the original treatment allocation should be high. If a substantial proportion of patients 'cross-over' (eg 30–40% by 5 years), then the ability to detect differences in survival drops dramatically.

These general considerations are the key to the interpretation of the trials comparing CABG surgery to PCI.

Among low-risk patients (annual mortality <2% per year), comparing PCI to CABG surgery would be pointless, if the aim were to assess the impact on mortality, because CABG surgery has not been shown to reduce mortality. Given the low risk of these patients, demonstrating differences in mortality would be extremely difficult. For example, if one assumed a 1% per year mortality rate in the medical group,

one would require 8000 patients followed up for 5 years to detect a 30% risk reduction reliably, or 16 000 patients followed up for the same period to detect a 20% risk reduction. Moreover, in such low-risk patients, any absolute benefit is likely to be too small to justify the costs and risks associated with CABG surgery unless it is very large (eg a 50% risk reduction which could be demonstrated with about 4000 randomized patients). Therefore, the medically relevant comparison in low-risk patients is between PCI and medical therapy. We are left with two options regarding this low-risk subgroup. First, we could accept that trials are unlikely ever to demonstrate a difference in mortality between PCI and medical therapy (unless the former was harmful). Second, one could compare their effects on a combined clinical outcome considered to be clinically important (eg death plus myocardial infarction, or death plus myocardial infarction plus hospitalization for severe angina, or death plus myocardial infarction plus hospitalization for severe angina plus the need for further revascularization procedures). Such trials are feasible and could provide clinically relevant answers.

In the remainder of this chapter we will describe the available data and provide interpretations combining both medical and scientific perspectives.

PCI versus medical therapy

Single-vessel disease

Angioplasty was initially intended for the management of single-vessel coronary artery disease. Although an increase in the number of multi-vessel disease patients treated with PCI has occurred, over 90% of PCI procedures are still limited to treating a single lesion.[8,9] Success and complication rates, both on a patient and a lesion-specific basis, have been well described.[8,9] Despite a large volume of observational data on lesion-specific and device-specific success and complication rates, there remains a relative paucity of randomized data addressing whether a patient with single-vessel disease would be best treated with medical therapy, PCI or CABG. Only two randomized studies have specifically compared PCI and medical therapy in patients with single-vessel disease.

The first such study, a comparison of angioplasty with medical therapy in the treatment of single vessel coronary artery disease (ACME), was published in 1992.[2] Two hundred and twelve patients with 70–90% stenosis of one epicardial coronary artery and exercise-induced myocardial ischaemia were enrolled. Patients were randomly assigned to PTCA or medical therapy. Follow-up continued for 6 months and, as expected, there was no difference in mortality. The percentages of patients on nitrates, calcium channel blockers and beta blockers were 50%, 71%, and 50% in the medical group. In the PTCA group, the utilization of the same medications was 24%, 35%, and 30%, respectively. A significant reduction of medication use was observed among patients who underwent PTCA ($P < 0.01$). Of the 100 patients who actually underwent PTCA, 80 procedures were clinically successful (angiographic success with no significant complication). Two patients underwent emergency bypass surgery and four patients had an acute myocardial infarction, (one Q-wave and three non-Q-wave). No deaths occurred in the PTCA group at any time. During follow-up, 16 patients required a total of 19 repeat PTCA procedures. Five additional patients required bypass surgery, and one more patient had a myocardial infarction. Of the 107 patients assigned to medical therapy, none had bypass surgery, but 11 underwent PTCA. Three patients had myocardial infarctions during follow-up and one died as a result of a PTCA procedure.

The 6-month follow-up of the ACME trial indicated that 64% of the PTCA group and 46% of the medical group were free of angina. Patients assigned to PTCA had a mean decrease of 15 episodes of angina per month, as compared with seven fewer episodes per month for those assigned to medical therapy. The medical group experienced a 0.5 minute mean increase in exercise duration over their baseline value, while the PTCA group had a stress test duration improvement of 2.1 minutes ($P < 0.0001$). Although patients in the medical group continued anti-anginal medication prior to the stress test, the PTCA group patients had their anti-anginal medication held for 24 hours prior to their test. The difference between the two groups may be even greater in clinical practice, where PTCA patients with residual angina are often treated with small doses of anti-anginal medications. The overall psychological well-being score improved by 8.6 for patients in the PTCA group and by 2.4 for patients in the medical therapy group ($P = 0.03$). In summary, PTCA provided earlier and more complete relief of angina, but was associated with a high frequency of complications and greater initial costs. From this trial it is reasonable to conclude that patients with single-vessel coronary artery disease whose symptoms are not adequately controlled by medical therapy can be treated with angioplasty with a good expectation for functional improvement. However, if symptoms are controlled with medical treatment, PTCA need not be done or can be delayed.

The second study was a randomized, prospective trial in 88 patients with asymptomatic single-vessel coronary artery disease who were randomized to medical therapy versus PTCA.[10] The procedures were performed in the early 1990s and after 2 years of follow-up there was no difference in clinical outcomes between the two groups. There was procedural success among all PTCA patients and no significant complications occurred. At 2 years after randomization, 32 patients in each group were still asymptomatic, with unchanged exercise tolerance. In the medical group, seven patients required PTCA and two patients CABG surgery because of new angina. In the same 2 years of follow-up, seven patients in the PTCA group required repeat PTCA and none required CABG. Only one myocardial infarction occurred in the 44 medically treated patients, but unfortu-

nately this was fatal. Two of the 44 patients with PTCA had a myocardial infarction, and no deaths occurred in this group during the 2 years of follow-up. The investigators concluded that after 2 years of follow-up there was no difference in clinical outcomes between the two groups.

Multi-vessel disease

More recent trials of PCI versus medical therapy for CAD have expanded recruitment to include selected low-risk patients with multi-vessel disease. The second Randomized Interventional Treatment of Angina (RITA-2) trial was a prospective, randomized trial of 1018 patients with stable coronary artery disease that was conducted at 20 sites in the United Kingdom and Ireland.[11] It tested the hypotheses that elective PTCA would reduce the combined frequency of all-cause death and definite non-fatal myocardial infarction. Patients with recent unstable symptoms were excluded and 80% of patients had Canadian Cardiovascular Society (CCS) class 0 to II angina (47% class O or I and 33% class II) and 78% were taking one or two anti-anginal drugs at enrolment. Also, 60% of the patients had single vessel coronary artery disease, 33% had two-vessel disease, and 7% had three-vessel disease; only 6% of the patients had significant left ventricular dysfunction. Results over a median 2.7 year follow-up period are summarized in Fig. 18.2. Eighteen deaths occurred (average mortality, 0.7% per year), and the primary end-point of death or myocardial infarction occurred in 6.3% of PTCA patients and 3.3% of patients assigned to medical therapy (absolute difference, 3.0%; 95% confidence interval 0.4–5.7%; $P = 0.02$). The difference was attributable mainly to one death and seven myocardial infarctions among patients undergoing PTCA. The combined rates of death, myocardial infarction, and non-protocol revascularization were about 25% in both groups by 3 years of follow-up and were primarily due to worsening of symptoms among the medical group. Angina pectoris and treadmill exercise time improved significantly in both groups, especially in the PTCA group (absolute 16.5% excess of grade 2 or worse angina in the medical group at 3 months). As patients with severe symptoms among both groups underwent non-protocol revascularization during 3 years of follow-up, the difference in reported angina decreased (absolute 7.6% difference in grade 2 angina or worse). Patients with grade 2 or worse angina appeared to benefit from PTCA, with a 20% lower incidence of angina and a 1 minute longer exercise time, whereas patients with mild symptoms at enrolment derived no significant improvement in symptoms. A substudy of RITA-2 concluded that PTCA substantially improved patient-perceived quality of life, especially physical functioning and vitality, as compared with continued medical therapy.[12] These differences are attributed to alleviation of cardiac symptoms, specifically breathlessness and angina. Overall the RITA-2 program would indicate that medical treatment in such patients is associated with fewer deaths and myocardial infarcts, but more angina. The continuation of medical treatment is acceptable if symptoms are controlled. If symptoms are not adequately tolerated then PTCA is helpful.

The Atorvastatin Versus Revascularization Treatment (AVERT) trial randomized 341 patients with CCS class 2 or less angina, one- or two-vessel disease and relatively normal left ventricular function to aggressive lipid lowering with atorvastatin, 80 mg daily, or PCI.[13] The atorvastatin group had a 46% reduction in LDL cholesterol to 2.0 mmol/l (77 mg/dl), while the PCI patients' LDL cholesterol was reduced by only 18% to 3.0 mmol/l (119 mg/dl). Over 18 months of follow-up, the combination end-point of all ischaemic events occurred in 22 of the atorvastatin and 37 of the PCI patients, $P = 0.048$. PCI tended to offer better control of angina, but this was at the expense of an increase in repeat revascularization, which accounted for the increase in events in the PCI group. This again would suggest that PCI could be deferred until symptoms are not adequately controlled by medical therapy.

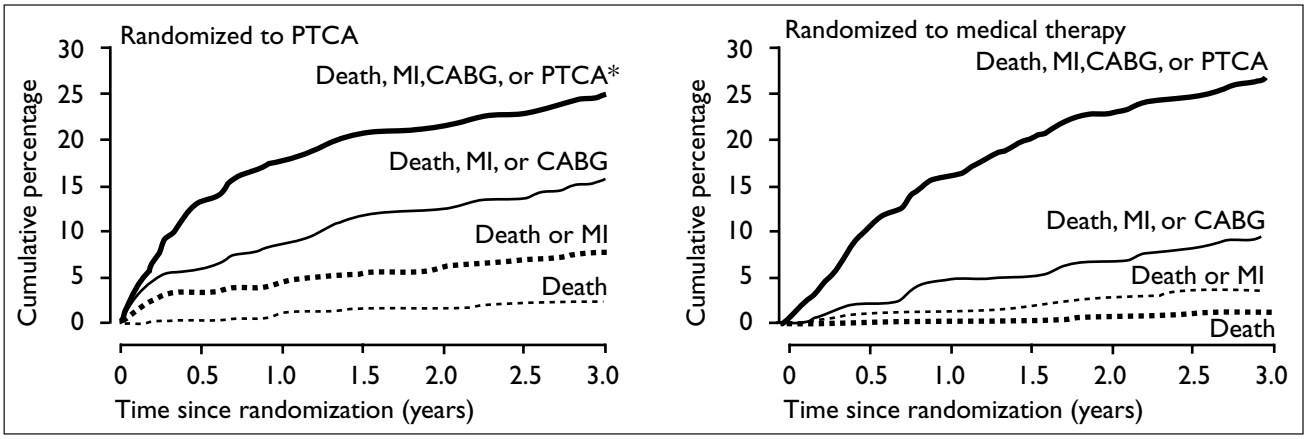

Figure 18.2
Cumulative risk of PTCA (*indicates repeat-PTCA), CABG, myocardial infarction (MI), or death in patients randomized to PTCA and medical treatment in the RITA-2 trial. Reproduced from the RITA-2 participants. *Lancet* 1997; **350**: 461–8.

Conclusions and limitations

These trials imply that medical therapy and PCI may have complementary roles in the management of CAD patients. While PCI will decrease angina and improve quality of life, medical therapy (including aggressive lipid lowering) decreases ischaemic events and mortality. PCI will reduce the stenosis of haemodynamically significant lesions causing angina, but does not deal with the majority of culprit lesions causing myocardial infarction and its complications. These latter lesions are mild and generally do not cause angina.[14] We can conclude that among low-risk patients with one- or two-vessel disease, medical therapy should be considered the initial line of therapy, and that PCI should only be considered when maximally tolerated medical therapy does not provide adequate control of symptoms. Although most agree that this is a reasonable approach, there is substantial evidence showing that this is often not followed in clinical practice. In a large insurance company database, Topol noted that less than a third of patients undergoing single-vessel angioplasty had a stress test.[15] It was concluded that many patients undergo angioplasty on the basis of anatomical stenosis rather than symptomatic or objective evidence of myocardial ischaemia.

These trials of PCI versus medical therapy have several limitations. Given the extremely small total sample size and short follow-up, the possibility that clinically important differences were missed cannot be excluded. There may be certain patient subgroups that would particularly benefit from one mode of therapy over the other. These data do not address whether new interventional and medical therapies, such as stents (used in only 8% of RITA-2 and 25% of AVERT patients), statins, and GP IIb/IIIa receptor platelet blockers, may significantly mitigate the observed risks and benefits. Stents, in particular, may significantly enhance observable benefits among patients undergoing PCI. In a report of 120 patients randomly assigned to undergo PTCA or stenting for the treatment of a proximal left anterior descending artery stenosis, both angiographic restenosis (19% vs 40%, $P = 0.02$) and survival free of death, myocardial infarction, or recurrent angina by 1 year (13% vs 30%, $P = 0.04$) were significantly lower among patients undergoing stenting. The long-term benefits of stenting were observed even though initial procedural success rates were equivalent (95% stent group, 93% PTCA group).[16] The optimum percutaneous transluminal coronary angioplasty versus routine stent strategy trial (OPUS-1) enrolled 479 patients from 44 hospitals in the US and Canada over 19 months in 1996–98.[17] These patients had single-vessel disease that was not adequately controlled with medical therapy. Many patients had complex lesions. They were randomized to either routine stent implantation or to an initial approach of balloon angioplasty with provisional stenting. Patients were followed for 6 months, with a primary composite end-point of death, MI, cardiac surgery, and target vessel revascularization (TVR). Stents were implanted in 227 (98.7%) of those assigned to routine stenting. In the angioplasty group, 93 (37%) received at least one stent when PTCA results were not deemed optimal. At 6 months the composite end-point was reached in 6.1% of the routine stent group and 14.9% of the PTCA with provisional stent patients ($P = 0.003$). Although all components of the composite end-point trended in favour of the routine stent group, only 6 month TVR was individually statistically significant (3.0% versus 10.1%, $P < 0.05$).

PCI versus CABG surgery

Single-vessel disease

It has been inferred that revascularization will control symptoms better than medical therapy in patients with single-vessel disease and is indicated among these patients if symptoms are not adequately relieved by maximally tolerated medical therapy. Although both PCI and CABG therapies offer a high rate of procedural success in these patients, whether one offers the optimal mode of revascularization in such patients has been unclear. Until 1994 there had been no randomized study directly comparing PCI to CABG in patients with single-vessel coronary artery disease. A Swiss study from a single centre randomized 134 patients with isolated proximal LAD stenosis to angioplasty versus left internal mammary artery grafting.[18] Over 2.5 years of follow-up, no death occurred in the PTCA group and one cardiac death occurred in the CABG cohort. The PTCA group had two Q-wave and six non-Q-wave myocardial infarctions. The CABG group had one Q-wave and one non-Q-wave myocardial infarction. There was no significant difference in the combined outcome of cardiac deaths plus myocardial infarction between PTCA and CABG surgery ($P = 0.21$). The only significant difference between the two groups was the need for repeat revascularization. In the PTCA group, 17 patients (34%) required a second revascularization procedure, compared with only 3 patients (5.1%) treated with CABG surgery. A clinical (CCS angina functional class) and functional comparison (exercise testing) of the two groups did not reveal any significant difference. At 6 months, the proportion in the CCS class I were 88% for PTCA and 95% for CABG, at 1 year, 96% and 97%, and at 2 years, 94% and 95%. The proportion of patients with no symptoms at all was lower in the PTCA than in the CABG group ($P = 0.07$): 79% versus 92% at 6 months, 84% and 94% at 1 year, and 77% and 89% at 2 years. Stress test exercise duration was not clinically or statistically different (6.2 versus 6.0 minutes for PTCA and CABG, $P = 0.6$). After 2 years of follow-up the PTCA group was taking significantly more anti-anginal drugs than those treated by CABG, but this did not appear to adversely influence their quality of life. In this study, no clinical or significant difference in early complication rates was found and both groups benefited equally from their respective

procedures (with the exception of the need for increased procedures to deal with restenosis in the PTCA group). Restenosis-related events in the PTCA group occurred during the first 6 months of follow-up, but after this period the two groups had similar outcomes. Since graft attrition associated with LIMA surgery and PTCA restenosis after 6 months are both equally infrequent during intermediate (2–10 years) follow-up, it is more likely that clinically significant events in the intermediate period will be caused by new lesions not involving the site of revascularization.

A second, randomized comparison of PCI versus CABG in patients with single-vessel disease is a component of the RITA study.[19] This multicentre British study randomized 1011 patients with coronary artery disease to PTCA versus CABG. The primary end-point was the combined 5-year incidence of death and non-fatal myocardial infarction. After 2.5 years of follow-up, 40 primary end-point events were observed among the 456 patients with single-vessel disease. Overall, the difference in death and myocardial infarction was not statistically significant (24 PTCA, 16 CABG), although the trend was in favour of CABG. The only statistically significant difference between the two groups was an increased need for repeat intervention in the PTCA group, again related to restenosis. The Brazilian MASS study was a very small trial of 214 patients with isolated stenosis of the proximal left anterior descending coronary artery and, to date, incorporated the only three-way randomization among PTCA, CABG, and medical therapy.[20] Rates of death (one in each group) or non-fatal myocardial infarction (2 PTCA, 1 CABG) were very low over a mean 3-year follow-up period, indicating a low-risk cohort of patients. Twenty-one PTCA patients (29%) required repeat revascularization. After 3 years, 98% of patients assigned to CABG and 82% assigned to PTCA were free from angina, compared with only 32% of those in the medical group. No patient in any treatment group had severe angina (class III or IV).

In the meta-analysis of Pocock et al, 732 patients had single-vessel disease.[21] Of the 374 patients in the PTCA group, 27 (7.2%) experienced cardiac death or myocardial infarction in the first year, versus 16 (4.5%) of 358 CABG patients. Because no such difference was found for multi-vessel disease, caution is needed to avoid overinterpretation of these data. When all-cause death over all patient years of follow-up was considered, no significant differences were found (3.7% PTCA vs 3.1% CABG; odds ratio 1.13; 95% CI 0.50–2.6). Rates of all-cause death or myocardial infarction were higher in the PTCA group than the CABG group (10.1% vs 6.1% odds ratio 1.71; 95% CI 1.01–2.90, $P < 0.05$). Rates of angina grade 2 or worse were low at 1 year in both groups (14.6% PTCA, 6.5% CABG, $P < 0.01$) and at 3 years (15.4% PTCA, 12.5% CABG, $P = 0.11$). Rates of additional revascularization procedures were significantly lower at 1 year in the CABG group (3.6% vs 30.5%) than in the PTCA group.

In summary, the data available suggest that both PTCA and CABG are highly effective in providing symptom relief for patients with severe single vessel coronary artery disease. Neither procedure is associated with an unequivocal reduction in mortality, although CABG tends to be associated with lower risk of myocardial infarction compared to PTCA. The mortality and myocardial infarction confidence intervals are wide, leaving uncertainty in whether one mode of therapy has superiority in these outcomes. Patients undergoing PTCA have a greater likelihood of repeat procedures, because of the unsolved problem of restenosis. Coronary stenting and possibly intracoronary radiation therapy have reduced restenosis, such that the difference in the need for repeat procedures between PCI and CABG may have narrowed in contemporary practice. Patients with proximal LAD disease may represent a group requiring special consideration. A meta-analysis of CABG versus medical therapy trials suggested a mortality benefit for CABG in one- or two-vessel disease with involvement of the proximal LAD (RR 0.58; 95% CI 0.34–1.01).[7] These patients have a large area of myocardium at jeopardy and are at higher risk of death than patients with other forms of single-vessel disease. If revascularization is indicated for proximal LAD disease, then either PTCA or CABG are effective in controlling symptoms, but only CABG surgery has been proven to improve survival in this group of patients. As discussed below, this may be particularly true for diabetics with proximal LAD disease.

Multi-vessel disease

The group of patients with multi-vessel disease represents a heterogeneous mixture of patients. Heterogeneity exists in the location and extent of anatomical stenosis, clinical symptoms, ventricular function, and coexistent disease. It must be also noted that despite the large number of percutaneous devices available today, the vast majority of patients with multi-vessel disease, including those screened for the recent randomized trials, remain unsuitable for PCI. Chronic total occlusion is the most common specific lesion characteristic necessitating exclusion of patients from PCI in these trials. Thus, the current studies represent a minority of patients with multi-vessel disease. Moreover, about 60% of enrolled patients in these trials had two-vessel disease with normal or only mildly reduced left ventricular function. In such low-risk patients CABG surgery has not been shown to reduce mortality when compared to medical therapy.

During the late 1980s to mid-1990s seven trials randomized patients with multi-vessel disease to PTCA or CABG. Although these studies have significant differences in their design, methods, and follow-up duration, they are broadly comparable and it is instructive to consider them together. The main design features, patient characteristics, and results are outlined in Tables 18.1 and 18.2 and discussed later. The death, death or non-fatal myocardial infarction, and repeat revascularization end-points are summarized in Figs. 18.3–18.5, respectively.

In the Randomized Intervention Treatment of Angina (RITA) study that randomized 1011 patients with one-, two- or three-vessel disease,[19,22] the ability to achieve equivalent degrees of revascularization was mandatory for inclusion. Because of this and other reasons, only 2.3% of patients undergoing revascularization in the study centres were randomized. RITA was designed with 80% power to detect a one-third reduction in the primary end-point death, or non-fatal myocardial infarction. After 6.5 years of follow-up the primary end-point occurred in 87 (17.1%) of the PTCA group and 80 (16.0%) of the CABG group ($P = 0.64$). Although residual angina was more common in the PTCA

Table 18.1 Main characteristics of prospective randomized trials of PTCA vs CABG.

	ARTS	*BARI*	*CABRI*	*EAST*	*ERACI-I*	*ERACI-II*	*GABI*	*MASS*	*RITA*	*Swiss*	*Toulouse*
Location	Europe, S. America, Canada, Australia	North America, multi-centre	Europe, multi-centre	Emory University USA, single-centre	Argentina, single-centre	Argentina, multi-centre	Germany, multi-centre	Brazil, single-centre	Britain, multi-centre	Switzerland, single-centre	France, single-centre
Patients screened *(n)*	?	25 200	23 047	5118	1409	2759	8981	?	33 359	?	1939
Randomized (%)	1205	1829 (7.3)	1054 (4.6)	392 (7.7)	127 (9.0)	450 (16)	359 (4.0)	214	1011 (3.2)	142	152 (7.8)
Equivalent revascularization required	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Follow-up duration (yr)											
Initially planned	5	10	5–10	3	3	5	1	3.5	5	2.5	3
Presently available	1	7	4	8	3	1.5	1	3.5	6.5	2.5	5
Completed	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Primary end-point	Event-free survival	Death, Mi	Death, MI, angina, functional capacity	Combined death, MI, and large thallium defect	Combined death, MI, and angina	Combined death, MI, repeat PTCA/ CABG	Freedom from angina at 1 year (>CCS2)	Combined cardiac death, MI, refractory angina	Combined death and MI	Combined death, MI, repeat PTCA/CABG	Event-free survival
Stents as primary form of PCI	Yes	No	No	No	No	Yes	No	No	No	No	No

Table 18.2 Patient profiles in nine randomized trials of PTCA vs CABG.

	ARTS	*BARI*	*CABRI*	*EAST*	*ERACI-I*	*ERACI-II*	*GABI*	*MASS*	*RITA*	*Swiss*	*Toulouse*
No of stenotic vessels (%)											
1	1	0	0	0	0	0	0	100	45	100	0
2	67	56	60	60	55	39	81	0	43	0	49
3	32	43	40	40	45	61	19	0	12	0	14
Mean ejection fraction (%)	60	58	63	61	61	?	56	75	?	?	?
Average age (yr)	61	61	61	62	57	?	59	56	57	56	?
CCS class 3 or 4 angina (%)	64	81	65	80	83	91	65	?	60	89	40
Mammary artery used (% of CABG procedures)	90	82	?	90	77	90	37	100	74	100	?
Male/female	75:25	74:26	63:37	74:26	54:46	?	80:20	58:42	81:19	80:20	?
Previous MI (%)	43	?	41	41	32	?	47	?	43	0	?

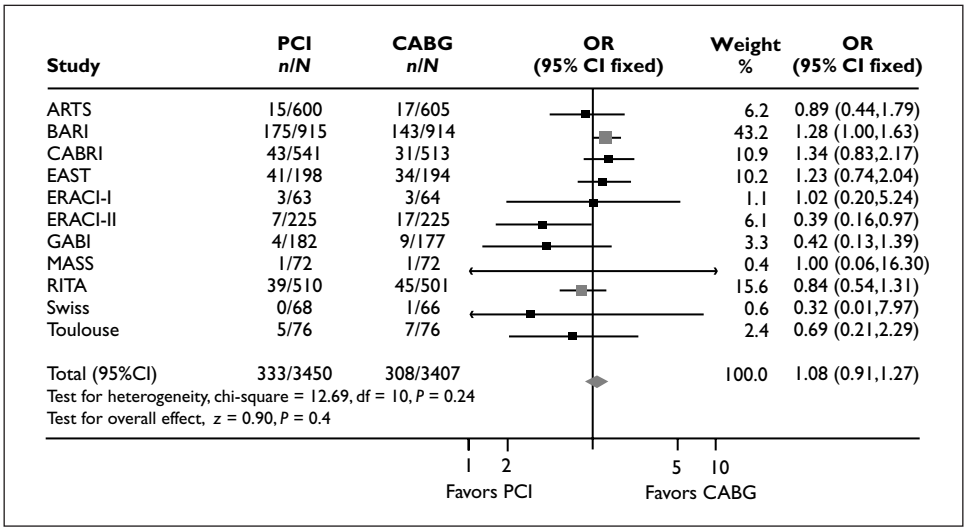

Figure 18.3
Meta-analysis of death in patients randomized to PCI versus CABG trials. (*n*: number of deaths; *N*: number randomized to treatment arm.)

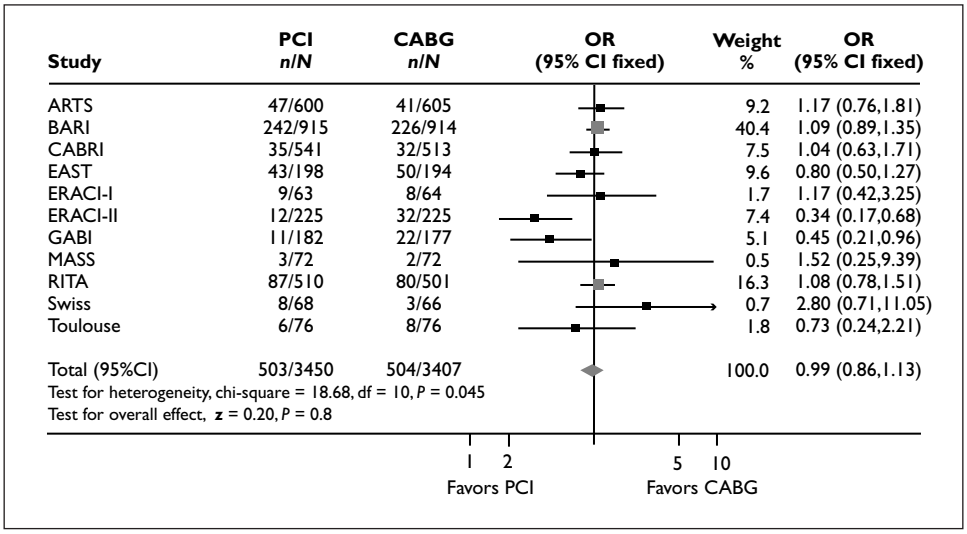

Figure 18.4
Meta-analysis of death or non-fatal myocardial infarction in patients randomized to PCI versus CABG trials. (*n*: number of deaths; *N*: number randomized to treatment arm.)

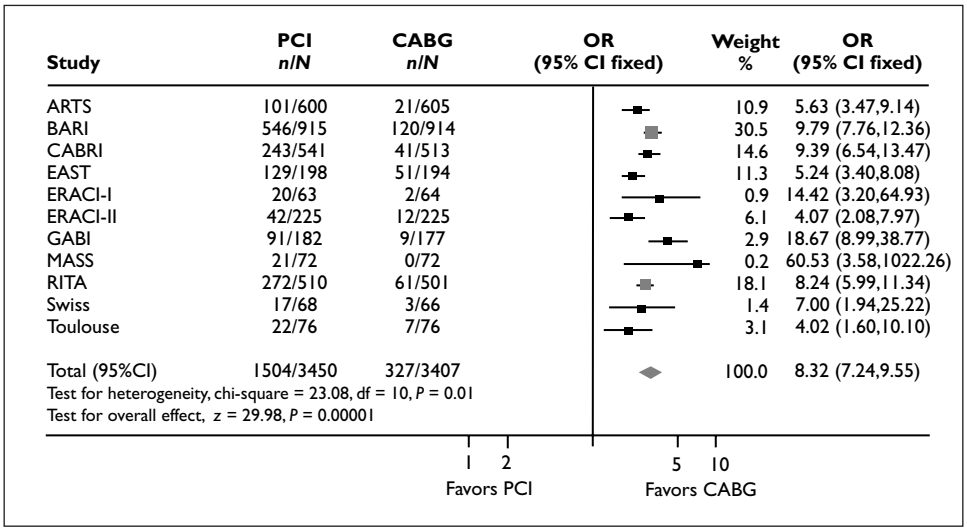

Figure 18.5
Meta-analysis of repeat revascularization in patients randomized to PCI versus CABG trials. (*n*: number of patients with repeat revascularization, *N*: number randomized to treatment arm.)

group, there was no significant difference in severe angina or exercise capacity. In the first 2.5 years of follow-up, repeat revascularization was more common in the PTCA group (38% versus 4%), but no further difference was seen in the subsequent 4.5 years. Over 5 years of follow-up, PTCA patients spent a total average of 15.9 days in hospital, compared with 20.5 for those in the CABG group. After 3 years there was no difference in quality of life assessment or employment status in the two groups. At the end of 2 years, the costs involved as a result of an initial policy of PTCA were 80% of an initial CABG. Follow-up from 2 to 5 years showed that the average cost differential diminished. An important observation regarding the generalizability of these results can be inferred from the RITA registry. This registry of all coronary disease patients ($n = 33\ 359$) undergoing angiography at the 17 RITA centres revealed a marked difference in management of patients between the centres. The revascularization rate varied from 47.6 to 83.4%, with 32.4–72.9% referred for CABG and 7.9–26.6% for PTCA. Not only was the RITA cohort a highly selected group from all the patients undergoing angiography, but the various RITA centres also had strikingly different thresholds for both angiography and revascularization. Whether a patient's disease was judged to be 'equally revascularized' by PTCA and CABG, and thus eligible for the trial, also varied among centres.

The Emory Angioplasty Surgery Trial (EAST) was a single-centre, prospective, randomized trial of angioplasty versus bypass surgery in patients with multi-vessel disease from a single centre.[23] Of 5118 patients screened, 392 (7.7%) were randomized to the study. Proximal LAD disease was present in 73% of the randomized patients and 40% of the patients had three-vessel disease. The primary end-point was the composite of death, Q-wave myocardial infarction and large ischaemic defect on thallium scanning over 3 years. It was reached in 28.8% of PTCA and 27.3% of CABG patients ($P = 0.81$). The PTCA group had a 54% further revascularization incidence (mainly in the first 6 months), while 13% of the CABG patients required further revascularization over 3 years ($P = 0.001$). CCS Class II or greater angina occurred in 20% of the PTCA patients and 12% of the CABG patients at 3 years ($P = 0.039$). Despite the observed difference in angina, no difference in activity level or employment status was found. Initial costs were lower in the PTCA group, but after 3 years no significant differences in cost existed because of the greater number of repeat procedures in the PTCA group. An extended 8-year follow-up of EAST has indicated a survival of 79.3% in the PTCA group and 82.7% in the surgical group ($P = 0.40$).[24] Patients with proximal left anterior descending stenosis and those with diabetes tended to have better late survival with surgical intervention, although this did not reach statistical significance. After the first 3 years, repeat interventions remained relatively equal for both treatment groups. Similar to the RITA registry, the EAST registry has indicated that physician judgment is an important predictor of outcome, even in patients judged equally suitable for PTCA and CABG in clinical trials.[25] Of the 842 EAST eligible patients, 450 did not enter the trial and these had similar characteristics to those eligible for randomization. In these registry patients there was bias towards selecting CABG in patients with 3-vessel disease and in those with diabetes. Three-year survival was better for the registry patients than the randomized ones, 96.4% vs 93.4%, $P = 0.044$. Angina relief in the registry was equal for PTCA and CABG patients and was better for the PTCA registry (87.6%) than for PTCA randomized patients (80.4%) ($P = 0.079$).

The German Angioplasty Bypass Investigation (GABI) was a German multicentre study which screened 8981 patients with symptomatic multi-vessel disease and randomized 359 (4.0%) to PTCA or CABG surgery.[26] Complete revascularization of at least two major coronary arteries had to be clinically necessary and technically feasible. Reasons for excluding screened patients were similar to those in the other studies. One-third of the patients could not be randomized because of specific protocol restrictions (previous PTCA, CABG, or recent myocardial infarction). The remainder had lesions unsuitable for PTCA (35% had total occlusions, 17% had left main or equivalent lesions, and 8% had large areas at risk). Of the randomized patients, 81% had double-vessel disease, 19% triple-vessel disease and 80% disease involving the LAD. The average ejection fraction was not stated but 47% of patients had had a previous myocardial infarction. PTCA was performed as a staged procedure in 30% of patients and was successful in 92% of all treated lesions. The primary end-point was freedom from greater than CCS 2 angina after 1 year of follow-up, and was achieved in 71% of PTCA and 74% of CABG patients (P = NS). Although exercise capacity was similar in both groups, anti-anginal medications were required less frequently after CABG. Patients treated with PTCA were more likely to require further intervention (44% versus 6%; $P = 0.001$), while the patients treated with CABG were more likely to sustain a Q-wave myocardial infarction at the time of the procedure (8.1% versus 2.3%; $P = 0.022$). All-cause mortality occurred in four of the PTCA and nine of the CABG patients ($P = 0.10$). The GABI trial was not designed to detect differences between PTCA and CABG with respect to major cardiac events or mortality.

The Coronary Artery Bypass Revascularization Investigation (CABRI) is a European multicentre study that randomized 1054 patients with multi-vessel disease to PTCA or CABG.[27] Of patients randomized, 58% had double-vessel disease, 40% triple vessel disease and 41% previous myocardial infarction; the mean ejection fraction was 63%. The primary end-points were mortality, myocardial infarction, angina, and functional capacity after 5–10 years of follow-up. After 1 year, 21 deaths occurred in those allocated to PTCA compared to 11 deaths in the CABG group ($P = 0.07$). Up to this point there were 15 myocardial infarctions in the PTCA group and 17 in the CABG patients ($P > 0.10$). A second revascularization procedure was

required in 2% of those randomized to CABG and in 30% of the PTCA cohort. The 4-year follow-up showed no statistically significant difference in mortality between PTCA (8%) and CABG (6%) patients ($P = 0.4$), although there continues to be a trend in favour of CABG. The small 1-year advantage in angina status for CABG had been overcome by year 2. The need for repeat revascularization also narrowed, but remained markedly in favour of CABG (8% vs 45%). While only 10% of the PTCA repeat revascularizations were done after the first year, almost half of those in the CABG patients were performed in years 2–4.

There were also two small trials of PTCA versus CABG in multi-vessel disease. The single-centre Argentine randomized trial of coronary angioplasty versus bypass surgery in multiple-vessel disease (ERACI) randomized 127 patients, of whom 55% had two-vessel disease, 45% three-vessel disease, and 37% significant LAD stenosis.[28] The mean ejection fraction was 61%; 32% of patients had a previous myocardial infarction. After 3 years of follow-up, three deaths occurred in each group, six non-fatal myocardial infarctions in the PTCA patients, and five non-fatal myocardial infarctions in the CABG group. Repeat revascularization was needed in 37% of the PTCA patients and in only 3.2% of the CABG surgery group ($P < 0.001$). Angina recurred in 40% of the PTCA patients and 20% of the CABG patients ($P < 0.001$). The small numbers and 13% cross-over between randomization and revascularization limit the power of the study, but its results are similar to those of the larger studies. The other trial randomized 152 patients with two- or three-vessel disease from a single centre in Toulouse, France to PTCA or CABG.[29] After 5 years of follow-up there was no difference in death and non-fatal myocardial infarction. Repeat revascularization was required more frequently in the PTCA patients, 29% versus 9%, $P < 0.01$.

The largest of the PTCA versus CABG trials is the Bypass Angioplasty Revascularization Investigation (BARI), a multicentre North American trial which has randomized 1829 (7.3%) of 25200 patients screened with multi-vessel disease.[30] Of the randomized patients, 56% had double-vessel disease and 43% had triple-vessel disease; the mean ejection fraction was 58%. The 5-year mortality among patients assigned to PTCA was 13.7% and 10.7% in CABG patients (95% CI –0.2 to 6.0; $P = 0.19$). By the 7-year follow-up this difference had reached statistical significance with Kaplan–Meier estimates of survival for the total population being 80.9% for PTCA and 84.4% for CABG ($P = 0.043$).[31] As noted below this difference could be explained by the negative interaction between diabetic patients and PTCA (Fig. 18.6). Among the remaining 1476 patients without treated diabetes, survival was virtually identical by assigned treatment (86.8% PTCA, 86.4% CABG, $P = 0.72$). Secondary 7-year BARI results indicated that freedom from death and MI were not significantly different for PTCA (73.5%) versus CABG (75.3%) ($P = 0.46$). The PTCA group had substantially higher subsequent revascularization rates than the CABG group (59.7% vs 13.1%, $P < 0.001$). After the first 3 years the CABG group had significantly less angina, the 5-year angina rates were closer but still statistically different (20.3% PTCA vs 15.6% CABG, $P = 0.015$). Among survivors who completed their 7-year follow-up, the treatment difference in angina was not statistically significant (15.1% PTCA vs 11.4% CABG, $P = 0.075$). The large majority of angina reported throughout follow-up was stable CCS class II or I (Fig. 18.7).

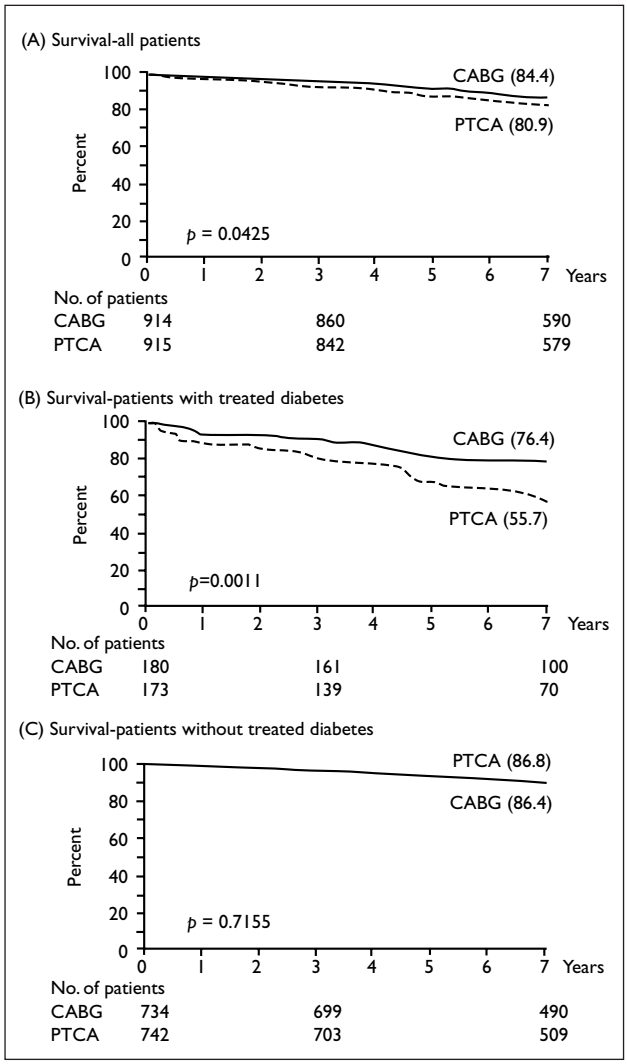

Figure 18.6
Kaplan-Meier estimates of overall survival for all BARI randomized patients (A), for randomized patients with treated diabetes (B) and for randomized patients without treated diabetes (C). Solid lines indicate patients assigned to CABG and dashed lines indicate patients assigned to PTCA. The numbers of patients at risk are shown below the graph at baseline, three years and seven years. CABG = coronary artery bypass grafting; PTCA = percutaneous stransluminal coronary angioplasty. Reproduced with permission from The BARI Investigators. *J Am Coll Cardiol* 2000; **35**: 1122–9.

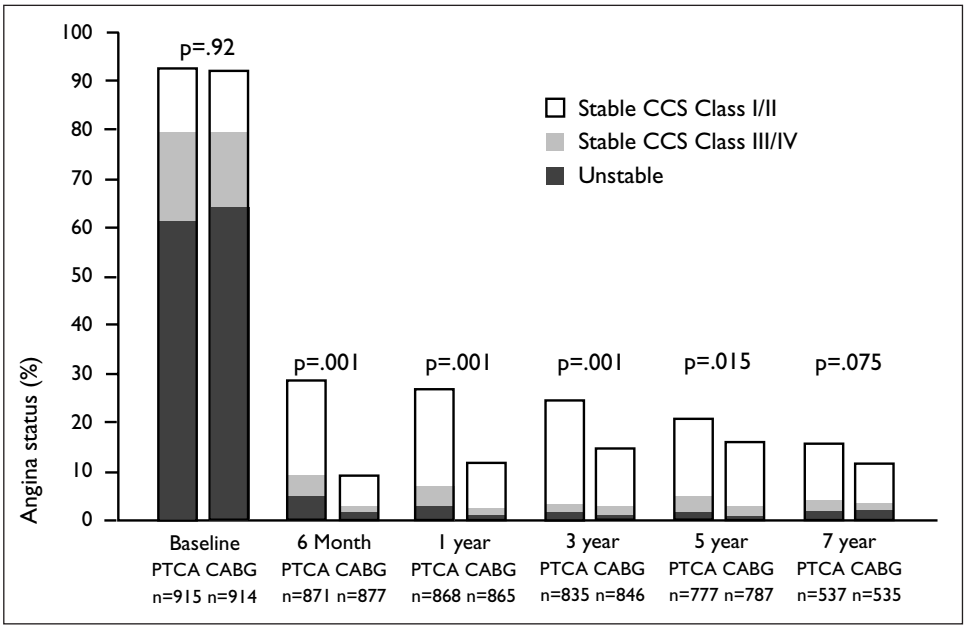

Figure 18.7
Angina status at baseline, 6 months, 1 year, 3 years, 5 years and 7 years after study entry among surviving patients randomized to PTCA and CABG. P values for the treatment difference between the percentage of patients with angina are presented on top of the bars for each follow-up. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty. Reproduced with permission from The BARI Investigators. *J Am Coll Cardiol* 2000; **35**: 1122–9.

PCI versus CABG in diabetics

The BARI trial suggests that diabetics have a significantly better outcome if managed with initial CABG rather than PTCA. After 5 years the 353 BARI patients with diabetes mellitus had a dramatic mortality benefit if initially treated with CABG (20.6 vs 5.8%, $P = 0.0003$).[32] The overall CABG mortality benefit seen at 7 years could be explained by the diabetic subgroup, in which survival was 55.7% for PTCA and 76.4% for CABG, $P = 0.0011$ (Fig. 18.3). The diabetic patients assigned to CABG who received at least one IMA graft had better seven-year survival (83.2%, $n = 140$) compared with those who received only saphenous vein grafts (SVGs) (54.5%, $n = 33$). The survival rate in the diabetic SVG group was almost identical to that for diabetic patients who received PTCA (55.5%, $n = 170$). Among the non-diabetic patients who received their assigned treatment, these three groups had nearly identical survival rates: 86.5% for IMA vs 85.2% for SVG only vs 86.8% for PTCA patients. The potential mechanism by which PTCA and CABG procedures lead to such different clinical outcomes in diabetic patients was recently addressed.[33] In this analysis all patients eligible for BARI who underwent coronary revascularization were classified according to whether they had diabetes and whether they had undergone CABG, either initially or after PTCA. CABG greatly reduced the risk of death after spontaneous Q-wave myocardial infarction in the 641 patients with diabetes (relative risk, 0.09; 95% CI, 0.03 to 0.29). Among patients with diabetes who had undergone CABG, but did not have spontaneous Q-wave myocardial infarction, the corresponding relative risk of death was 0.65 (95% confidence interval, 0.45 to 0.94). It was concluded that the main mechanism of mortality benefit from CABG among patients with diabetes is by greatly reducing the risk of death after spontaneous Q-wave MI. Retrospective subgroup analysis of CABRI and EAST has indicated a tendency for a survival advantage in diabetics treated with initial CABG rather than PTCA.

Caution must be exercised in the interpretation of the diabetic BARI data, as this is mainly a post-hoc subgroup analysis. Such retrospective analyses of small subgroups have been recognized to overestimate or misdirect the treatment effect. The BARI registry provides a clue that the diabetic subgroup analysis may not be generalizable to all diabetics.[34] In this registry of 2010 BARI eligible patients, treatment assignment was physician-guided rather than randomized to PTCA or CABG. Despite nearly twice as many patients being selected for PTCA (1189) as CABG (625), the registry 7-year survival was similar for PTCA (86.1%) and CABG (85.8%) ($P = 0.66$). Among the 340 diabetic registry patients, 7-year mortality was equal with PTCA and CABG at 26%. In the registry, diabetic and non-diabetic patients with more severe angiographic disease profiles were more frequently selected for CABG than PTCA. Since diabetic patients tend to have more severe angiographic disease it is possible that it is not the diabetes alone that mitigates a poor outcome with PTCA, but that it occurs through the association between diabetes and more severe diffuse CAD. One potential conclusion that accounts for the discrepancy in the BARI trial and registry diabetic outcomes is that selected diabetics may do as well with PTCA and CABG. Conversely, non-diabetic patients with diffuse CAD should do better with CABG rather than PTCA.

Conclusions and limitations

In summary, these seven studies have randomized 4924 patients with multi-vessel disease to PTCA or CABG. With the exception of diabetics, no clear superiority of one

procedure over the other has been demonstrated. Whereas patients who initially undergo multi-vessel PTCA require more repeat procedures, initial morbidity is less and overall anginal relief is nearly equivalent by 3 years. Clearly, restenosis is the major limitation of PTCA, but most patients can be managed successfully with a strategy of one or more PTCA procedures, as needed, avoiding CABG (or perhaps keeping it in reserve) in about two-thirds of patients over 5 years.

These trials are limited to relatively low-risk multi-vessel disease patients and do not exclude a clinically important mortality benefit in higher-risk patients. There is a large spectrum of heterogeneity in what is classified as 'multi-vessel disease'. A patient with discrete lesions of the right coronary and circumflex arteries who has a normal left ventricle or a patient with diffuse three-vessel disease and an ejection fraction of 30% can be rightly classified under the term 'multi-vessel disease', yet the prognoses, risks, and potential benefits of revascularization vary considerably. The 4924 patients enrolled in the above trials had an average first year mortality of approximately 3.0%, which places them in the low risk group in which CABG has not been shown to be superior to medical therapy. As discussed in the initial section of this chapter, we cannot therefore expect these trials to show a mortality difference between CABG and PTCA. In addition, the total enrolment of 4924 patients falls short of what would be needed to demonstrate clinically important differences in mortality of 20–30% among low- and moderate-risk patients. It is reasonable to surmise that if CABG were superior to PTCA in moderate- to high-risk patients, the current trials would have low power to reliably detect significant differences and that such differences cannot be ruled out. Large mortality differences of the order of 40–50%, however, are unlikely, given the current data.

In addition to the statistical limitations discussed above, a number of other caveats apply when considering the results of the current trials. First, temporal changes in each mode of therapy (including medical) continue to occur and may significantly mitigate the published results. Examples include the use of internal mammary arteries, minimally invasive surgical techniques, intracoronary stents, GP IIb/IIIa platelet receptor blockers, angiotensin-converting enzyme inhibitors, and statins. Intracoronary stents have been shown to partially address the increased repeat revascularization associated with PTCA.[15,16] Brachytherapy holds hope for further decreasing restenosis after PCI. The addition of the GP IIb/IIIa platelet receptor blocker, abciximab, has decreased 1-year mortality associated with PCI in diabetics.[35] In BARI, the average LDL cholesterol did not change from baseline (143 mg/dl) to the 5-year follow-up (141 mg/dl). Would aggressive LDL lowering with a statin influence the result seen in diabetics? A second major limitation is the short follow-up periods to date. Differences between CABG surgery and medical therapy did not emerge until 2–3 years after the procedure and are only clearly evident after 4–7 years of follow-up. Since end-points occur at different time intervals (restenosis and graft attrition, for example), follow-up of at least 10 years is needed to assess long-term outcome adequately. Cross-over to the other therapy occurs with increasing frequency during the course of follow-up, necessitating consideration of therapeutic strategies rather than specific treatments. The third major limitation is the enormous heterogeneity in the patients having coronary artery disease. In reality, it is likely that there are different subsets of multi-vessel disease patients that may be better managed medically or by PTCA or CABG surgery, depending on a variety of anatomical and patient-related factors. Such outcomes will be difficult to elucidate from the present studies. The apparent better outcomes in the trial-eligible registry patients when compared to their randomized counterparts would indicate that cardiologists and cardiovascular surgeons have recognized patients who would benefit from one revascularization mode over the other. As with many large surgical trials, generalization of results to centres with lower volumes and different levels of experience remains unproven. Lastly, it must be remembered that the three modes of therapy are not utilized in a mutually exclusive fashion, but in fact are complementary. In clinical practice, both PCI and CABG surgery may be used in the same patient at different times, while medical therapy and aggressive risk factor reduction is generally used in all patients with significant coronary artery disease. The question, therefore, is not which mode of therapy is best, but in which sequence and in what combination are treatments appropriate for a specific patient, at a specific point in the disease process. Several of these limitations will be addressed in second-generation trials comparing initial strategies of medical therapy versus PCI versus CABG.

Second generation CABG vs PCI trials

The trials outlined above have been criticized as being non-applicable to contemporary clinical practice as the techniques used in both revascularization arms have dramatically changed. The use of coronary stents and GP IIb/IIIa platelet receptor blockers has respectively reduced repeat revascularization and post-procedural MI's in patients undergoing PCI. In CABG patients, the wider use of arterial conduits has increased graft patency and minimally invasive surgical approaches have decreased perioperative morbidity. Aggressive risk reduction with statins, antiplatelet agents, and ACE inhibitors may mitigate the results in both arms of therapy. In order to address these concerns a new generation of trials is being undertaken. These trials not only utilize contemporary techniques, but attempt to be more applicable by being less selective in the eligibility criteria.

Recently the ERACI-II trial was presented and has provided a potential clue to the effect of stenting in the PCI versus

CABG question.[36] In this trial 450 multi-vessel disease patients from seven Argentinian centres were randomized to CABG or PCI with stenting. The PCI group had an average of 1.4 stents per patient and 28% received abciximab. After 19 months of follow-up the PCI patients had better survival rates and fewer myocardial infarctions. Although the need for repeated revascularization is still greater in the PCI patients compared to CABG, it has narrowed greatly when compared to the older trials that did not utilize stenting (Table 18.3). Only 6.2% of PCI patients crossed over to CABG after randomization. Although there is very limited statistical power, there was no mortality or myocardial infarction difference between the two treatments in the 90 diabetic patients in ERACI-II. Severe proximal or ostial left anterior descending artery disease (along with disease in at least one other vessel) was present in 230 of the 450 patients. In these patients death or non-fatal myocardial infarction occurred in 3.5% of the PCI and 9.4% of the CABG patients ($P = 0.10$), suggesting that both forms of revascularization may be similarly effective in this high-risk subgroup.

The Arterial Revascularization Therapy Study (ARTS) has also recently been presented.[37] This trial was conducted in 68 sites, 19 countries and randomized 1205 patients with multi-vessel CAD to coronary artery stenting or CABG. Importantly, the average number of anastomoses in surgical patients and the average number of lesions stented in the PCI group were both 2.7. Over 90% of the surgical patients received LIMA grafts. The primary end-point of major adverse cardiac or cerebrovascular events at 1 year occurred in 12.2% of CABG patients and 26.3% of stented patients ($P = 0.01$). The 14% difference was almost totally due to restenosis in the PCI group. This is much smaller than the 30% repeat revascularization gap seen in the first generation trials. There was no difference in freedom from death, stroke, and MI at 1 year: 91.2% for CABG and 90.5% for PCI. After 1 year the total average CABG patient cost was 3100 USD greater than for PCI (11 200 vs 14 300 USD).

The Stent or Surgery (SoS) trial is similar to ARTS and has randomized 1000 multi-vessel disease patients to CABG or PCI with stent implantation. The trial is being conducted in over 40 centres in 12 countries throughout Europe and Canada. Unlike prior studies, SoS's design is pragmatic and imposes few protocol restrictions in patient selection, surgical and intervention techniques, or adjunctive medication schedules. Realizing that the SoS trial is not powered to assess differences in mortality and MI, the investigators are comparing CABG and PCI with respect to repeat revascularization, symptoms, quality of life, neuropsychological outcome, cost, and cost benefit. Results from this trial are not expected until 2002.

The Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) trial is enrolling 3000 moderate-risk CAD patients and will assess whether PCI offers incremental benefit over medical therapy, which includes aggressive and intensive risk modification. The BARI II trial will answer the question of whether aggressive treatment of diabetes and lipids, along with early revascularization, would result in better outcomes in 2000 diabetic patients over 5 years.

Table 18.3 ERACI-II 19-month results ($n = 225$ for both PCI and CABG).

	PCI (with stenting) %	*CABG %*	*P*
Mortality	3.1	7.5	<0.017
Myocardial infarction	2.3	6.6	<0.017
Repeat revascularization	18.6	5.3	<0.002

Updated meta-analysis of PCI versus CABG

In 1995, a meta-analysis of short-term results of eight randomized trials with a total of 3371 patients comparing CABG and PTCA was published.[21] The incidence of major end-points during an aggregate mean follow-up period of 2.7 years was found to be nearly identical: 4.4% of patients randomized to CABG and 4.6% of patients randomized to PTCA had died (RR 1.08; 95% CI 0.79–1.50); death or MI occurred in 7.6% of those who had CABG and in 7.9% of those who had PTCA (RR 1.10; 95% CI 0.89–1.37). Repeat revascularization within 1 year was required in 33.7% of PTCA patients (including 18% who underwent CABG), but in only 3.3% of those initially assigned to CABG ($P < 0.0001$). The prevalence of angina (≥ CCS class 2) was significantly higher in the PTCA group at 1 year, but at 3 years this difference had decreased as repeat revascularization increased in the PTCA patients. This meta-analysis did not include the BARI, ERACI-II and ARTS data. We have performed a meta-analysis of all PCI versus CABG randomized data available to the end of 2000. This analysis includes the updated 7-year BARI, 8-year EAST, 4-year CABRI, and 6.5-year RITA follow-up data as well as ERACI-II and ARTS. Using a fixed effects model it combines data on all 11 trials randomizing 6857 patients with single- or multi-vessel-disease to PCI or CABG. Total mortality did not differ between the PTCA and CABG groups (9.6% vs 9.1%; odds ratio 1.08; 95% CI 0.91–1.27). Similarly, the combined end-point of death or MI did not differ between the groups (14.6% PCI vs. 14.8% CABG; odds ratio 0.99; 95% CI 0.86–1.13). Repeat revascularization is significantly more common after PCI compared to CABG (43.6% vs 9.6%; odds ratio 8.32; 95% CI 7.24–9.55). Given the heterogeneity in trial design, patient

populations, PCI and CABG techniques, and follow-up duration, caution has to be used in interpreting this meta-analysis. Despite these limitations, this meta-analysis and the individual trial data give amazingly similar and consistent results. This provides a great degree of confidence and validity in the conclusions given below.

Conclusions

PCI vs medical therapy

(1) Among patients in whom medical treatment inadequately controls angina, PCI is indicated for symptomatic improvement.
(2) In the absence of symptoms or myocardial ischemia, PCI is not indicated to correct an anatomic stenosis.
(3) PCI may be indicated in the presence of a large ischaemic burden, particularly if this is being caused by a proximal LAD stenosis. This has not been proven directly, but only inferred by an integration of data from the CABG, PCI, and medical management trials.

PCI vs CABG therapy

(1) For single-vessel disease, both PCI and CABG provide excellent symptom relief, but repeat revascularization procedures are required more frequently after PCI. Early results from second generation trials indicate that intracoronary stenting is generally preferred to plain PTCA as this reduces the need for repeat revascularization.
(2) For non-diabetics, both multi-vessel PCI and CABG are acceptable alternatives. The choice of PCI or CABG for initial treatment will depend primarily on local expertise and patient and physician preference. The following caveats should be considered:

    - In general PTCA will be preferred for patients at low risk and CABG for patients at high risk.
    - Large differences in mortality (40–50%) are unlikely, but smaller, potentially important differences in mortality (20–30%) cannot be ruled out, given the available data.
    - CABG is associated with more complete revascularization and superior early relief of angina, but these differences are lessened after 3–5 years.
    - No significant differences in rates of myocardial infarction have been demonstrated.
    - Repeat revascularization procedures are required significantly more often after PTCA, although recent trials indicate that the difference is narrowing with the use of coronary stents.
    - Initial costs, quality of life, and return to work are initially more favourable with PTCA than CABG, but these variables roughly equalize over 3–5 years.

(3) For treated diabetics with two- or three-vessel disease, CABG may be the treatment of choice. Early data suggest that PCI may be an acceptable alternative in selected diabetics with isolated lesions in two or three vessels. Such patients may benefit from the adjunctive use of abciximab with intracoronary stenting. Further revascularization trials in diabetic patients are required.

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19

Restenosis: the problem and how to deal with it

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Facing the new millennium, the costly problem of restenosis after percutaneous transluminal coronary angioplasty (PTCA) remains unresolved. Indications for angioplasty as well as the number of percutaneous interventions performed each year[1] have been expanded considerably since the early days. In 1994, a total of 224 722 coronary angioplasty (PTCA) procedures were reported in Europe, an increase of 52% compared with 1992,[2] and the latest European statistics estimate that the annual need for PTCA is 739 per million inhabitants.[3] In view of these considerations, clinicians may realize why researchers are spending so much time and money in attempts to finding a solution for this 'iatrogenic' condition, which first appeared shortly after Gruentzig et al[4] reported the first coronary balloon angioplasty procedure in the late 1970s. The aim of this chapter is to summarize the current data regarding pathophysiology and prevention and/or treatment of restenosis.

Pathophysiology of restenosis

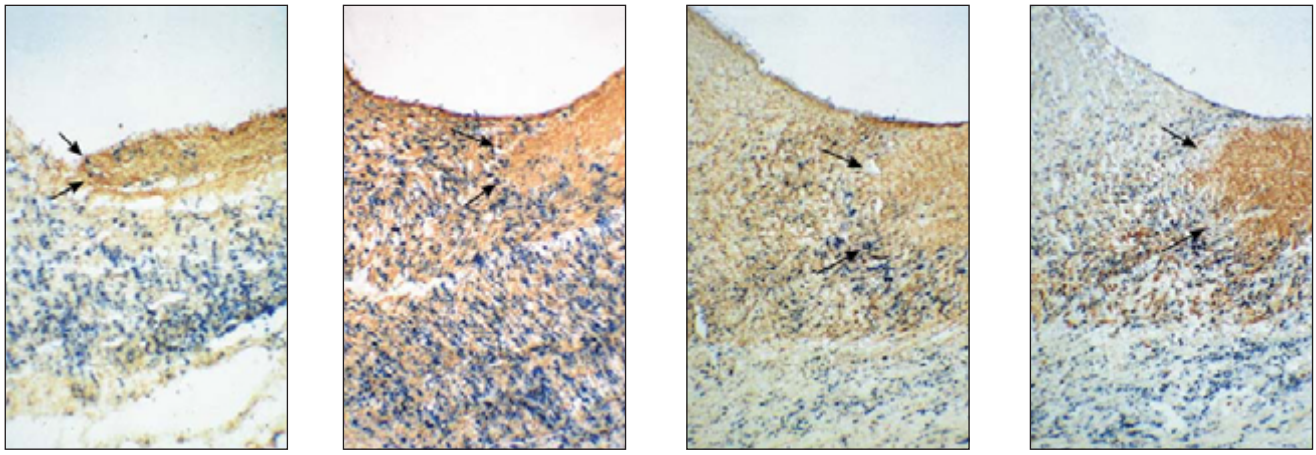
The biological aspects of restenosis are too complex for a clinical article; thrombosis, inflammation, smooth muscle cell (SMC) migration/proliferation and extra cellular matrix formation/degradation represent the fundamental sequence of healing and ultimately lumen reduction after catheter-based vascular intervention.[5–11] The interplay between these factors is coordinated by multiple intra- and extra cellular elements (growth factors, cytokines, hormonal factors, nitric oxide, protein kinases, etc).[10–12] Local mechanical stimuli, chronic shear and/or tensile stress, may further influence the restenotic process.[13–15]

On the basis of experimental results, it has been suggested that platelet aggregation and thrombus formation constitute the most significant process leading to restenosis.[7,8,16,17] At the site of injury, platelet aggregation, so-called white thrombus, may represent the major source for attractants and mitogens for smooth muscle cells. The platelet derived growth factor (PDGF), which may also be secreted by endothelial cells and macrophages, has been considered as the major promoter of SMC migration.[18–21] In addition, thrombin may stimulate SMC proliferation[22] and precipitate endothelial dysfunction.[23] The hypothesis that thrombus represents the core of the restenotic process has been supported by angioscopic studies that have provided clinical evidence of early thrombus formation after PTCA.[24,25]

Inflammation has also been associated with restenosis, since leukocytes have been found early and abundantly at the site of vascular injury.[26–28] The inflammatory cell component of the restenotic process appears to play a greater part following stent (foreign body) implantation than balloon angioplasty.[29–32] Whether the association between enhanced inflammatory response and vessel enlargement, as observed in a recent experimental study,[33] represents a potential beneficial effect of inflammation[34] on vessel remodeling remains to be elucidated.

The smooth muscle cell has long been implicated in the restenotic process,[35,36] due to its ability to migrate, proliferate and synthesize extra cellular matrix upon stimulation.[20,29,37–41] After transformation from the contractile to the synthetic phenotype, SMCs may proliferate from 24 hours to 2–3 months after vascular injury, returning to the contractile phenotype after this period. Through fracture of the internal elastic membrane, these cells migrate into the intima, where they may continue to proliferate and synthesize extra cellular matrix, which will ultimately constitute the bulk of the restenotic lesion.

Recent experimental data have suggested that adventitial myofibroblasts (α-actin staining cells) also proliferate and migrate into the neointima (Fig. 19.1).[42] Therefore, the adventitia has been proposed to be an important factor in



a b c d

Figure 19.1
Identification of proliferating cells by double-label immunohistochemistry using antibodies directed against BrDU (blue), smooth muscle actin (brown) (a and b), smooth muscle myosin (brown, c), or h-caldesmon (brown, d) in animals that received BrDU between days 2 and 3 after angioplasty and were killed on day 3 (a) or day 14 (b to d) without subsequent BrDU administration. Administration of BrDU between days 2 and 3 predominantly labels adventitial cells when analyzed on day 3 (a). A number of cells that had proliferated between days 2 and 3 were found remaining in the adventitia on day 14. Double-label immunohistochemistry indicated that the BrDU-positive cells stained uniformly with smooth muscle actin antibodies in both the adventitia and neointima (b). Comparison of the adventitial BrDU/smooth muscle actin staining in a and b suggests that the adventitial cells changed phenotype and increased production of actin by day 14. Smooth muscle myosin was colocalized with the BrDU-positive cells in the intima and some of the adventitial cells (c). h-Caldesmon staining was not uniform throughout the neointima, and only a few BrDU-positive cells in that region also stained with h-caldesmon (d). h-Caldesmon staining was much more specific for the medial SMCs and was absent in the adventitia. Arrows indicate the border of the broken end of the media (magnification x32). Reproduced with permission from Scott et al.[42]

supplying the intima layer with proliferative cellular elements for new lesion formation. The adventitia may be further implicated in vascular remodeling,[33,42–44] since myofibroblasts are capable of collagen synthesis and tissue contraction as seen in wound healing.[45]

Last but not least, extra cellular matrix (ECM), composed of various collagen sub-types and proteoglycans,[46] actually constitutes the major component of the restenotic lesion; neointimal hyperplasia has been shown to be predominately a low cellular tissue.[47] Constituents of ECM, such as hyaluronan, fibronectin, osteopontin and vitronectin, also facilitate SMC migration.[48–50] In addition, reorganization of the ECM, replacing hydrated molecules by collagen, may result in retraction of the vessel wall.[51]

A new paradigm of restenosis: vascular remodeling

The ultimate clinical consequence of these puzzling processes is late lumen renarrowing. The relative contribution of each of the phenomena of vascular remodeling and neointimal hyperplasia to the occurrence of restenosis may vary considerably from one patient to another, and even from one site to another in the same vessel.[52]

It was established a decade ago by quantitative angiography[53] that elastic recoil occurs immediately after balloon angioplasty[54,55] as a consequence of the natural elastic property of blood vessels in response to stretch. Thus, this phenomenon is unlikely to be responsible for the process of late lumen renarrowing.

Neointimal proliferation was originally described as the most important mechanism of restenosis on the basis of extensive experimental and autopsy findings as described above.[56–58] Based on this assumption, several clinical studies were conducted in attempts to prevent restenosis using pharmacological anti-proliferative agents, but results were largely disappointing.[59–72] We now know that only half of late lumen loss following PTCA procedures is due to intimal hyperplasia[59] and a new paradigm of restenosis has emerged: vascular remodeling.[14,63,73–76]

Changes in coronary artery dimensions were first described in 1972 by Mann et al,[77] who observed that African Masai tribesmen maintained lumen dimensions despite substantial atherosclerosis. Later, Glagov et al demonstrated that vessel enlargement compensates for atherosclerotic plaque increase, maintaining lumen dimensions.[78] In this elegant autopsy work, up to a 40% increase in plaque volume was neutralized by

vessel enlargement; after this threshold was reached, lumen reduction was directly proportional to plaque growth. Subsequently, similar compensatory mechanisms have been proposed to explain the restenotic process[14,74] and vessel shrinkage has been observed as an important determinant of late lumen reduction (Fig. 19.2).[75,76] Intravascular ultrasound (IVUS), due to its ability to image structures of the vessel wall in vivo,[79,80] has played a central role in clarifying the relative contribution of new tissue growth and vessel constriction to restenosis. Such studies have provided clinical evidence that neointimal hyperplasia accounts for less than 50% of lumen reduction in non-stented coronary segments.[81–84]

The term remodeling has been applied largely to describe either vascular shrinkage or enlargement.[85] The definition proposed by Schwartz et al,[85] in which remodeling is characterized by a continuous spectrum of changes in vascular dimension, may better describe this compensatory phenomenon. Quantitative angiographic studies showing that changes in lumen diameter after PTCA present a near-Gaussian distribution (Fig. 19.3)[86,87] suggested that the response to PTCA is a generalized phenomenon rather than the previously held notion that restenosis was an 'all or nothing' event. Subsequently, IVUS studies showing good correlation between changes in plaque and vessel cross-sectional areas have determined the compensatory aspect of the remodeling process after PTCA.[81,83,84] In this regard, our group carried out a detailed three-dimensional IVUS analysis of the local processes of restenosis. We observed that local changes in plaque volume correlated with changes in total vessel (external elastic membrane) volume, although both patterns of remodeling (enlargement and shrinkage) were found in individual balloon-injured coronary segments (unpublished data). Similarly, individual variability of the remodeling process has been reported by Pasterkamp et al in atherosclerotic femoral arteries.[52]

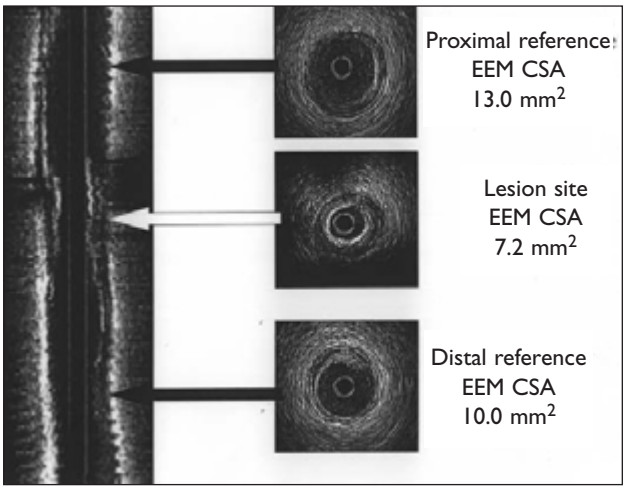


Figure 19.2
Negative vascular remodeling demonstrated by three-dimensional IVUS. Left panel: longitudinal view showing the constriction of the coronary segment compared to the proximal and distal segments. Right panel: planar views showing that external elastic membrane cross-sectional area (EEM CSA) is smaller at the restenotic site (white arrow) than in the reference segments (black arrows).

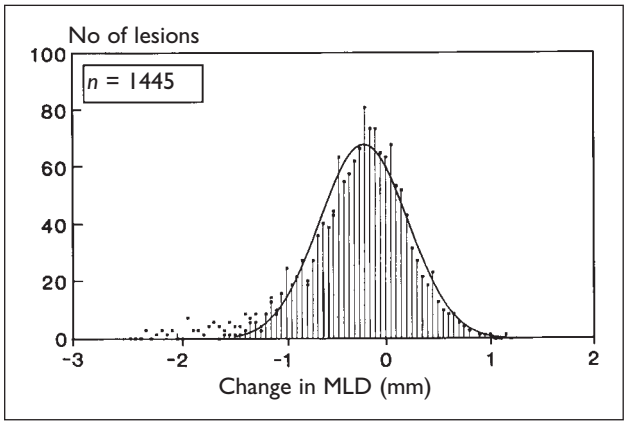


Figure 19.3
Frequency histogram of luminal change during follow-up (minimal luminal diameter post-PTCA–minimal luminal diameter at follow-up) after successful angioplasty among the 1445 lesions treated in the CARPORT and MERCATOR trials, showing a near-Gaussian distribution. (Reproduced with permission from Rensing et al.[86])

The restenotic process was reputed by our group to be a device-specific phenomenon (Fig. 19.4),[88] which has been recently supported by IVUS studies.[89] Studies using volumetric IVUS analysis have further confirmed that remodeling is almost absent after stenting, whereas it plays a major role in late lumen reduction after directional coronary atherectomy or balloon angioplasty.[90–92]

Detection of restenosis

Gruentzig and Meier[93] first observed that most clinical ischemic events related to vessel renarrowing occurred between 3 and 9 months after PTCA, mirroring the appearance of angiographic restenosis.[94,95] In view of the fact that up to 30% of asymptomatic patients may exhibit angiographic restenosis (diameter stenosis >50% at follow-up)[96] and that exercise electrocardiographic testing has limited value in detecting 'silent' restenotic lesions, other non-invasive tests such as thallium scintigraphy and stress echocardiography have been used to improve the sensitivity and specificity of non-invasive assessment of restenosis.[97–99] In clinical trials testing the effect of a given therapy on restenosis, objective angiographic criteria of restenosis have been preferred. When clinical outcome is also taken into account, repeat target vessel revascularization has been proposed as the most specific

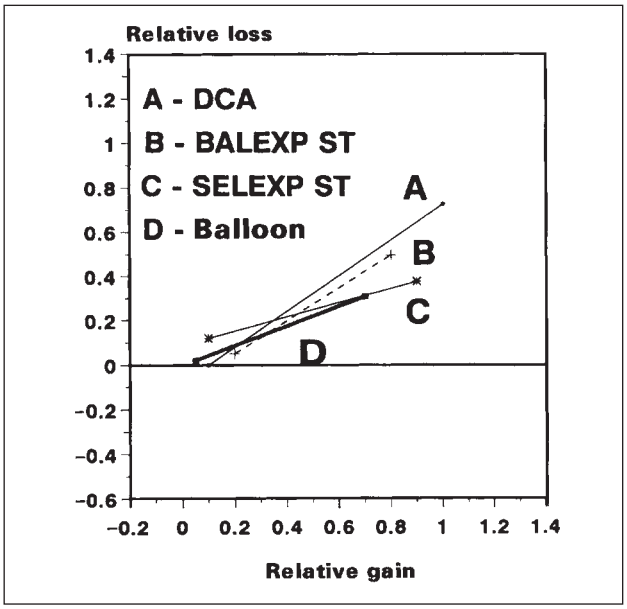


Figure 19.4
Linear regression relationships obtained from evaluation of four patient groups, treated by directional atherectomy (DCA), balloon-expandable (BALEXP ST) stent implantation (Wiktor stent), self-expanding (SELEXP ST) stent implantation (Wallstent) and balloon angioplasty (Balloon) showing significant differences in the nature of the relationship between relative luminal gain (acute gain corrected for reference diameter) and relative loss (late loss, corrected for the reference diameter). These differences may, if verified in larger studies, represent angiographic manifestations of a device-specific response of coronary vessels to injury during intervention.

clinical restenosis end-point among other clinical markers (i.e., death, myocardial infarction, symptom recurrence or combined major adverse cardiac events — MACE).[100] Conversely, for clinical purposes, non-invasive assessment of recurrence of stenosis (symptomatic status and stress tests) in patients treated with PTCA appears to be an appropriate approach. This latter recommendation is based on a series of previous observations:

1) Routine angiographic follow-up may have increased, albeit small, morbidity and mortality.[101]
2) Asymptomatic patients with non-functional angiographic restenosis experience a benign course.[102–104]
3) The so-called occulostenotic reflex[105] leads to a higher rate of repeat revascularization with no clear clinical benefit at 12 months after the initial intervention.[106]
4) Late lesion regression at the dilated site may occur after both stenting and balloon angioplasty.[107–109]

Undoubtedly, these data warrant a practical strategy of 'watchful waiting' until recurrence of symptoms or non-invasive detection of ischemia occurs. If repeat angiography is carried out without clear clinical evidence of ischemia, sensor-tipped guidewires for measurement of distal flow velocity or pressure may be useful to assess the functional status of restenotic lesions in the catheterization laboratory and assist physiologically based decision-making regarding the need for reintervention.[102,110] In fact, many clinical trials include the requirement for such testing at follow-up angiography in patients with asymptomatic restenosis.

Coronary angiography for detection and quantification of restenosis

The angiographic detection of lesions of 50% diameter stenosis or more at follow-up has been historically considered as representing 'restenosis'.[111] This apparently arbitrary cut-off point was in fact founded on good scientific evidence, being based on physiological experimental studies which demonstrated that when the arterial lumen diameter is reduced to 50% or less, coronary flow reserve becomes impeded.[112] For purposes of scientific studies, many definitions of angiographic restenosis have been used[113] (Table 19.1). The classical binary definition based on percentage diameter stenosis has not been universally accepted since it does not depict the concept of degree of deterioration in stenosis severity since angioplasty and does not convey a measure of the vessel response to injury.[94,100,114] The use of the term percentage diameter stenosis itself carries with it the assumption of reference segments of normal appearance, which is known from IVUS studies to be an erroneous assumption.[79,80,115] It seems unlikely that, in clinical practice, the pragmatic angiographic binary view of restenosis will be replaced by a less practical scientific perspective of a continuous phenomenon, although true progress in this area can only be made through the adoption of such a scientific approach, particularly by the use of IVUS analysis.[116] In view of these considerations, clinical restenosis studies have been adopting a more comprehensive approach in reporting findings from both perspectives (categorical and continuous), to determine whether the agent under investigation had a restraining or inhibitory effect, and whether the ultimate clinical/angiographic outcome has been improved by the use of any new therapy. Quantitative coronary angiography (QCA) has been largely used to determine lesion severity and define restenosis in the clinical context,[117,120] since visual assessment may lead to overestimation of the degree of narrowing in 'severe' lesions and underestimation of the severity in 'mild or moderate' lesions (Fig. 19.5).[121–123] Furthermore, digital systems now permit on-line QCA in the catheterization laboratory, providing fast, easy and clinically relevant information for patient care.[124] Although angiography has been widely used as the guiding tool for coronary disease management,

Table 19.1 A number of angiographic definitions of restenosis which have been used in various clinical studies. NHLBI 1, 2, 3 and 4 are criteria for angiographic restenosis, as laid out by the National Heart, Lung and Blood Institute of the United States.

(1) A diameter stenosis ≥50% at follow-up.
(2) An immediate post-PTCA diameter stenosis <50% that increases to ≥50% at follow-up.
(3) As for (2) above, but a diameter stenosis ≥70% at follow-up (NHLBI 2).
(4) Loss during follow-up of at least 50% of the initial gain at PTCA (NHLBI 4).
(5) A return to within 10% of the pre PTCA diameter stenosis (NHLBI 3).
(6) Loss ≥20% diameter stenosis from post -PTCA to follow-up.
(7) Loss ≥30% diameter stenosis from post -PTCA to follow-up. (NHLBI 1)
(8) A diameter stenosis ≥70% at follow-up.
(9) Area stenosis ≥85% at follow-up.
(10) Loss ≥1 mm^2 in stenosis area from post-PTCA to follow-up.
(11) Loss ≥0.72 mm in minimal luminal diameter from post-PTCA to follow-up.
(12) Loss ≥0.5 mm in minimal luminal diameter from post-PTCA to follow-up.
(13) Diameter stenosis >50% at follow-up, if >10% deterioration in diameter stenosis since PTCA in a successfully dilated lesion (defined as diameter stenosis <50%, with a gain of >10% at PTCA).

the clinician should also consider functional, invasive or non-invasive, assessment of the restenotic lesion before referring the patient for additional coronary revascularization.

Is restenosis predictable?

Identification of factors associated with higher risk of restenosis may be useful in counseling patients whether to select a percutaneous intervention or other therapeutic strategies (medical treatment or bypass surgery). Unfortunately, there have been inconsistencies in linking restenosis to baseline demographic and clinical characteristics.[125–128] Diabetes mellitus and unstable angina have consistently been demonstrated to be important clinical risk factors for restenosis.[125,126,129–132] Preliminary results from the Arterial Revascularization Therapy Study (ARTS) have further confirmed that diabetes mellitus is an important independent predictor of late clinical events in patients treated with multivessel PTCA.[133] Some anatomic characteristics have also been implicated with increased likelihood of restenosis: left

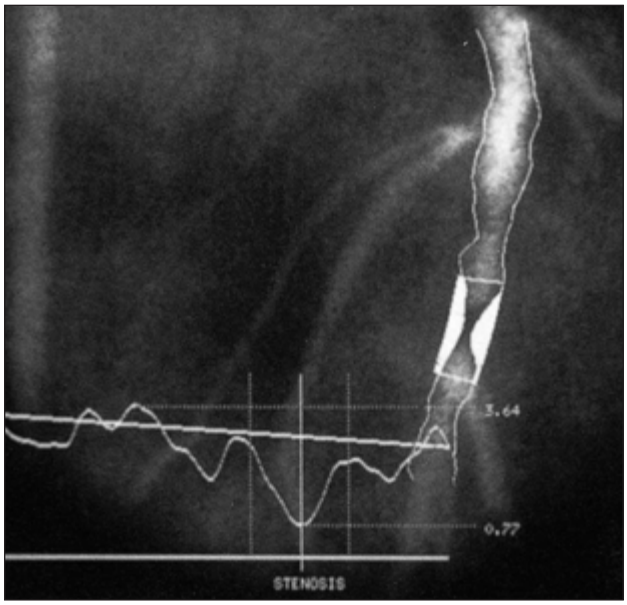


Figure 19.5
Quantitative angiographic analysis (Cardiovascular Angiographic Analysis System) of a mid-circumflex lesion pre-PTCA to demonstrate that a 73% diameter stenosis indeed corresponds to 93% area stenosis.

anterior descending coronary artery, saphenous vein graft, small vessel diameter, lesion length and chronic total occlusion represent important anatomic characteristics that have been associated with a higher incidence of angiographic restenosis.[126,134–139] Others have reported a higher incidence of restenosis for lesions located proximally[140] and for restenotic lesions.[141,142]

Although, prior knowledge of the subset of patients at higher risk of restenosis may be useful for clinical decision making, angiographic and IVUS studies have extensively demonstrated that the principal determinant of restenosis is the lumen size achieved at the end of the procedure.[137,143–149] The amount of residual plaque burden has also been considered as an important predictor of restenosis.[143,150] Conversely, the PICTURE study investigators[151] did not identify any IVUS parameter related to categorical angiographic restenosis. The use of long or multiple overlapping stents have also been associated with an increased risk of restenosis,[144,152] whereas the influence of balloon inflation pressure and residual dissection on vessel renarrowing has yet to be clarified.[153–155]

To help in predicting restenosis in the cath lab at the end of a procedure, our group has constructed simple reference charts, based on serial QCA and IVUS studies (Tables 19.2 and 19.3). These charts, derived from large cohorts of patients enrolled in prospective trials, provide useful information for patient care, considering that QCA and/or IVUS analysis may be performed online and that such parameters are partially

Table 19.2 Angiographic predictors of 6-month in-stent restenosis.

	% DS post procedure								
Vessel size	1.5–5.9	5.9–10.3	10.3–14.7	14.7–19.1	19.1–23.5	23.5–27.9	27.9–32.3	32.3–36.7	36.7–41.1
1.83–2.14	0.24[a]	0.28	0.33	0.38	0.44	0.49	0.55	0.61	0.66[a]
2.14–2.45	0.17	0.21	0.25	0.29	0.34	0.39	0.45	0.50	0.56
2.45–2.76	0.12	0.15	0.18	0.21	0.25	0.30	0.35	0.40	0.46
2.76–3.07	0.08	0.10	0.12	0.15	0.18	0.22	0.26	0.31	0.36
3.07–3.38	0.06	0.07	0.09	0.11	0.13	0.16	0.19	0.23	0.27
3.38–3.69	0.04	0.05	0.06	0.07	0.09	0.11	0.13	0.16	0.20
3.69–4.00	0.03	0.03	0.04	0.05	0.06	0.07	0.09	0.11	0.14
4.00–4.31	0.02[a]	0.02	0.03	0.03	0.04	0.05	0.06	0.08	0.10[a]
4.31–4.62	0.01[a]	0.01[a]	0.02	0.02	0.03	0.03	0.04	0.05[a]	0.06[a]
4.62–4.93	0.01[a]	0.01[a]	0.01[a]	0.01[a]	0.02	0.02[a]	0.03[a]	0.04[a]	0.04[a]

Figures obtained by extrapolation.
Modified from Serruys et al.[137]

Table 19.3 IVUS predictors of 6-month in-stent restenosis.

	Minimum in-stent area, mm^2									
Stent length	3.0–3.9	3.9–4.8	4.8–5.7	5.7–6.6	6.6–7.5	7.5–8.4	8.4–9.3	9.3–10.2	10.2–11.1	11.1–12.0
10–15	0.30	0.25	0.21	0.17	0.13	0.11	0.08	0.07	0.05	0.04
15–20	0.30	0.28	0.23	0.19	0.15	0.12	0.10	0.08	0.06	0.05
20–25	0.36	0.31	0.25	0.21	0.17	0.14	0.11	0.09	0.07	0.05
25–30	0.40	0.34	0.28	0.23	0.19	0.15	0.12	0.10	0.08	0.06
30–35	0.43	0.30	0.31	0.26	0.21	0.17	0.14	0.11	0.09	0.07
35–40	0.46	0.40	0.34	0.29	0.24	0.19	0.16	0.13	0.10	0.08
40–45	0.50	0.43	0.37	0.31	0.26	0.22	0.18	0.14	0.11	0.09
45–50	0.53[a]	0.48	0.40	0.34	0.29	0.24	0.20	0.16	0.13	0.10
50–55	0.57[a]	0.50	0.44	0.38	0.32[a]	0.27[a]	0.22[a]	0.18[a]	0.14[a]	0.11[a]
55–60	0.60[a]	0.54[a]	0.47[a]	0.41[a]	0.35	0.29[a]	0.24[a]	0.20[a]	0.16[a]	0.13[a]

[a] Figure obtained by extrapolation.
Modified from de Feyter et al.[144]

operator dependent.[137,144] Functional parameters derived both from post procedure coronary flow reserve (CFR) or fractional flow reserve (FFR) in combination with morphological (angiography) have been shown to predict restenosis after PTCA.[156–158] In the DEBATE study,[157] distal CFR >2.5 associated with angiographic residual stenosis <35% identified lesions with a low restenosis rate (16% v 41%). Similarly, another non-randomized study[158] has shown that patients with both FFR >0.9 and angiographic residual stenosis <35% had a high event-free survival rate at 12 months (92% v 69%).[158] The combination of these parameters must be thus considered a relevant practical approach in interventional therapy in day to day practice.

Luminal geometry and restenosis: the importance of interventional effectiveness

The 'bigger is better' philosophy,[159] in which the lumen size obtained after PTCA will ultimately determine the occurrence of restenosis, has been largely accepted. One may question the beneficial effect of optimized intervention since neointimal response has been shown to be proportional to the magnitude of vessel injury,[47,160] in other words 'the more you gain, the more you lose'. Both concepts, apparently contradictory, are fundamentally correct and the ultimate determinant of late

lumen size will be the balance between acute gain and late loss. It is now clear that the 'the bigger, the better' principle holds true for any interventional device, although the favorable relationship between late loss and acute gain appears to be a device-specific phenomenon (Fig. 19.4).[88] Recent studies applying the concept of optimized intervention have reported lower restenosis rates as compared to previous studies using similar devices (Fig. 19.6).[105,157,161–172] Although IVUS is unequivocally useful to guide and confirm the achievement of an optimal lumen gain, particularly in stented segments, the risk of restenosis still remain clinically relevant.[148] In addition, the cost-effectiveness of IVUS-guided optimized stent deployment has yet to be demonstrated. In the MUSIC study, applying a strict IVUS criterion of optimal stent deployment in a selected population, impressive long-term results were observed (binary restenosis rate of 8.3%).[165] The CRUISE study investigators have also shown favorable results after IVUS-guided stenting: reduction of target lesion revascularization from 14.9% (IVUS documented group) to 8.9% (IVUS guided).[148] In contast, final results from the RESIST[173] and preliminary data from the AVID and OPTICUS trials have not confirmed the benefit of IVUS-guided stenting on late outcome.

Provisional stenting and direct stenting

The strategy of 'stent-like' balloon angioplasty with a stand-by stent to be implanted whenever needed (so-called provisional stenting) has emerged from the impressive long-term results observed in the cohort of patients treated by balloon angioplasty and with a post procedure diameter stenosis <30% in the BENESTENT trial.[174] Although others have not confirmed these results,[175,176] provisional stenting has become an attractive strategy,[157,158,177–180] since it may represent a reduction in costs and good long-term outcome when a 'stent-like' result is obtained with balloon angioplasty alone. Additionally, the treatment and the long-term outcome of patients with in-stent restenosis remain a matter of concern.[181–184]

Before unconditionally applying the strategy of provisional stenting in daily practice, one should consider that routine stent implantation was cost-effective in the BENESTENT II trial, and that the sub-group of patients with 'stent-like' results after balloon angioplasty had a clinical outcome still 6% inferior to the stented patients.[105,164] Reduction in both costs and restenosis rate may be obtained by applying a strategy of direct stenting (without balloon predilatation), although such benefit needs to be confirmed in randomized clinical trials.[185,186]

It is unlikely that stent-like results will be achieved by balloon angioplasty without adjunctive IVUS or physiological assessment, which may ultimately increase the cost of the procedure.[153] Indeed, preliminary data from the DEBATE II trial, in which optimal results were guided by QCA (residual diameter stenosis <35%) and Doppler flow wire (CFR >2.5) measurements, showed that both primary (unconditional) and provisional stenting strategies had a similar 1-year clinical outcome and primary stenting was more cost-effective. Interesting and somewhat puzzling was the observation that an improvement in event-free survival at one year was achieved by stent implantation after an initial stent-like balloon angioplasty. In view of these considerations, a strategy of provisional stenting will not improve clinical outcome or reduce costs of PTCA procedures, but it may postpone stenting in up to 50% of the patients, which may have some benefit, considering the insidious and 'malignant' problem of in-stent restenosis.

The role of 'new' intervention devices in the prevention of restenosis

Over the past decade several new devices (stent, directional, rotational or extractional atherectomy devices, excimer laser

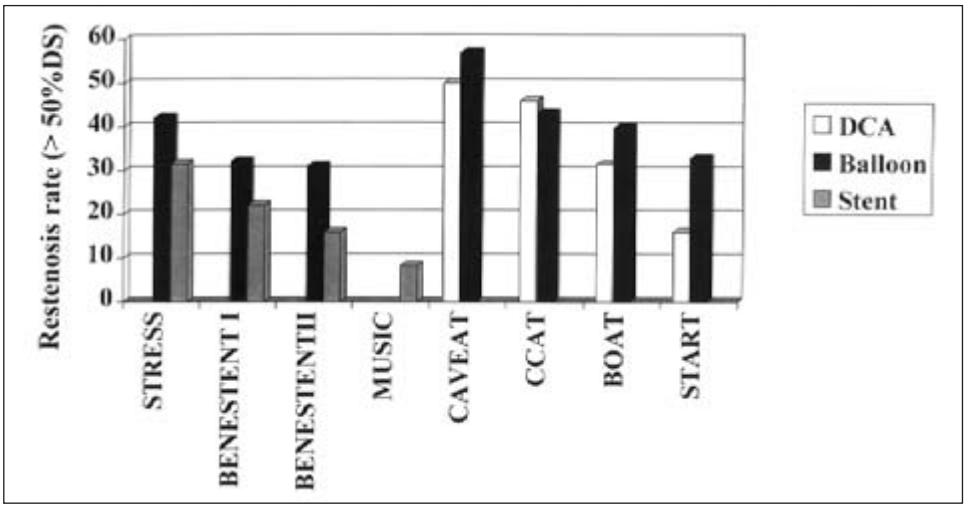


Figure 19.6
Reduction in angiographic restenosis reported in recent studies using more 'aggressive' approaches than the pioneer clinical trials.

angioplasty, cutting balloon, etc) and strategies have been developed to limit the occurrence of restenosis, but no therapy has consistently achieved a single-digit incidence of restenosis.

Intracoronary stents have unequivocally been shown to result in superior acute and late outcome as compared to balloon angioplasty.[105,157,161–164,187–191] Therefore, these metallic prostheses are being used in more than 50% of all interventional procedures worldwide.[179,192] It is nevertheless important to note that a stent does not inhibit, but rather enhances, the proliferative vascular response and that this metallic prosthesis diminishes restenosis as compared to balloon angioplasty by achieving a larger residual lumen and preventing vessel shrinkage (elastic recoil and negative remodeling).

Debulking devices (DCA, TEC, rotablator, laser angioplasty) have been reported as conferring no superior long-term results as compared to conventional balloon angioplasty, and somewhat less than stenting.[168–171,193–196] Favorable results after directional atherectomy studies using a strategy of aggressive debulking guided by IVUS have been reported recently.[166,167] However, these were obtained by operators experienced in the technique of DCA and such a strategy is more costly, so that the use of DCA should be restricted to non-calcified lesions proximally located in the left descending anterior coronary or to bifurcation lesions.[153,197,198] The SOLD registry[199] has suggested a potential benefit (11% angiographic restenosis) of aggressive plaque debulking followed by stent implantation in such selected lesions. The synergistic hypothesis of debulking prior to stenting,[199–201] although not yet validated in a large randomized trial, is supported by a recent IVUS study from the same group of investigators involved in the SOLD registry showing that the amount of residual plaque outside the stent correlates with long-term outcome.[150]

Preventive therapies

Pharmacological prevention of restenosis

The focus of the prevention of restenosis over the past two decades has been through the application of pharmacological agents. Unfortunately, the great majority of clinical studies have not reproduced the promising results observed in the experimental laboratories.[59–72]

Data from the EPIC study suggested a reduction in the need for a second intervention in high-risk patients treated with monoclonal antibody against the platelet glycoprotein IIb/IIIa receptor.[202] However this hypothesis was not confirmed in subsequent trials using either a similar medication (abciximab) or other antagonists of GP IIb/IIIa.[69,203] A potential anti-restenotic effect of abciximab on diabetic patients has been observed in a sub-analysis of the EPISTENT study,[204] but these results have yet to be validated.[205] A small number of studies on pharmacological intervention to prevent restenosis have shown satisfactory results (Fig. 19.7).[206–211] Before sweeping changes in clinical practice are made these findings should be confirmed.

Local drug delivery devices, including drug-coated stents, and even more sophisticated cell-based vascular gene-delivered systems have been developed.[192,212] However, the clinical application and efficacy of such therapies remain to be demonstrated.

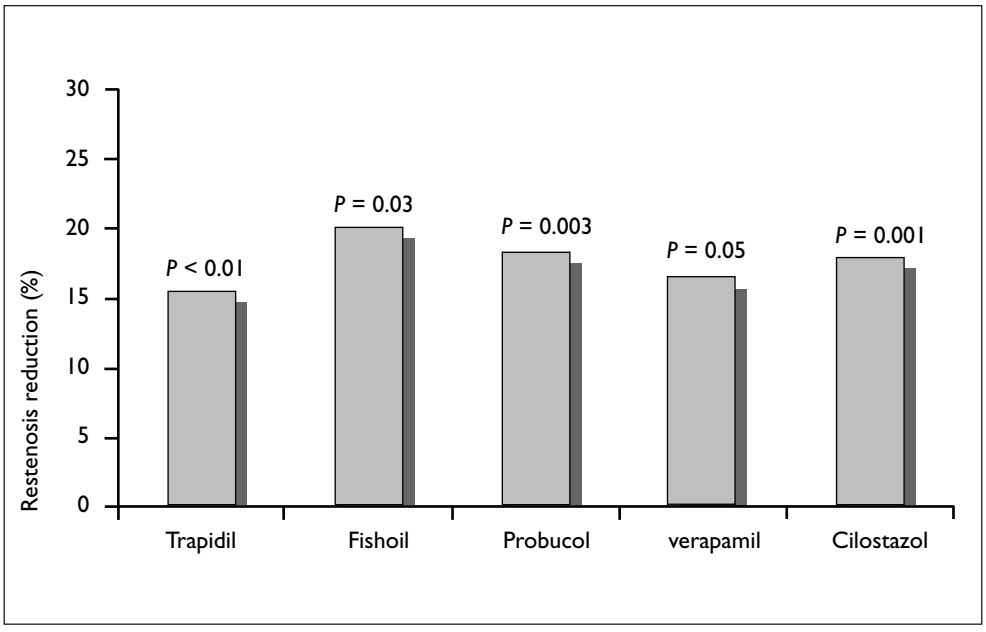


Figure 19.7
Reduction of restenosis by pharmacological therapy.

What about brachytherapy for prevention of restenosis?

A new therapy, intracoronary radiation, has been reported to significantly reduce re-restenosis after successful restenting of in-stent restenosis.[213] Preliminary data from prospective studies, using either beta (BETA WRIST) or gamma radiation (WRIST, GAMMA1), have recently confirmed the favorable results of catheter-based radiation therapy for the treatment of in-stent restenosis: a 40–70% reduction in restenosis as compared with placebo was reported (see Chapter 20).

Brachytherapy, by means of either catheter-based systems or radioactive stents, has also been used for prevention of restenosis in less 'malignant' de novo coronary lesions.[214–218] However, the long-term safety of this novel therapeutic modality has been disputed,[219] and before intracoronary radiation is incorporated in daily clinical practice, some problems must be solved: stent and/or radiation edge restenosis,[216] late thrombotic occlusions[220] and potential delayed restenosis.[221–224]

How do we deal with restenosis if we failed to prevent it?

Restenotic lesions have been associated with an increased risk of re-restenosis as compared with de novo lesions. Although, satisfactory results (18% restenosis rate) have been observed by treating restenosis after PTCA with stent implantation,[191] without doubt treatment of in-stent restenosis represents the new challenge for the interventional cardiologist.[153,182] Treatment of diffuse in-stent restenosis has been associated with high (45–80%) rates of target lesion revascularization, regardless of the device used (balloon angioplasty, stent, rotational atherectomy or laser angioplasty).[181,183,184,225,226] As discussed above, intracoronary radiation is the only therapeutic approach to date that has proved clinically effective for the treatment of in-stent restenosis.

Future directions

Researchers are still seeking solutions for restenosis, but the cure has not yet been found. Taking advantage of the knowledge accumulated over the past two decades, many innovative approaches have been developed. Biodegradable stents, which 'dissolve' 9 months after implantation, have recently been implanted in humans with promising results and drug eluting stents (eg: Taxol, Rapamycin eluting stents) may be even more exciting and are currently being evaluated.[227] Sophisticated energy-based therapeutic modalities (photodynamic therapy, sonotherapy, cryotherapy) have also emerged as potential solutions and clinical studies are already under way.

Undoubtedly we have come a long way in the last decade. More patients with complex coronary disease are being treated percutaneously using innovative strategies, many on an out-patient basis. PTCA is acutely safer than ever before and bypass surgery is progressively being reserved for patients when percutaneous techniques appear impossible or inappropriate.

The frequency of significant clinical recurrence of treated lesions is certainly less than 20 years ago, but still represents the 'Achilles heel' of the percutaneous approach. We have not found the 'magic bullet' or the 'Holy Grail' and maybe we never will since the search seems to reveal more and more the complexity and multifunctional nature of the pathological process leading to the renarrowing we see on the angiogram. Nevertheless, we and our patients take heart from the progress already made and the commitment shown to find a solution for restenosis.

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20

Management of restenosis through radiation therapy

Ron Waksman

Post angioplasty restenosis continues to be a major obstacle in catheter-based cardiovascular interventions. While cellular proliferation after balloon injury is the most likely mechanism for the development of clinical restenosis, the degree of the proliferative response remains unknown.[1–4] Early and late remodelling of the vessel lumen following angioplasty have been identified as contributors to restenosis.[5–8] Stents have been used to eliminate vessel remodelling, and maintain a higher patency rate as compared to angioplasty alone.[9,10] Often, however, a higher degree of proliferative response and an increase in late lumen loss occurs with stent placement.[11]

Used in other clinical situations to stunt excess growth, vascular brachytherapy – the intraluminal delivery of radiation following angioplasty – was viewed as a viable solution to inhibit restenosis.[12,13] After its introduction in 1992, several investigators performed preclinical studies using vascular brachytherapy and demonstrated consistently profound reductions in neointimal formation following balloon injury.[14–37] In these experiments, radiation was delivered into the vessel wall either through high dose rate catheter-based systems or through low dose rate radioactive implants, such as radioactive stents. The results of these preclinical trials were so encouraging that they facilitated the initiation of feasibility clinical trials in peripheral arteries first, and later in coronary arteries through pivotal trials. Beginning in 1999, the success from these studies led to the technology's commercialization in Europe for clinical use.

Radiation biology and mechanism

The principle of the application of radiation biology to prevent restenosis is to induce apoptosis (programmed cell death) in radiosensitive cells, especially those that are undergoing mitosis following vascular injury. The administration of subtherapeutic doses of irradiation will only delay the eventual process of restenosis, as an inadequate dose will not eliminate enough cells to prevent cell division. This will also occur if the vessel is not exposed to radiation for a long enough period of time. Therefore, the overall effect of radiation therapy is strongly dependent on the cumulative doses, dose rate, and cell cycle.[38] Through a series of studies on the coronary arteries of pigs by Waksman et al, it was deduced that restenosis is reduced by radiation therapy because the radiation inhibits the first wave of cell proliferation in the adventitia and the media, thereby inducing favourable remodelling.[39]

Radiation physics and radiation systems

Different isotopes on various platforms and systems have been developed for the use of endovascular brachytherapy. Although there are multiple platforms for radiation delivery, the commonest are catheter-based systems varying from line source wires embedded with radioactive seeds, to radioactive gas and liquid filled balloons or stents utilizing beta or gamma emitters.

The choice of which isotope to use for vascular brachytherapy is complicated by a number of factors. Before this decision can be reached, the anatomy of the vessel, properties of the treated lesion and identification of the target tissue need to be examined. Other important parameters are the diameter and curvature of the vessel, the eccentricity of the plaque, the lesion length, the composition of the plaque, the amount of calcium and the presence or absence of a stent in the treated segment. The ideal radioisotope would have a

minimal dose gradient which could deliver a therapeutic effect within a treatment time of 10 minutes. A dose distribution within a few mm from the source, resulting in a low dose exposure to surrounding tissues and with a sufficient half-life, is particularly favourable for use with catheter-based systems. Other aspects that need consideration include the potential radiation exposure to the patient and operator, necessary shielding equipment, and associated costs. An example of the dose distribution of iridium-192 is presented in Fig. 20.1.

Understanding gamma radiation

Gamma rays are photons originating from the centre of the nucleus and are distinct from X-rays, which originate from the orbital outside of the nucleus. Gamma rays have deep penetrating energies between 20 keV and 20 MeV, which require an excess of shielding as compared to beta and X-ray emitters. The only gamma ray isotope currently in use is iridium-192 (Ir-192). There are isotopes that emit both gamma and X-rays, such as iodine-125 (I-125) and palladium-103 (Pd-103). However, these isotopes have lower energies, and require higher activity levels in order to deliver a prescribed dose within the acceptable dwell time (<20 minutes). It is difficult to use these isotopes for vascular brachytherapy as they are either not available in high activity levels or are too expensive for this application.

The dosimetry of Ir-192 is well understood and is associated with an acceptable dose gradient, as Ir-192 has a lower fall-off in dose compared to beta emitters. Iridium-192 is available in activities of up to 10 Ci, but due to high penetration additional shielding will be needed, as the average shielding of a catheterization lab will not be able to handle a source with an activity of more than 500 mCi. This limitation is associated with dwell times of more than 12 minutes for doses above 15 Gy when prescribed at a 2 mm radial distance from the source.

Understanding beta radiation

Beta rays are high-energy electrons emitted by nuclei that contain too many or too few neutrons. These negatively charged particles have a wide variety of energies, including transition energies, particularly between parent–daughter cells, and a diverse range of half-lives from several minutes (Cu-62) up to 30 years (Sr/Y90). Beta emitters are associated with a higher gradient to the near wall, as they lose their energy rapidly to surrounding tissue and their range is within 1 cm of tissue. Vascular brachytherapy using beta emitters appears promising, as safety levels are higher because of the limited range of these emitters.

Several dosimetry issues remain controversial, namely the choice of isotope, beta versus gamma emitting radioisotopes, centering versus non-centering devices, and the administration of high versus low dose rates of radiation. In order to determine an accurate dosimetry, it is essential to identify the treatment dose and the exact tissue needing treatment. Despite the notion that the adventitia is the target, it is difficult to ignore the fact that the wall and the residual plaque receive much higher doses, which may be essential to obtain efficacy. The doses prescribed today in clinical studies are empirical, they are based on doses used in animal studies and the limited experience gained from treating other benign diseases. Since a wide range of doses demonstrated effectiveness in preclinical studies, a therapeutic window must exist that allows some flexibility in selecting the isotope for this application.

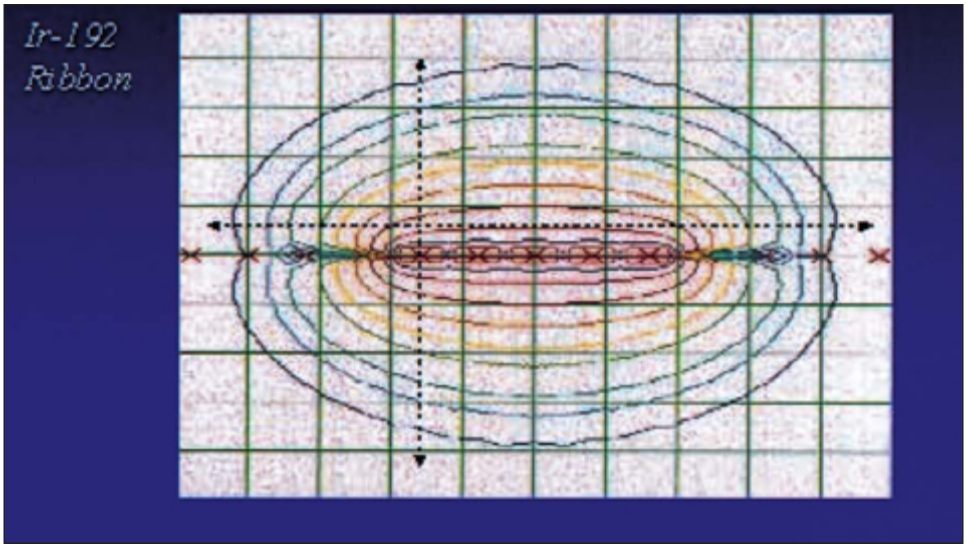

Figure 20.1
Example of dose distribution along an Ir-192 5-seed ribbon.

Dosimetric calculations

Isotope selection should take into account the influence that variables such as effective energy, penetration properties, and different dose gradients have on potential target areas and different half-lives of beta and gamma isotopes. Ignoring these dosimetric considerations may result in treatment failure.

The dosimetry of radioactive stents is even more complicated and depends on the geometry of the stent, which varies with the design. Current tested radioactive stents lack dose homogeneity across the entire length of the stent. This could affect the biological response to radiation, especially at the stent edges. Also, low activity radioactive stents may be associated with an ineffective low dose rate. While radioactive stents with high activities may deliver toxic doses to the stented area that delay reendothelialization, too much radiation might promote stent thrombosis and tissue necrosis in the area surrounding the stent.

Clinical trials

An analysis and update of the current status of clinical trials in vascular brachytherapy for the last quarter of 1999 will lend insight into the progress of the field. Three-year follow-up of clinical and angiographic data from several studies indicates that radiation therapy is a safe and effective treatment for prevention of restenosis following angioplasty and stenting. These trials are still ongoing with nearly 4000 patients enrolled. The 3-year follow-up data, along with new data from larger trials, demonstrate different levels of efficacy and raise questions regarding dosimetry perfection and its impact on related complications, such as edge effect, late thrombosis, and late restenosis.

Despite differences in trial design, more trials have very recently focused on examining the use of vascular brachytherapy for preventing the recurrence of in-stent restenosis. New data related to the use of radioactive stents, liquid filled balloons and the use of intravascular radiation for the peripheral system are now being collected. However, questions still remain as to whether beta emitters will be as effective as gamma ones and whether centering delivery systems perform better than non-centering systems. Various pilot studies with intracoronary brachytherapy have examined the feasibility and safety of this technology with new systems utilizing different emitters. The following is a summary of some clinical trials conducted with gamma and beta emitters. A listing of all clinical trials using gamma emitters is displayed in Table 20.1; beta emitter trials are featured in Table 20.2.

Gamma trials

The first clinical trial using intracoronary radiation in human coronary arteries was conducted in 1995 by Condado et al.[40] In this study, 21 patients (22 arteries) with unstable angina (UA) underwent PTCA followed by intracoronary radiation with Ir-192 (19–55 Gy). Repeat angiography at 30 to 60 days demonstrated total occlusions in two arteries, a new pseudoaneurysm in one artery, and significant dilatation at the treatment site of two additional arteries. The remaining arteries were patent. Angiographic follow-up at 6 months showed a restenosis rate of 23% (5 patients); all remaining arteries (17) were patent with a loss index of 0.19. One more patient (5%) presented with additional restenosis at 5 years. Target lesion revascularization (TLR) at 6 months was performed in three patients (14%). No additional patients required TLR over the 5-year period. Similarly, target vessel revascularization (TVR) was also 14% at 6 months, with only one additional patient requiring TVR during the 5-year duration. The percentage diameter stenosis remained the same at 6 months, 2, 3 and 5 years: 40%, 43%, 42%, 41%, respectively (P = NS). Among the complications, there were four aneurysms (18%), which remained the same at 5 years. Clinical follow-up revealed that only one patient presented with non-Q-wave MI at 6 months, no additional MIs were seen at 6 month or 5-year follow-up. The rate of total occlusion at 6 months was 9% (two patients) and one patient presented with total occlusion at 2 years. There were no subsequent total occlusions.[41]

SCRIPPS (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting) is the first randomized trial on the safety and efficacy of intracoronary gamma radiation given as adjunct therapy to stents to reduce in-stent restenosis. In this study, 26 of 54 patients were randomized to receive Ir-192 (8–30 Gy, dosimetry guided by IVUS) utilizing a ribbon (19–35 mm) delivered in a non-centred, closed-end lumen catheter at the treatment site (dwell time: 20–45 minutes). This study demonstrated a 6 month angiographic restenosis rate of 17% vs 54% in the placebo group. At 3 years, these results remained consistent (15.4% vs 48.3%, respectively). Subanalysis of the lumen diameter for patients who did not have intervention demonstrated minimal reduction of the MLD of the irradiated segments versus control at 3 years. There were no evident clinical complications resulting from the radiation treatment, and clinical benefits were maintained at 3 years, with a significant reduction in the need for target lesion revascularization at 3 years, $P = 0.004$.[42,43]

WRIST (Washington Radiation for In-Stent Restenosis Trial) is a series of studies designed to evaluate the effectiveness of radiation therapy for in-stent restenosis.[44] In the first study, 130 patients (100 patients with native coronaries and 30 patients with vein grafts) with in-stent restenosis lesions (up to 47 mm in length) were blindly randomized to treatment with either placebo or 15 Gy of Ir-192 at 2 mm from the source of the vessel wall. At 6 months, clinical and angiographic follow-up showed a dramatic reduction of the restenosis rate between the irradiated group and the control group: 19% vs 58%, respectively. There was a 79% reduction in the need for revascularization and a 63% reduction in major adverse

Table 20.1 Clinical trials using catheter-based systems with gamma radiation Ir-192 source in coronary arteries.

Principal investigator (sponsor)	*Study name and design*	*Radiation system*	*Dose (Gy)*	*Results and status*
Condado[40] (Angiorad)	Open label, radiation post balloon angioplasty in 21 patients (22 native coronary arteries)	Hand delivered 0.014" or 0.018" 30 mm iridium wire into a non-centred 4.0F closed end lumen catheter. (Angiorad)	20 + 25 Gy Range of actual doses 19–55	Completed. Clinical and angiographic follow-up at 8 and 60 months demonstrated restenosis rate of 28% and low late loss indices
Teirstein (Best Medical)	SCRIPPS, single centre, double-blind, randomized in 55 patients with restenosis	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centred closed end lumen 4.5F (Navius)	≥8–<30 Gy to media by IVUS	Completed. Showed reduction of restenosis in the irradiated group maintained at 3 years
Waksman[44] (WHC)	WRIST, single centre, double-blind, randomized in 130 patients with in-stent restenosis (100 natives, 30 vein grafts)	Hand delivered 0.030" nylon ribbon with Ir-192 seeds (Best Medical) into a non-centred closed end lumen 5.0F catheter (Medtronic)	15 Gy to 2.0 mm distance from source for vessels 34 mm: 18 Gy for vessels <4 mm	Completed. Showed reduction in restenosis (67%) and revascularization (63%) in treated group. At 2 years reduction in TLR and TVR <40%
Waksman (WHC)	SVG WRIST, multicentre, double-blind, randomized in 120 patients with in-stent restenosis	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centred closed end lumen 5.0F catheter (Medtronic)	15 Gy to 2.4 mm for vessels >4.0 mm	Enrolment completed. Initial results in 30 patients from WRIST showed reduction in restenosis in the irradiated vein grafts
Waksman (WHC)	LONG WRIST, two centre, double-blind, randomized in 120 patients with in-stent restenosis lesions (36–80 mm)	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centred closed end lumen 5.0F catheter (Medtronic)	15 Gy to 2.0 mm for vessels 3–4 mm	Completed. At 6 months, restenosis rates lower in irradiated group 32% versus control 71%
Waksman (WHC)	LONG WRIST HD, single centre, registry in 60 patients with in-stent restenosis. Lesions (36–80 mm)	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centred closed end lumen 5.0F catheter (Medtronic)	18 Gy to 20 mm for vessels 3–4 mm	Completed. Demonstrated further reduction of the restenosis rate compared to 15 Gy
Leon[45] (Cordis)	GAMMA 1, multicenter, randomized double blind study in 252 patients with in-stent restenosis	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centred closed end lumen 4.0F catheter (Cordis)	≥8–<30 Gy to media by IVUS	Completed. Patients with radiation therapy have significant reduction of the restenosis 21.6% versus 50.5% and the clinical TLR at 9 months
Leon (Cordis)	GAMMA 2, multicentre, registry in 125 patients with in-stent restenosis	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centred closed end lumen 4.0F catheter (Cordis)	14 Gy at 2.0 mm from the source	Completed. Similar to Gamma 1. MACE was reduced by 36% and TLR was reduced by 48% as compared to placebo
Waksman (Vascular therapies)	ARTISTIC, multicentre, double-blind, randomized in 300 patients with in-stent restenosis	Mechanical delivery of 0.014" fixed wire 30 mm (Angiorad) into a monorail closed end lumen balloon centering 3.2F catheter	12–15–18 Gy to 2.0 mm from the source	Feasibility phase completed, with low restenosis rate 12%. Multicentre, initiated in the summer of 1998
Waksman (WHC)	PLAVIX WRIST, a registry of 120 patients with in-stent restenosis with 6 months of PLAVIX	Hand delivered 0.030" nylon ribbon with IR-192 seeds into a non-centred closed end lumen 4.0F catheter (Cordis)	14 Gy to 2.0 mm distance from the source	Enrolment completed. Late thrombosis rate 2.5%. 6-month TLR and MACE rates 23%
Teirstein (SCRIPPS)	SCRIPPS 2, single centre randomized study for patients with diffuse in-stent restenosis	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into a non-centred closed end lumen 4.0F catheter (Cordis)	≥8–<30 Gy to media by IVUS	Enrolment completed
Teirstein (SCRIPPS)	SCRIPPS 3, a registry of 200 patients with in-stent restenosis with 6 months of PLAVIX	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into a non-centred closed end lumen 4.0F catheter (Cordis)	14 Gy to 2.0 mm distance from the source	Enrolment completed
Waksman (WHC)	PLAVIX WRIST 12, a registry of 120 patients with in-stent restenosis with 12 months of PLAVIX and 15 months of angiographic study	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into a non-centred closed end lumen 4.0F catheter (Cordis)	14 Gy to 2.0 mm distance from the source	Enrolment completed. Results available summer 2001

Table 20.2 Clinical trials using catheter-based systems with beta emitters in coronary arteries.

Principal investigator (sponsor)	*Study name and design*	*Radiation system*	*Isotope and dose (Gy)*	*Results and status*
Verin[47] (Schneider)	GENEVA, open label in 15 patients after PTCA in de novo lesions	Mechanical loading of 0.014" 29 mm fixed wire via a segmented centred 30 mm balloon (2.5–4 mm)	Y-90, 18 Gy to the surface of balloon	Completed. Showed feasibility and safety with restenosis rate of 45%
King[48] (Novoste)	BERT, open label registry in 84 patients post PTCA in de novo lesions	BetaCath system. Hydraulic hand delivery of a train of 12 radioactive seeds (30 mm) in a non-centred 5.0F catheter	Sr/Y90, 12, 14, 16 Gy to 2.0 mm from the source	Completed. Showed feasibility, safety, restenosis rate of 17% with late loss index of 4%
Serruys (Novoste)	BRIE, European registry in 150 patients after PTCA in up to 2 vessels	BetaCath system	Sr/Y90, 14, 18 Gy to 2.0 mm from the source	Interim results reported target vessel restenosis of 30%. Late loss index for the total population 13%
Kuntz (Novoste)	BetaCath, multicenter, randomized blinded in 1450 patients after PTCA and provisional stenting	BetaCath system	Sr/Y90, 14, 18 Gy to 2.0 mm from the source	Study initiated in July 1997, enrolment completed. Results will be available in the Autumn of 2001
Verin (Boston Scientific)	Dose findings, European multicentre open label study in 160 patients after PTCA (120 patients) and stenting (49 patients)	Automatic afterloader (ITS) of a 0.014" 29 mm fixed wire via a centred balloon (Schneider)	Y-90, 9, 12, 15, 18 Gy at 1.0 mm from balloon	Completed. Restenosis of 28% with 9 Gy, and 15% in the 18 Gy dose. Restenosis: 3.9% in the balloon group treated with 18 Gy (40 pts)
Raizner (Guidant)	PREVENT, multinational open label feasibility study in 80 patients after PTCA or stenting	Automatic afterloader (Nucletron) 0.018" 27 mm fixed wire via a helical centering balloon 2.5–4.0 mm 30 mm length	P-32, 16–20–24 Gy to 1.0 mm into the vessel wall	Completed, Showed: safety and restenosis rate of 6.6% at the treated site. Lower late loss and TLR in the irradiated group
Weinberger[50] (Columbia University)	CURE, registry open-label in 25 patients for de novo lesions	Liquid Re-188 from a generator (Oak Ridge) fills a perfusion coronary balloon (Lifestream™)	Re-188, 13 Gy at the adventitia	Completed, demonstrated safety with TLR rate of 17% at 6 months
Waksman (WHC)	BETA WRIST, registry for 50 patients with in-stent restenosis	Schneider System Y-90 source centering balloon and an afterloader	Dose 20.6 Gy to 1.0 mm distance from the balloon surface	Completed. Reported restenosis rate of 22% at 6 months. Similar results to the gamma WRIST group
Waksman (Guidant)	INHIBIT, multicentre for patients with in-stent restenosis for 320 patients	Automatic afterloader (Nucletron) 0.018" 27 mm fixed wire via a helical centering balloon	P-32 Dose 20 Gy to 1.0 mm from source	Study was initiated in June 1998 and enrolment completed. Safety was shown at 30 days
Popma (Novoste)	START, multicentre randomized double-blind design for 476 in-stent restenosis lesions (20 mm)	BetaCath system, 30 mm source train	Sr/Y90 18–20 Gy at 2.0 mm	Completed. Showed reduction in TLR, TVR and MACE (35%) in the irradiated group. No late thrombosis
Lasky (Novoste)	START 40/20, a registry of 250 patients with in-stent restenosis	BetaCath system, 40 mm source train	Sr/Y90 18–20 Gy at 2.0 mm	Completed. Compared to START, START 40 ↓ restenosis in analysed segment by 44% and reduced MACE by 26%
Colombo (Radiance)	BETTER, European registry of 120 patients, lesions <25 mm all indications	Radiance system with a deployable P-32 balloon for de-novo and ISR lesions	P-32 20 Gy at 1.0 mm from the balloon	Ongoing registry demonstrated safety at 30 days
Waksman (Radiance)	BRITE, feasibility study in patients with in-stent restenosis, lesions < 25 mm	Radiance system with a deployable P-32 balloon	P-32 20 Gy at 1.0 mm from the balloon	Enrolment completed, demonstrated safety at 30 days, 6 months TVR 3.7% (n = 26)
DeScheerder (Mallinckrodt)	MARS, two centre registry for non-stented lesions	Liquid filled balloon manually delivered	Re-186	Study initiated in December 1998 and was terminated after 35 patients. Restenosis rate >30%
Park	R4, registry in 52 patients with in-stent restenosis in South Korea	Liquid filled balloon 36 mm in length	Re-188 15 Gy at 1.0 mm into the vessel wall	6-month binary angiographic restenosis 10.4%

cardiac events (death and Q-wave myocardial infarction) in the irradiated group compared to control. Intravascular ultrasound subanalysis demonstrated a 53% regression of tissue in the irradiated arteries at follow-up. The WRIST study is considered to be a landmark in establishing gamma radiation for the treatment of in-stent restenosis. A brief overview of the other studies in this series can be found in Table 20.1

GAMMA 1 is a multicentre, randomized, double-blind trial studying the effects of hand-delivered Ir-192 ribbon using intravascular ultrasound to guide dosimetry (dose range between 8 and 30 Gy) in 252 patients with in-stent restenosis. Six-month angiographic results revealed significant reduction in the in-stent angiographic restenosis rate of the radiation arm versus control (21.6% vs 52%). Subanalysis for lesion length demonstrated a 70% reduction in the angiographic restenosis rate for lesions <30 mm in length versus 48% for 30–45 mm lesions.[45] In addition, an edge effect was noted in patients who did not have enough coverage of the lesion by the radioactive seeds. Clinical events demonstrated a reduction in target lesion revascularization (TLR) from 42.1% to 24.4%. However, death (3.1% versus 0.8%) and acute MI rates (12.2% vs 6.2%) were higher in the irradiated group versus control. These complications were related in part to the late thrombosis phenomenon.

GAMMA 2 is a registry of 125 patients who were treated for the same inclusion/exclusion criteria as GAMMA 1, but with a fixed dosimetry of 14 Gy at 2 mm from the centre of the source. The treated lesions in Gamma 2 were more heavily calcified, whereby 45% of patients required rotablation in contrast to 26% of patients in GAMMA 1. Despite the differences in lesions, the results between GAMMA 1 and 2 were remarkably similar. Both studies had similar and infrequent in-hospital adverse clinical events (1.6%). GAMMA 2 patients had a lower post-procedural MLD. This is perhaps due to increased lesion complexity and the fact that fewer stents were placed in GAMMA 2 patients, as compared to GAMMA 1. Similar to GAMMA 1, there was a 52% in-stent and a 40% in-lesion reduction in restenosis frequency. MACE was reduced by 36% and TLR was reduced by 48%. The late thrombosis rate was 4.0% at 270 days with only 8 weeks of anti-platelet therapy. It is believed that prolonged anti-platelet therapy will remedy the incidence of late thrombosis.

ARTISTIC (Angiograd Radiation Technology for In-Stent Restenosis Trial in Native Coronaries) is a blinded, randomized trial examining the benefits of using a fixed, 30 mm Ir-192 wire in 300 patients with in-stent restenosis in native coronary arteries. The pilot phase of the study was recently completed and involved 26 patients at two centres, all of whom received radiation treatment. Inclusion criteria consisted of lesions <25 mm in length with a reference vessel diameter between 2.5 and 5.0 mm, and a degree of stenosis between 50% and 99%. Radiation was successfully delivered to 25 of 26 patients. At 6-month angiographic follow-up, low binary restenosis rates of 10% were reported with a late loss index of 0.12, and a 1.5% rate of major adverse cardiac events.[46] The randomized phase of this trial began in 1999 and enrolment of 300 patients is expected to be completed by late 2000.

Gamma radiation in conjunction with prolonged anti-platelet therapy

A series of studies is currently underway to examine whether prolonged anti-platelet therapy can diminish the late thrombosis phenomenon. Among these are PLAVIX WRIST and SCRIPPS III, in which Plavix (clopidogrel) is prescribed for 6 months, and WRIST 12, in which clopidogrel is prescribed for 12 months. It is anticipated that data from these studies will indicate that prolonged anti-platelet therapy will significantly decrease the incidence of late thrombosis.

Beta trials

Initial beta-emitter clinical trials used designs to examine the effectiveness of beta radiation therapy for the prevention of restenosis in de novo lesions found in native coronaries. New studies have been initiated to test the effectiveness of beta radiation for post intervention restenosis.

The GENEVA experience examined a yttrium-90 source, and a centering balloon catheter following PTCA in a small cohort of 15 patients. Although the investigators were able to demonstrate feasibility of the radiation system, the outcome of this study was disappointing, since five of the 15 patients experienced angiographic and clinical restenosis.[47] The investigators related their results to insufficient doses to the adventitia (less than 5 Gy).

The dose finding study evaluated 160 patients throughout five centres in Europe using the same Y-90 radiation system. Doses of 9, 12, 15 and 18 Gy at 1 mm from the surface of the balloon were examined. Patients and investigators were blinded to dose administration. Angiographic follow-up was conducted at 6 months. A dose–response was demonstrated, with an 8% angiographic restenosis rate in patients who had received the highest dose of 18 Gy and a 28% restenosis rate in patients receiving the lowest rate of 9 Gy. The intermediate doses of 12 and 15 Gy were associated with similar restenosis rates of 15% and 16%, respectively. An analysis for patients who were treated without stents demonstrated restenosis rates of 4.2% when receiving the highest dose. The late thrombosis rate was about 10%. Edge effect was not evaluated in this study. The results from this study indicate that restenosis rates can be dramatically changed with correct dose.

BERT (Beta Energy Restenosis Trial) is a feasibility study approved by the FDA and limited to 23 patients in two centres (Emory and Brown Universities). The study is

designed to test the Sr-Y90 source delivered by a hydraulic system. The prescribed doses in this study were 12, 14 and 16 Gy and the treatment time did not exceed 3.5 minutes. The radiation was successfully delivered to 21 of 23 patients following conventional PTCA without any complications or adverse events at 30 days. At follow-up, two patients at 6 months and one patient at 9 months underwent repeat revascularization to the target lesion.[48] At the 6-month follow-up, the angiographic restenosis rate for the entire cohort of 83 patients was 17%, with a low late loss of 9%. However, six additional patients required revascularization due to edge effect near the treated lesion.

The BetaCath trial was initiated in July 1997 as a prospective, randomized, placebo-controlled trial to evaluate the safety and effectiveness of the Sr-Y90 BetaCath system versus placebo in de novo or restenotic lesions of native coronary arteries. A total of 1100 patients who underwent elective PTCA or provisional stent placement have been enrolled in 27 centres. Angiographic follow-up at 8 months will be available by late 2001. An additional 300 patients were added to the stent arm of the study due to higher rates of late thrombosis. The results of this study will determine the future of this technology for clinical use for prevention of restenosis.

BRIE (Beta Radiation In Europe) is a registry with 180 patients who were enrolled in nine sites in Europe. In this trial, treatment of up to two vessels was allowed with the BetaCath system using the Sr-Y90 source doses 14 and 16 Gy. The primary angiographic endpoints of the BRIE registry were target lesion revascularization, and late loss index measured at 6 months. The first 90 patients with 98 lesions at angiographic follow-up evaluation had a target vessel revascularization rate of 30% with 19% in the PTCA subgroup and 35% in the stent group. The late loss index for the total population was 12%, with 3% in the PTCA subgroup and 17% in the stent group. The main problem in this study was incomplete coverage of the treated area resulting in 'geographic miss' and was found in 30% of the treated lesions. The study supports the notion that radiation and stenting resulted in more events than radiation and balloon angioplasty.

PREVENT (Proliferation Reduction with Vascular Energy Trial) is a prospective, randomized, blinded, multinational, and multicentre study. The objective of this study is to demonstrate the safety of the beta radiation system in human coronaries immediately following PTCA or stent placement. The system consists of a 27 mm, P-32 isotope delivered into a centering helical balloon delivery catheter via an automatic afterloader apparatus. The doses used in this open-label phase are 16, 20 and 24 Gy prescribed to 1 mm from the source. Preliminary results suggested low rates of late loss in the irradiated group compared to control, 4.8% versus 51.3%, respectively. There was a significant reduction in the need for target lesion revascularization (4% versus 18%). However, due to an increase in edge effect, the target lesion revascularization rates were similar in the treated vessels compared to the control vessels, 24% versus 29%, respectively. Subanalysis of patients with in-stent restenosis treated with P-32 demonstrated lower rates of recurrences compared to a matched control group from the WRIST study.

CURE (Columbia University Radiation Energy) is the first liquid filled balloon system used in a feasibility clinical trial for either post intracoronary stenting or post balloon angioplasty patients (25 patients).[49,50] The liquid form of the Re-188 isotope is retrieved from a Tungsten-188 generator and injected via a syringe into a perfusion balloon and allowed to dwell for up to 10 minutes. The prescribed dose was 13 Gy to the adventitia and the clinical restenosis rate with the need for target vessel revascularization was nearly 17%.

MARS (Mallinckrodt Angioplasty Radiation Study) is a multicentre, feasibility study utilizing a liquid Re-186 beta emitter source for the prevention of restenosis in de novo and restenotic lesions. Preliminary results demonstrated angiographic restenosis of >30% with evidence of high rates of edge effect.

BETTER is a feasibility study to test the Radiance radiation system using a balloon catheter encapsulating a P-32 radioactive sleeve. Patients have been enrolled in several centres in Europe for all indications for lesions <20 mm and a pilot trial in the US has started.

Beta radiation for in-stent restenosis

BETA WRIST is the first study to examine the efficacy of beta radiation for prevention of in-stent restenosis. This registry included 50 patients who underwent treatment for in-stent restenosis in native coronaries and were treated with a beta radiation system using the yttrium-90 source, a centering catheter and an afterloader system. The clinical outcome of these patients was compared to the control group of the original cohort of WRIST which was randomized to placebo versus Ir-192. The reported angiographic restenosis rate at 6 months in BETA WRIST was 22% and about 10% of the patients had late thrombosis. The overall use of beta radiation for the treatment of in-stent restenosis demonstrated a reduction of over 50% for the need of target lesion or vessel revascularization compared with the historical control of WRIST. Comparison of the outcome of the irradiated beta with the gamma group did not detect major differences between these two groups.[51] This study suggested that for in-stent restenosis treatment with beta emitters may have a similar outcome to treatment with gamma emitters.

START (Stents and Radiation Therapy Trial) is a FDA pivotal multicentre randomized trial involving 385 patients in over 55 centres in the US and Europe which will determine the efficacy and safety of the BetaCath system for the treatment of in-stent restenosis. Patients eligible for START included those with native artery lesions treatable with a 20 mm angioplasty balloon. On average, patients enrolled in the study had 16 mm long lesions in arteries 2.8 mm in diameter. Following

angioplasty, these patients were treated with the BetaCath system which contained strontium-90 seeds that deliver beta radiation through a closed-end lumen catheter following angioplasty. They were randomized to either placebo or an active radiation train 30 mm in length. Depending on the diameter of the target vessel, a dose of either 16 or 20 Gy was administered at 2 mm from the centre of the source. Restenosis rates in irradiated segments were 29% vs 45% in the placebo group ($P = 0.001$). TLR was necessary in 16% of the irradiated group, as compared to 22% of control ($P = 0.008$). Rates for TVR were also similar (16% and 24%, respectively). Additionally, patients treated with radiation had a considerably lower rate of major adverse cardiac events than those in the placebo group (18% vs 26%). Similar to the findings of BETA WRIST, these results indicate the safety and effectiveness of using beta emitters for vascular brachytherapy.

INHIBIT is a multicentre randomized study in the US and Europe for patients with in-stent restenosis to test the efficacy of the GALILEO system using a P-32 source with a dose of 20 Gy at 2 mm from the surface of the balloon. The antiplatelet therapy for this study is prescribed for 3–5 months and all patients will undergo angiographic follow-up at 7 months. The study was initiated in July 1998 and enrolment was completed by October 1999.

Thus far, the lessons from the beta feasibility studies were that the radiation effect is confined to the length of the source and longer beta sources are required to cover the entire segment undergoing intervention to eliminate the edge effect phenomenon.

BRITE is a US feasibility study to test the Radiance radiation system using a balloon catheter encapsulating a P-32 radioactive sleeve for the treatment of in-stent restenosis. The feasibility study of 27 patients has been completed and the launch of the randomized study is planned to take place by the last quarter of 2000.

Radioactive beta emitting stents

The clinical trials with the radioactive stent have demonstrated safety but were disappointing in efficacy. The isotope examined on this radioactive stent is P-32.

IRIS (Isostent for Restenosis Intervention Study) was the first feasibility study using radioactive P-32 Palmaz–Schatz stents. In this study, 30 patients with stenosis in de novo or restenotic lesions of native coronaries underwent radioactive stent implantation (with an activity of 0.5–1.0 μCi) with a mean stent activity of 0.69 μCi. There were no adverse effects at 30 days in any of the treated patients; however, at the 6-month angiographic follow-up there was a binary restenosis rate of 31% and clinical driven target lesion revascularizatiion of 21%. Late loss data by segment was 0.94 mm for de novo and 0.70 mm for restenosis legions. IVUS detected a significant amount of diffuse disease with a mean CSA stenosis of 41% in the reference vessel at the time of the stent implantation.[52,53] Angiographic and IVUS images of a profile from the IRIS trial are shown in Fig. 20.2.

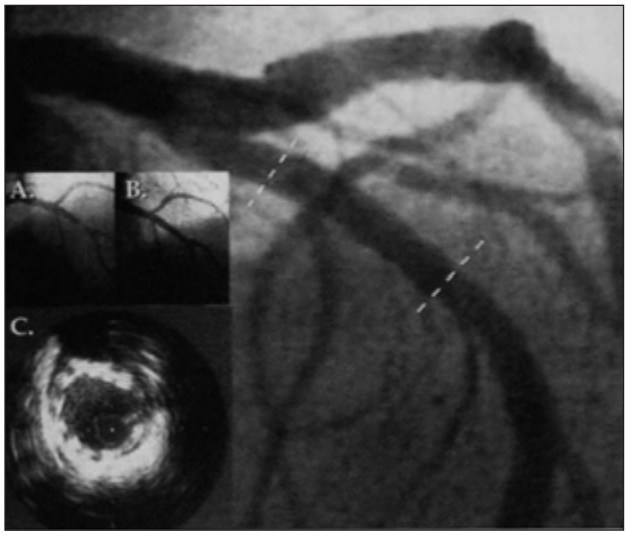

Figure 20.2
IRIS trial case profile: (a) before stenting, (b) after stenting, (c) IVUS image of stented vessel.

The IRIS trial was expanded to include an additional 25 patients who underwent intracoronary stent implantation with a higher activity (0.75–1.5 μCi) stent. This cohort indicated that the radioactive stent was safe, with no evidence of thrombus or subacute closure. However, the overall restenosis rate was higher than rates reported with non-radioactive stents.[54]

In a dose finding study conducted in Milan, higher activities above 6 μCi detected nearly complete neointima formation in the body of the stent, but was associated with high degrees of restenosis at the edges of the stent (range of 36–44%) with a unique angiographic pattern of stenosis at the edges, known as the 'candy wrapper' effect.[55]

Studies with activities of up to 20 μCi are conducted to evaluate whether higher activities will minimize the edge effect phenomenon. Other approaches to eliminate the edge effect are being investigated; for instance cold end radioactive stents have failed and hot end radioactive stents with an activity of up to 50 μCi also did not eliminate the edge effect phenomenon. New isotopes and delivery system platforms such as nitinol stents are currently under investigation to overcome the limitations of radioactive stents.

Limitations to brachytherapy

Although clinical trials using vascular brachytherapy for both coronary and peripheral applications have demonstrated positive results in reducing restenosis rates, these trials have

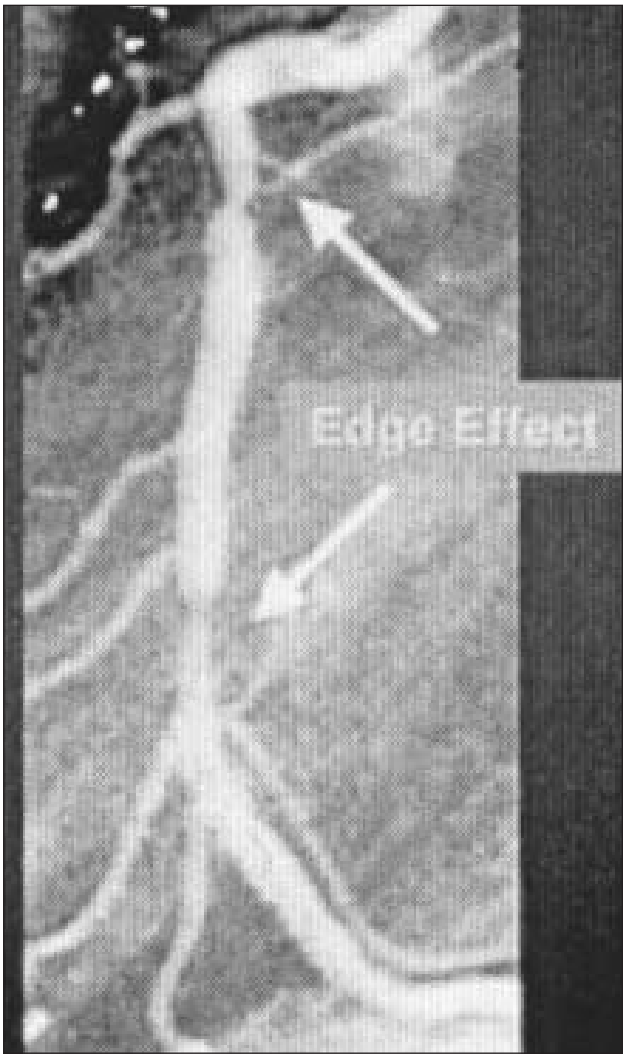

Figure 20.3
Angiogram depicting the 'candy wrapper' phenomena.

also identified two major serious complications related to the technology: late thrombosis and edge stenosis effects seen at the edges of radiation treatment segments. Late thrombosis is probably due to the delay in healing associated with radiation. It has been estimated that late thrombosis can be remedied through the prolonged administration of anti-platelet therapy following intervention.

Identified as a major limitation to radioactive stents, the edge effect phenomenon is not exclusive to stented lesions. The incidence of the edge effect has also been known to occur with catheter-based systems utilizing both beta and gamma emitters, especially when the treated area is not covered with wide enough margins. The main explanation for the incidence of the edge effect is a combination of low dose at the edges of the radiation source and an injury created by the device for intervention which is not covered by the radiation source. It is hypothesized that wider radiation margins of treatment to the intervening segment may eliminate or significantly reduce the edge effect seen so far in all radiation trials. An example of an angiogram demonstrating the 'candy wrapper' effect is shown in Fig. 20.3. Finally there is a late restenosis phenomenon reported in a small cohort of patients who were treated with radiation. In those patients radiation therapy only delayed restenosis.

Conclusion

Vascular brachytherapy is a promising technology in research for a cure for restenosis. The technology is a moving target and is on its way to become a recognized standard of care for the treatment of restenosis. Revelation of the technology's major complications has led to immediate solutions which it is hoped will nearly eliminate late thrombosis and minimize the edge effect phenomenon.

As of now, the studies with both beta and gamma radiation only serve as a proof of principle to the technology. It appears that if the right dose is used on the right target tissue, radiation will be an effective therapy for restenosis regardless of the type of isotope or delivery system used. Although caution may be applied to the interpretation of data from small cohorts of patients in non-randomized trials, it is hard to ignore the findings of minimal and occasionally negative late lumen loss after balloon angioplasty or extremely late indices in patients with restenosis and stenting. This phenomenon has not been demonstrated so far with any other alternative therapy, whether mechanical or pharmacological, proposed to combat restenosis.

It appears that with the continuation of positive results from the ongoing clinical trials, this technology will have a permanent role in the field of interventional cardiology and radiology for the prevention of restenosis. The first indication for marketing approval in the US is for in-stent restenosis, and was granted in November 2000. Careful expansion of the applications for high-risk patients (diabetes, small vessels, long lesion, etc) should be investigated in randomized controlled studies.

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21

Intravascular ultrasound imaging: assessment of coronary lesions, percutaneous interventions, and brachytherapy

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Introduction

Intravascular ultrasound (IVUS) is a safe catheter-based technique, which provides high-resolution cross-sectional images of both coronary lumen and vessel wall.[1–9] Some centres may use IVUS in all interventions. Others may use IVUS in selected clinical cases only or not at all, depending on the level of expertise or financial constraints. However, in many cardiac catheterization laboratories IVUS has found a well-established place in routine clinical practice, as it provides cross-sectional image information far beyond what is displayed by the projection-dependent 'silhouette technique' of coronary angiography.[12–15] The potential to evaluate meticulously borderline angiographic coronary lesions and to perform serial IVUS examinations for guidance, device selection, and endpoint assessment of catheter-based interventions makes IVUS a practical clinical tool.[11,16–22]

IVUS technology and imaging protocol

Principles of IVUS technology

There are two main technical configurations of IVUS systems currently in use. The mechanical system contains a flexible imaging cable which rotates a single transducer at its distal tip inside an echolucent distal sheath. The sheath prevents any direct contact between the transducer and the vessel wall and avoids friction during the pullback of the imaging core. The electronic (solid state) catheter system has multiple imaging elements at its distal tip, providing cross-sectional images by sequentially activating the imaging elements in a circular way. The image resolution of these devices is in the range of 0.1 mm for the axial and 0.15 mm for the lateral resolution. Zoom size can be altered for optimal visualization of the vessel, and gain setting can be adjusted to provide the best gray scale differentiation between lumen and vessel wall as well as between plaque components[9] (Fig. 21.1).

In the last decade, technical progress has resulted in a significant improvement in image quality for both systems and in a reduction of the IVUS catheter size to below 1 mm. This allows the application of IVUS through 6F guiding catheters, facilitating IVUS lesion assessment prior to coronary intervention.[11]

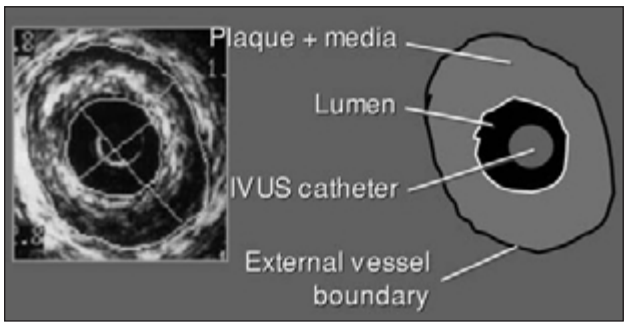


Figure 21.1
Example of atherosclerotic plaque as visualized by IVUS. The IVUS image shows lines indicating minimum and maximum lumen and plaque diameter measurements. The image on the right hand side explains the details.

IVUS imaging protocol

Each IVUS study should be performed according to standard protocols.[9] In our catheterization laboratory, a total of 5000 IU heparin is given prior to any diagnostic coronary angiography. Before advancing the guidewire for the IVUS examination, we give an additional weight-adjusted dose of heparin to reach a total dose of 100 IU/kg body weight. If the duration of the examination exceeds one hour, an additional 3000 IU dose of heparin is administered.

Although IVUS examinations have been shown to be safe,[10] it is important to inject intracoronary nitrates before advancing the IVUS catheter into the coronary artery in order to avoid vessel spasm. Standard 0.014 inch guide wires are used to guide the IVUS catheter in a monorail fashion. After carefully advancing the catheter with fluoroscopic guidance distal to the lesion or segment of interest, a motorized pullback device can be used for continuous (1.0 or 0.5 mm/s) retraction of the IVUS transducer (or the entire IVUS catheter, depending on the system used).

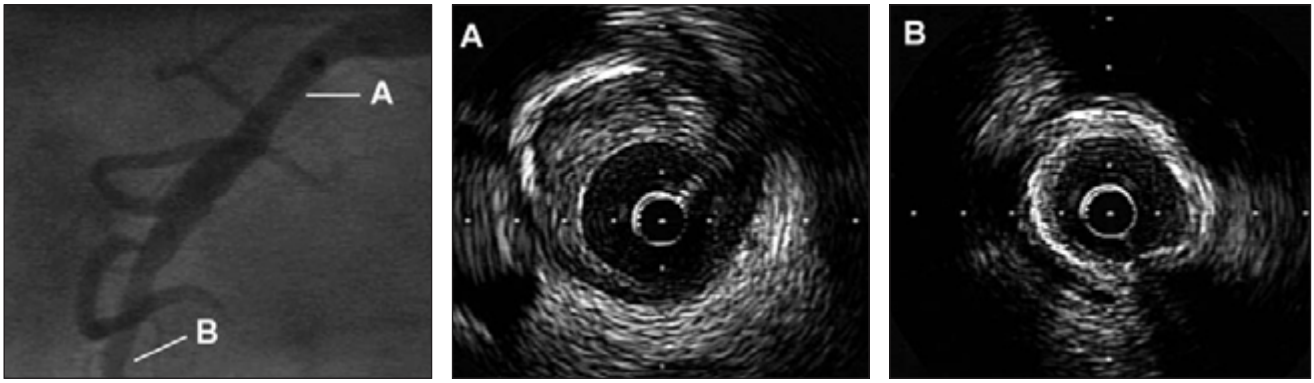
Note that during the first 5 to 10 seconds of a pullback the IVUS imaging core or catheter may be straightened, before the correct and constant pullback speed is reached and reliable length information (distance between particular images along the long vessel axis) can be obtained. Accordingly, the IVUS transducer should (if possible) be positioned 5 to 10 mm distal to the actual segment of interest before motorized pullback is started. In serial studies, side branches or spots of calcium are used as topographic landmarks to ensure reliable comparison of the same coronary segment.[23]

During the IVUS run, injections of contrast should be avoided. After completing the motorized pullback, the segment of interest may be investigated manually. Then, dye may be injected to define the luminal border or check the completeness of stent apposition. The entire IVUS examination should be recorded on super-VHS video tape and/or digitally for off-line assessment. In addition, there are systems available (eg, ECHO-MAP, Siemens) which allow digital image-in-image recording (on angio CD), indicating the IVUS transducer position and the corresponding IVUS image on the angiogram.[24] The ECHO-MAP system also allows online visualization of IVUS images in a full-screen mode on the angio screen and saving of IVUS runs on the angio CD.

IVUS plaque composition and lesion classification

Lesion calcification

IVUS is much more sensitive in detecting calcium than fluoroscopy or radiography.[6,25] Its value in the detection of calcium has been well validated.[25] On IVUS images, calcium is represented by a bright reflection of highly echogenic plaque material (ie of equal or greater intensity than adventitia) with intense signal attenuation and dropout of echos of deeper vessel wall structures, which is termed 'acoustic shadowing'. In addition, reverberations may or may not be seen. IVUS provides information on the circular extent, depth (superficial vs deep) and longitudinal distribution of calcium, but not on the thickness of the deposit of calcium. Calcification is classified as 'superficial', if it is located directly adjacent to the blood pool inside the lumen, whereas 'deep' calcification is separated from the lumen by a layer of non-calcified plaque tissue (Fig. 21.2).



a b

Figure 21.2

Plaque calcification in right coronary artery. Calcium is represented by a bright reflection of highly echogenic plaque with 'acoustic shadowing'. IVUS provides information on circular extent and depth of calcium location (deep vs superficial). Calcifications are classified as 'deep' (a), if the calcium is separated from the lumen by a layer of non-calcified plaque tissue, whereas 'superficial' calcium (b) is located directly adjacent to the blood pool inside the lumen. The plaque of panel b is 'predominantly calcified', as the total arc of calcium is >180°.

Target lesion calcium is a major determinant of both dissections following balloon angioplasty[16,26] and a less favourable outcome following directional coronary atherectomy.[11,27] Knowledge about the calcific nature of even non-significant proximal atherosclerotic disease prior to DCA or stenting is important, as it may prevent delivery of the atherectomy device, failure to advance the stent across the lesion or even stent loss. This latter problem is particularly relevant in the case of direct stenting. In predominantly calcified lesions, rotational atherectomy may be performed prior to adjunctive techniques, leaving a smoothly polished luminal surface of plaque.[28]

IVUS plaque composition

Coronary lesions are often classified according to their predominant plaque component.[7,9,26] Plaques are classified as predominantly 'calcified', if the largest total arc of target lesion calcium (measured in degrees, using a protractor centred on the lumen) is $>180°$ (Fig. 21.2b). Plaques consisting predominantly of tissue producing echoes that are as bright as or brighter than the reference adventitia, but without acoustic shadowing, are classified as 'fibrous' (high echogenicity). If plaques predominantly consist of tissue that is less dense (ie, low echogenicity) than the reference adventitia, they are classified as 'soft' (Fig. 21.3a). Plaques containing more than one type of tissue without evident predominance of one tissue type are classified as 'mixed'.

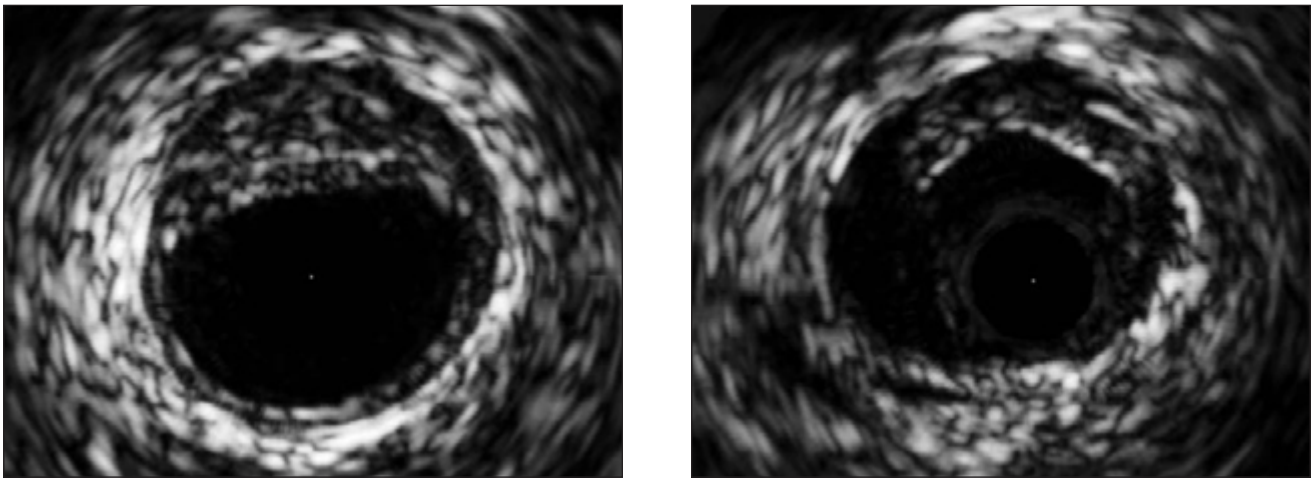
IVUS classification of atherosclerotic lesions

The Committee on Vascular Lesions of the Council on Atherosclerosis of the American Heart Association (AHA) recently classified the atherosclerotic process, on the basis of histopathological observations reported by Stary et al.[29] Erbel et al[30] used this classification as a model to form a more detailed IVUS classification of atherosclerotic coronary lesions, which may serve as a basis for further scientific dialogue. The first experience using the proposed classification in a series of patients with angiographically normal and significantly stenotic coronary arteries, in whom IVUS examinations were performed prior to any coronary intervention, has recently been reported.[30]

Challenges of diagnostic catheterization procedures

Silent plaques and reference disease

Coronary angiography portrays the silhouette of the lumen by dye injection, but it is unable to detect the early stages of atherosclerosis inside the vessel wall.[13,15,31] Furthermore, coronary arteries may enlarge during the earlier stages of plaque accumulation until a critical plaque burden is reached.[32] This positive adaptive remodeling process may compensate for a substantial plaque burden,[33–36] until luminal encroachment starts and the presence of atherosclerosis



a b

Figure 21.3
Deep dissection in reference segment with 'soft' eccentric plaque. Panel (b) displays a deep dissection, which ranges from 7 to 11 o'clock and reaches the media–adventitia interface. In panel (a), the adjacent non-dissected segment is shown.

can be detected on the angiogram.[32] The critical plaque burden and subsequent adaptive process have the potential for considerable variability.[15]

Accordingly, remarkable discrepancies between angiography and IVUS can be found.[15] Quantitative coronary angiographic (QCA) lesion assessment relies on the adjacent reference vessel to assess the severity of a distinct stenosis.[12] However, the angiogram often masks the severity of any underlying coronary disease and underestimates the size of the native coronary artery.[15,31] Routine use of IVUS has taught us that so-called (angiographically) 'normal' reference vessel sites may show that up to 50% of their cross-sectional area is occupied by plaque[13] — a result of the diffuse nature of atherosclerosis and positive remodeling of the atherosclerotic artery.[32–34,36]

IVUS is currently the only in vivo imaging technique which allows the operator to obtain information on the true total vessel dimensions, plaque burden, and the extent of vascular remodeling.

Angiographically ambiguous and hazy lesions

Vessel overlap and foreshortening are inherent problems of angiography which may render angiographic evaluation in proximal, very short or extremely eccentric coronary lesions difficult.[31] In addition, angiography provides only minimal information on the true arterial lumen cross-section, vessel wall thickness, and plaque morphology and composition. Tomographic lesion assessment with IVUS allows differentiation of significant coronary lesions from pseudo-stenoses. The latter may be the result of guidewire or guiding catheter-induced kinking of the vessel, coronary spasm, calcification, or an elliptical or slit-like luminal shape, which may still show a sufficient lumen cross-sectional area.

A hazy angiographic lesion appearance[37] will often trigger assessment with IVUS when the characteristics of such lesions can be fully examined. Following coronary interventions, hazy segments frequently correspond with dissections[37] that can be detected with IVUS, providing information on length, depth, and longitudinal extension of the dissection. IVUS information can be useful in deciding whether to stent the dissection or not. In addition, an angiographic filling defect or haziness prior to intervention may represent thrombus, excessive plaque mass (eg: at the site of extreme adaptive remodeling), or a calcium deposit.[25]

If the haemodynamic significance and the necessity of performing coronary intervention are unclear on the basis of angiographic assessment, an IVUS-measured minimal lumen cross-sectional area of ($\leq$ 4 mm^2 may be considered a useful threshold, below which intervention should be performed.[38] The cut-off value of a minimal lumen cross-sectional area of $\leq$ 4 mm^2 was derived from a clinical validation study performed by Nishioka et al, who compared IVUS lesion data with the results of stress myocardial perfusion imaging.[38]

Left main and ostial disease

Angiographically occult or borderline left main disease can usually be identified and quantified by IVUS,[15] which may alter the therapeutic strategy in favour of surgical treatment.[31,34] IVUS documentation of a significant plaque mass, extending from the proximal left anterior descending coronary artery into the distal left main stem, may discourage the operator from performing a percutaneous catheter-based intervention on the proximal left anterior descending coronary artery.

Assessment of lesion severity and identification of pseudo-stenoses by IVUS is particularly important at the site of an angiographically ambiguous ostium, particularly in left main stems. Several studies have demonstrated the clinical advantages of IVUS in complementing angiography in the assessment of left main stem disease.[15,31,34] At the site of the ostium, non-uniform rotation artifacts may sometimes be observed with mechanical IVUS catheters.[39] Such artifacts are not seen with solid state (electronic) IVUS catheters and these devices may be considered in this situation.

IVUS insights into unstable coronary syndromes

Detection of thrombus

Angiography is relatively insensitive for the detection of intraluminal thrombi.[40] Although thrombus formation in IVUS images is characterized by a heterogeneously reflecting, plaque-mimicking structure with characteristic signs such as a layering effect, oscillation or undulating fine speckles within the plaque, a rough luminal surface and the appearance of imprints of the IVUS catheter,[9,40–42] discrimination between thrombus formation and 'soft' fibrofatty plaques can be difficult.[9]

Unstable lesions and ruptured plaques

Spontaneous rupture of lipid-laden plaques is an important trigger of thrombus formation and acute coronary syndromes. For several years, the assessment of unstable and

ulcerated ruptured plaques (Fig. 21.4) with IVUS has been an important subject of our research[43,44] and there is clear evidence that plaque rupture can be detected by IVUS.[43–47] In addition, IVUS is able to distinguish ruptured plaques from aneurysms and pseudo-aneurysms. Conversely, all three entities may appear angiographically as 'aneurysms'. However, sometimes the angiogram of an IVUS-documented ruptured plaque may show neither a luminal crater nor other evidence of plaque rupture.[43] IVUS studies reported some degree of target lesion calcium in 30–60% of patients with unstable angina,[42,45] and in 20–65% of patients with IVUS-documented plaque rupture.[43,46] Predominantly soft plaque has been described in more than half of the patients with unstable angina.[45] The theory that internal shear stresses at the transition from calcium to soft plaque may be an important trigger of plaque rupture is supported by IVUS.

We recently showed that lumen position and plaque distribution are significantly more eccentric in ruptured plaques (Fig. 21.4) compared to both non-ruptured plaques in the same artery and plaques of matched controls.[44] In that study, more than 90% of the ruptured plaques were eccentric, which corresponds well with previous histological and IVUS studies. In addition, plaque rupture is associated with compensatory vascular enlargement. The arc of disease-free vessel wall in ruptured plaques was slightly larger than in non-ruptured plaques in the same vessel and significantly larger than in plaques of matched controls.[44] A disease-free portion of vessel circumference may be important for plaque rupture; recent in vivo data demonstrate that heterogenous vessel wall distensibility can be found at the site of non-circumferential atherosclerosis; this increases mechanical stress which may result in plaque disruption.[48] A predominance of compensatory vascular remodeling in unstable lesions and ruptured plaques has also been observed in some IVUS studies of other groups.[45–47]

IVUS in non-stent coronary interventions

Visualization and measurement with IVUS prior to percutaneous coronary intervention facilitates assessment of plaque distribution, and provides information about the composition of the target lesion,[7,14,25,26,30] the dimensions and atherosclerotic involvement of the references,[13,15] and the remodeling pattern and potential tapering of the entire segment to be treated.[27,49–55] This information is valuable and may influence the interventional strategy.[11] The benefit of IVUS is most significant in long, complex, and angiographically unclear lesions. In patients with diabetes, IVUS may be particularly helpful in evaluating the actual vessel size as these patients frequently show a diffuse pattern of atherosclerosis with lumen dimensions that appear angiographically small.[56]

Percutaneous transluminal coronary angioplasty

Accurate IVUS measurements of the lumen and vessel dimensions at the target and reference sites can be used for sizing the balloon catheter and for determining the length of the segment to be treated. As demonstrated in the CLOUT (Clinical Outcomes with Ultrasound Trial) study, preintervention IVUS measurement permits the selection of balloons which are on average significantly larger than those determined by QCA.[22] Aggressive IVUS-guided balloon angioplasty with balloons, traditionally considered to be oversized (using angiography), resulted in an increased lumen gain with larger final lumen dimensions but no increase in significant coronary dissections or in-hospital complications.[22]

The inherent mechanism of balloon angioplasty is to create tears and dissections in the vessel wall and to redistribute the plaque mass both radially and longitudinally.[16,17,20,26,57] After

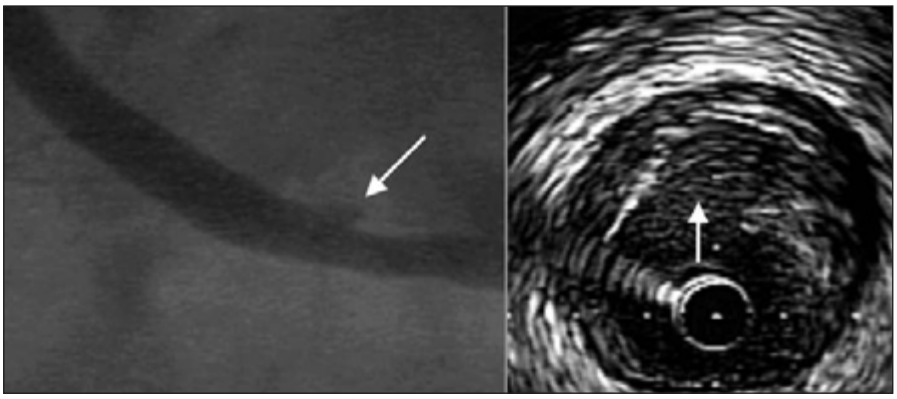


Figure 21.4
Ruptured ulcerated eccentric plaque in a distal right coronary artery. The rupture cavity is located at 12 o'clock in the IVUS image, corresponding with a small luminal crater on the angiogram at the site of a mild, certainly non-significant luminal narrowing. Note the highly eccentric plaque distribution.

balloon angioplasty, a significant benefit can be expected from the evaluation of postprocedural complications such as severe dissections, which may require the implantation of a stent. IVUS is more sensitive than angiography for detecting dissections and flaps in the vessel wall (Fig. 21.3) and permits assessment of their severity and exact location.[37,58,59] Information on dissection length—and hence the length of the stent that should cover it—can be derived from the time information of the motorized transducer pullback. As an alternative, systems for three-dimensional reconstruction and quantification of IVUS images allow one to directly measure the length of a flap on longitudinally reconstructed images.[23] The risk of abrupt vessel closure may be increased by the presence of large moving flaps, long dissection membranes, or extensive medial tears that comprise more than 50% of the vessel circumference (onion skin shape). In addition, dissections on the free vascular wall (pericardial side) may indicate an increased risk as further antegrade or retrograde propagation through the vessel wall may not be constrained by side branches or surrounding muscle.[59,60] In addition, dissections and tears of the vessel wall following balloon angioplasty[16,17,20] hamper reliable quantitative angiographic assessment, which results in only reasonable correlation between QCA and IVUS measurements.

Finally, if a false lumen has been created and the operator is uncertain whether his guidewire is in the true or the false lumen, IVUS should be used for clarification. This may be particularly important when the guidewire position is lost and requires re-positioning. Identification of the true three-layered appearance of the vessel wall, less echogenic blood reflection (slow, highly echogenic blood reflection is frequently seen in the false lumen), and side branches taking off from the true lumen are extremely helpful in distinguishing the true from the false.[60]

Directional and rotational coronary atherectomy

Lesion selection for directional coronary atherectomy can be significantly facilitated by the use of IVUS. Ideally, such lesions are located in proximal or mid-coronary segments and show no or only deep calcium as well as a relatively eccentric plaque distribution. While superficial calcium hampers plaque debulking and increases the restenosis rate,[17,61] deep calcium may even increase the safety of the procedure by preventing deep cuts into the vessel wall.[18] Guidance of directional coronary atherectomy is facilitated by IVUS imaging as IVUS-derived knowledge about the spatial relation between side branches and the orientation of the plaque may then help to direct the atherectomy cutter correctly, thereby potentially reducing the frequency of deep cuts and minimizing damage to the non-diseased vessel wall.

Furthermore, various IVUS studies also suggested a direct relation between the residual plaque burden and restenosis rate.[62] Serial IVUS runs may help to maximize plaque ablation safely. This approach has been shown to be associated with a lower restenosis rate in both the ABACAS (Adjunctive Balloon Angioplasty following Coronary Atherectomy Study) trial[21] and the OARS (Optimal Atherectomy Restenosis Study) trial.[63,64] Volumetric IVUS evaluation[35] before and after the atherectomy procedure may be used to obtain a reliable quantification of both plaque ablation and luminal enlargement[27,55] and thus the efficacy of the intervention. For the time being this volumetric approach is mainly used in research, but might become clinically valuable if technical refinement would permit reliable online measurements.[23]

Information on the presence, extent, and depth of plaque calcification provided by IVUS[25] may be helpful in the decision to use rotational atherectomy.[65] Calcified lesions (maximum total arc of calcium > 180°) with superficial calcium that extends along at least 50% of the lesions' length are ideal candidates for rotational atherectomy.[28] We propose a very simple and practical approach: if the IVUS catheter cannot be advanced through a heavily calcified lesion, rotablation is indicated.

IVUS in coronary stenting

Benefit of IVUS

Stenting is currently the principal interventional technique for the catheter-based treatment of significant coronary stenoses. However, deployed stents are frequently radiolucent and difficult to visualize on the angiogram, whereas intravascular ultrasound provides a detailed, high-quality, cross-sectional visualization of the bright echoreflective metallic stent struts.[19,66–70]

Stent expansion and apposition (Fig. 21.5), and the changes in coronary arterial dimensions which occur during intervention, can be studied with IVUS in a manner which was not previously possible.[19,66] The use of motorized pullback devices allows measurement of the exact length of the segment to be stented, facilitating accurate sizing of stent length. The extent of atherosclerotic involvement of side-branches, bifurcations, and ostia can be examined with IVUS, while angiographic information is frequently ambiguous. In addition, IVUS can distinguish between different causes of angiographic (side branch) obstruction following stent implantation, such as plaque shift, spasm, obstruction by a stent strut, or disturbed streaming of dye; the latter is an artifact that mimics stenoses on the angiogram.

Based on the early work of Colombo et al,[19] insight into vessel and stent geometry provided by IVUS has been instrumental in developing the concept of optimal stent deployment by high-pressure balloon inflations inside the stent,[19,66,67,71] which significantly reduced the incidence of stent thrombosis and permitted stenting without anticoagulation. In the MUSIC

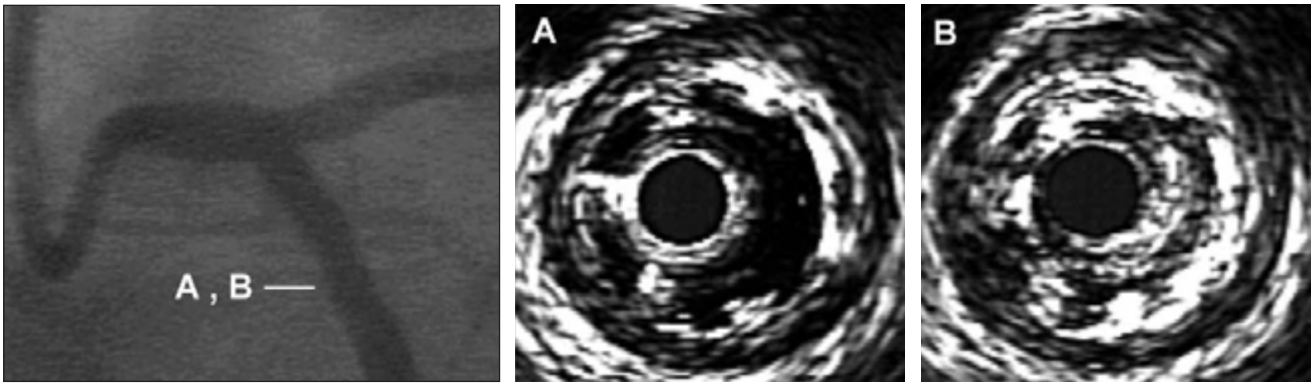


Figure 21.5
Malapposition of tubular-slotted stent identified with IVUS. Stent (bright structures) implanted in proximal left circumflex coronary artery. Malapposition (black space between stent struts and vessel wall) can be identified on panel (a) (left hand side). Note that the injection of dye (b) results in the opacification of this space, confirming the presence of stent malapposition.

(Multicentre Ultrasound Stenting in Coronaries) study,[72] this concept was applied in a non-randomized international multicentre registry, which demonstrated the feasibility and success of treating the patients with aspirin alone, leading to a restenosis rate as low as 10%. As IVUS measurements frequently result in the use of larger balloons for stent deployment or postdilatation, the final lumen dimensions following IVUS-guided interventions are often larger and frequently associated with a reduced restenosis rate.[73]

Various IVUS criteria have been suggested to judge the adequacy of IVUS guided interventions.[19,66,67] However, in clinical practice the IVUS demonstration of an absence of significant compromise of stent inflow or outflow, the absence of large edge dissections, complete stent-vessel wall apposition, and minimal stent cross-sectional area of > 80% of the mean reference lumen cross-sectional area or an absolute minimum stent cross-sectional area of more than 7.5 mm^2 [73] may characterize adequate interventional result following IVUS-guided stenting. The routine use of high pressures for the implantation of stents, without IVUS guidance has frequently been shown to fail to meet these or similar IVUS criteria[67,74] (Fig. 21.6).

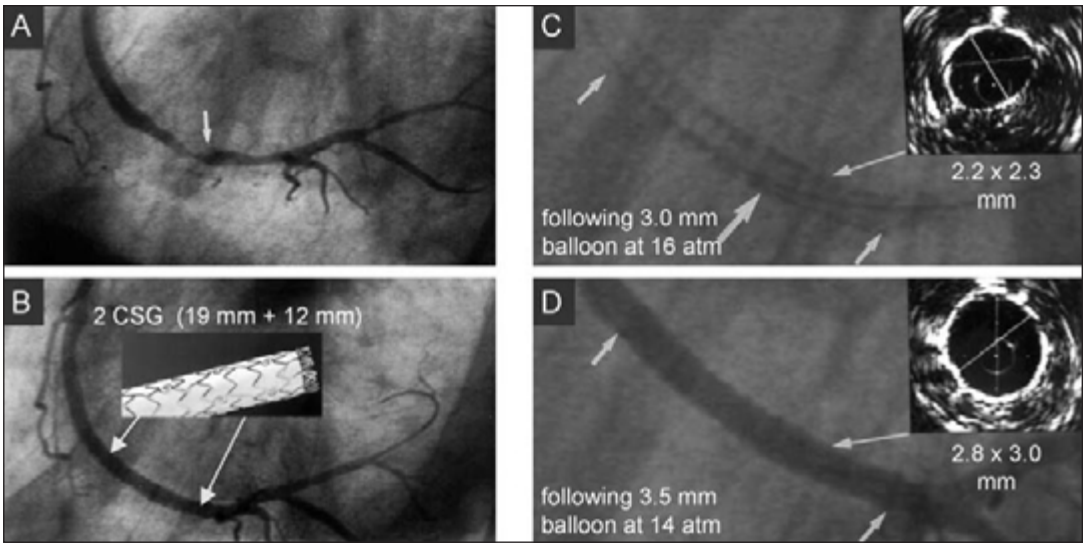


Figure 21.6
IVUS guidance of implantation of two synthetic coronary stent grafts. A thrombus-containing (arrow) right coronary lesion (a) was treated using two synthetic coronary stent grafts, and a 3.0 mm balloon at 14 atm (b). Panel (c) shows the radiographic image without dye. Overlap of the stent grafts (large arrow) was deliberately chosen to maintain patency of the distal branches. IVUS imaging (c, insert) revealed inadequate expansion of the distal stent graft (2.2 mm x 2.3 mm) which led to post dilatation with a larger balloon size (3.5 mm balloon at 14 atm). The final angiographic result and IVUS image of the post-dilated site (insert, 2.8 mm x 3.0 mm) are shown in panel (d). Small arrows indicate the entire stented segment in (c) and (d). Reproduced with kind permission of von Birgelen et al.[75]

The use of IVUS is particularly valuable in ostial and bifurcation lesions, diffuse atherosclerotic disease, calcified lesions, severe lumen narrowing of >70%, small vessels, diabetic patients, and if multiple, long, or novel stents[75] (Fig. 21.6) are implanted. In addition, IVUS is an invaluable educational tool which also permits the evaluation of complications, such as dissections and instent thrombus formation. Edge tears (Fig. 21.3) have been observed quite frequently with IVUS.[58] It has been suggested that they may require additional stent implantation to scaffold the flap, only if the dissection is large (occupying enough tissue to span the lumen diameter), long (>2 mm), and located at the free pericardial side of the vessel (which may increase the risk of further propagation due to lack of constraint by side branches or surrounding muscle).[59,60]

Instent restenosis

IVUS has clearly demonstrated that neointimal ingrowth is the main mechanism of late lumen loss and restenosis after stenting.[76,77] However, as a result of the larger acute lumen dimensions achieved, the minimization of elastic recoil, and the prevention of late unfavourable remodeling, stents have been successful in reducing restenosis rate.[72]

Various studies have demonstrated that IVUS helps to obtain a larger minimum in-stent lumen cross-sectional area. With balloon-expandable stents the thickness of neointimal ingrowth appears to be totally independent of the stent dimensions achieved.[78] Accordingly, a small in-stent cross-sectional area plays an important role as an 'amplifier of restenosis', as the same neointimal ingrowth results in a significantly higher relative reduction of lumen area in stents with a small as opposed to large lumen dimensions.

The restenotic process within stents can be studied with IVUS which visualizes both neointima and the metallic stent struts.[76,77,79] It allows one to distinguish between stents that were not sufficiently expanded during the initial implantation (suggesting the use of larger balloons) and stents with excessive neointimal response at follow-up.[79] The benefit of a follow-up IVUS examination may partly depend on whether the initial stent implantation was performed with IVUS guidance or not, as following IVUS-guided implantation stent underexpansion will be unlikely and luminal narrowing will be the result of neointimal ingrowth only. Not only is IVUS useful in evaluating the postinterventional result but it may help guide the treatment of in-stent restenoses with balloon angioplasty, rotational atherectomy, laser ablation, and brachytherapy, as it allows assessment of stent deployment and the amount of residual plaque and plaque protrusion.[80,81] In contrast, angiographic assessment of the results after treatment of diffuse instent restenosis is often hampered by haziness at the treated site.

Longitudinally reconstructed views and quantitative three-dimensional IVUS

IVUS permits the examination of the extent, distribution, and result of therapy of atherosclerotic plaques as it provides a unique tomographic visualization of both the lumen and vessel wall. However, in conventional IVUS there is a lack of an angiogram-like longitudinal visualization of the coronary segment examined. This is only provided by three-dimensional (3D) approaches[23,82–85] (Fig. 21.7). The option to longitudinally visualize an entire coronary segment is becoming integrated into standard IVUS systems. This display option avoids difficult mental conceptualization required when using conventional IVUS, provides a more detailed insight into the complex plaque architecture, and facilitates serial IVUS

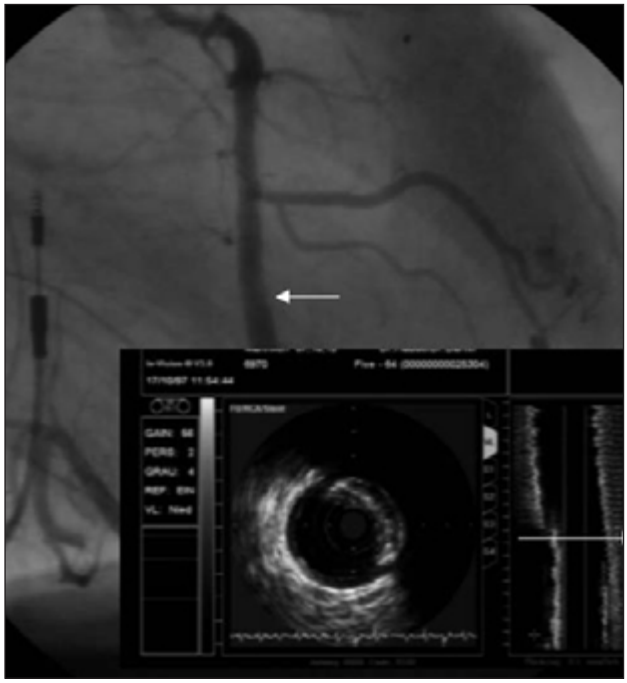


Figure 21.7
Cross-sectional and longitudinally reconstructed IVUS view. In this 79-year-old patient, we performed IVUS at follow-up after stenting the proximal mid segment of an important dominant right coronary artery (segment 2), which also subtended major parts of the LAD territory via collaterals (proximal LAD occluded). The cross-sectional IVUS image shows a heavily calcified plaque that was found using IVUS at the site of an angiographic filling defect (arrow) distal to the stent. On the longitudinally reconstructed IVUS view (Endosonics) the site corresponding to the cross-sectional IVUS image is indicated by an arrow. The 'angio–IVUS-assembly' represents a digital image-in-image recording obtained by use of the ECHO-MAP system (Siemens).

studies.[23] However, it should be noted that all commercially available 3D IVUS systems only provide artificially straightened 3D and longitudinal displays, whereas highly sophisticated 3D systems can be used to obtain geometrically correct spatial 3D reconstructions.[23,86,87]

In parallel with the progress in quantitative angiographic techniques which started with manual caliper assessment and finally reached computer-assisted methods, dedicated systems for quantitative 3D IVUS analysis have been developed.[88–93] These techniques reduce the analysis time and the subjectivity of manual boundary tracing,[94] and permit careful evaluation and accurate quantitative assessment of coronary segments.

Principles and processing steps

The IVUS images need to be acquired during a motorized pullback.[23,95] While non-ECG-triggered image acquisition can be associated with 'saw blade-shaped' image artifacts in longitudinally reconstructed views, ECG-gated image acquisition (during continuous or ECG-triggered stepping motorized pullback) can prevent such artifacts.[74,91,95,96] Image digitization can be performed on line or off line (from video tape) at a defined image digitization rate.

For any quantitative analysis, segmentation of the images has to be performed. This step identifies structures of interest by application of dedicated algorithms, which discriminate between the blood pool (ie, lumen), the vessel wall, and the adventitia. The quality of the reconstruction and the accuracy of the quantitative analysis are very sensitive to the characteristics of the algorithm applied. 'Acoustic quantification' uses an algorithm for statistical pattern recognition,[67,68] while 'contour detection systems',[88–93] apply a minimum cost algorithm to detect the lumen and external vessel boundary (ie, external elastic membrane, EEM). Specific shading and rendering techniques can be used to give reconstructed views a spatial aspect when displayed on the computer screen.[23] However, for the time being longitudinally reconstructed views without such rendering features are the most important.

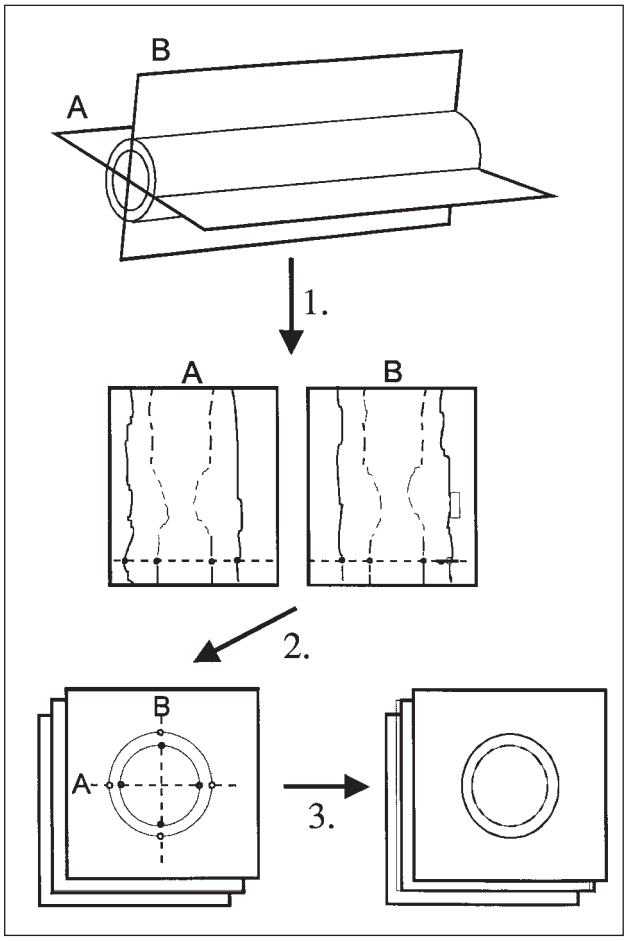


Figure 21.8
Scheme of computer-assisted contour detection in quantitative 3D IVUS. Detection of the contours corresponding to the lumen and external vessel boundaries is initially performed on two (or more) perpendicular longitudinal sections (a and b), reconstructed from the image data of the entire three-dimensional 'stack' of images. Edge information of the longitudinal contours is represented as points on the planar images, defining the centre and range of the final contour detection process.

Computer-assisted contour detection

The contour detection-based systems depend less on the image quality than acoustic quantification and permit reliable computer-assisted segmentation even with a suboptimal image quality.[88–91,93] In principle, online application of such systems is possible and has been demonstrated following ECG-gated image acquisition.[74] Contour detection may be based on three steps (Fig. 21.8). Firstly, the IVUS images are modeled in a voxel space, and at least two perpendicular longitudinal sections of the vessel segment are reconstructed.[88–91,93] In the second step, an automated detection of the longitudinal contours of the lumen and external vessel (EEM) boundaries is performed, based on the application of a minimum cost algorithm. In each individual cross-sectional image the contours of the longitudinal sections are depicted as points which guide the contour detection step in the cross-sectional IVUS images (third step). Finally, cross-sectional area (Fig. 21.9) and volume measurements[96,97] of both lumen and plaque can be derived.

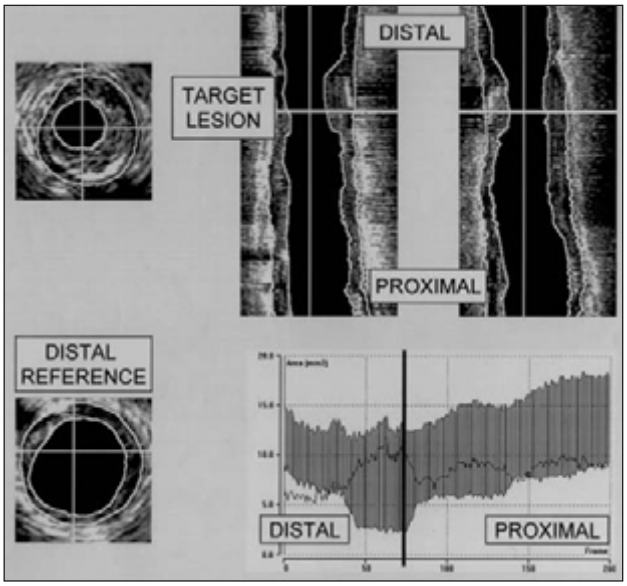


Figure 21.9
Coronary segment with inadequate compensatory vascular enlargement. This quantitative 3D analysis of a 'shrinkage' lesion shows clearly the smallest vessel cross-sectional area at target lesion site. Markers indicate that site on two reconstructed longitudinal views (right upper panels) and the display of the cross-sectional area measurements (right lower panels). Linear functions of the vessel and lumen cross-sectional area form the upper and lower boundaries of the grayish area, which represents the plaque cross-sectional area. Alternatively, the values of plaque cross-sectional area can be derived directly from a linear function (single black line), which partly overlaps the gray area. Reproduced with kind permission of von Birgelen et al.[53]

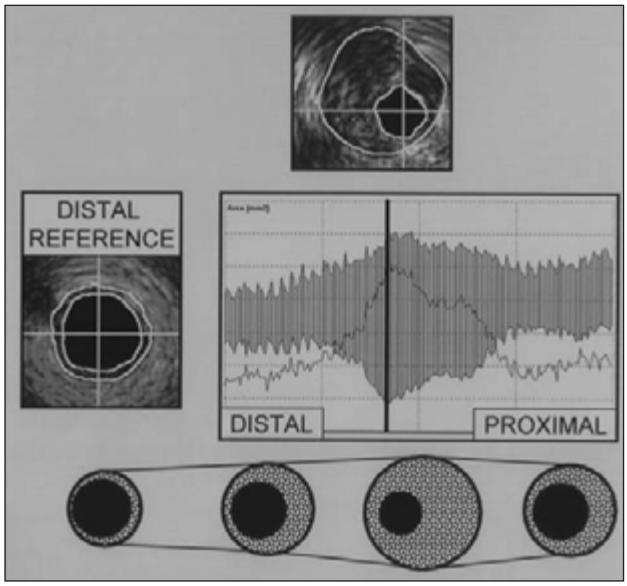


Figure 21.10
Adequate compensatory vascular enlargement lesion. The vessel cross-sectional area is larger at the target lesion site (upper panel) than at the reference site (left mid panel). Chart of IVUS measurements: linear functions of the vessel and lumen cross-sectional area form the upper and lower boundaries of the gray area, which represents the plaque cross-sectional area (right mid panel). The lower panel illustrates and underlines the principle of compensatory vascular enlargement. Reproduced with kind permission of von Birgelen et al.[53]

Validation and application of quantitative 3D IVUS

Quantitative 3D systems extend the measurement features of IVUS by longitudinal and volumetric measurements, and provide an automated quantitation of the plaque and/or the lumen. These measurements are frequently used for scientific studies.[53,55,77,93,97] It is therefore important to perform a validation study. Tubular phantoms and human coronary specimens can be used to perform a validation study in vitro, and show a good correlation with histomorphometry.[89,90] Intraobserver and interobserver measurements in vivo are probably acceptable.[90,93] By using ECG-gated image acquisition, the variability of the cross-sectional area measurements can be reduced even further.[91] In brief, contour detection-based measurements in 3D image data sets are the most accurate and are ideal for core lab activities and in the evaluation of scientific studies.[91,93]

There are various clinical scenarios where longitudinal reconstruction and/or computer-assisted measurements can be clinically helpful. Pre-intervention 3D examination of the coronary segment to be treated provides insight into the relation between plaque and side branches, which may permit appropriate stent sizing (diameter and length). The spatial geometry of coronary stents can be accurately reconstructed, and automated measurements of stent area facilitates the detection of stent underexpansion, as changes in stent lumen area during motorized pull backs are smooth, mostly gradual, and often difficult to recognize by the conventional use of IVUS.[70,74]

Rational for the use of IVUS in coronary brachytherapy

Plaque distribution as well as lumen and vessel dimensions can be examined with IVUS along an entire coronary segment. Accordingly, vascular remodeling can be studied by comparing the lesion with the reference vessel dimensions.[33–36] Previous IVUS studies have demonstrated that many significant coronary lesions reflect the process of adaptive 'Glagovian'

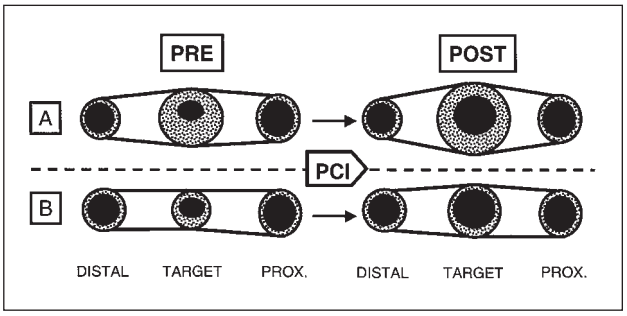


Figure 21.11
Rationale for the use of IVUS in brachytherapy. Lesions with compensatory 'Glagovian' (a) and inadequate 'shrinkage' remodeling (b) show considerable difference in the distance between the lumen centre and the external vessel boundary, both before (left panels) and after (right panels) percutaneous coronary interventions (PCI). In fact, IVUS is the only technique that allows the in vivo assessment of the true vessel dimensions and the remodeling state inside the catheterization laboratory. This information may be most useful in the context of β-radiation and could be used for dosimetry.

remodeling[32] (compensatory vascular enlargement with an increase in plaque burden) (Fig. 21.10), while other lesions show no or even inadequate compensatory vascular enlargement (or so-called 'shrinkage')[33,34,36,49–54] (Fig. 21.9).

Coronary lesions with an extreme difference in vascular remodeling show a great difference in the distance between the centre of the lumen and the external vessel boundary,[53] both pre-intervention and following percutaneous interventions (Fig. 21.11). Importantly, β-radiation shows a relatively steep dose-decline with increasing distance from the source, while γ-radiation shows a gradual decline. For γ-radiation, differences in vessel remodeling may be less important. But despite using the same β-source with the same in-situ time, lesions with very different vascular remodeling show large differences in β-radiation exposure at the external vessel boundary or the adventitia. In fact, IVUS is the only technique that allows the in vivo assessment of the true vessel dimensions and of vascular remodeling inside the cardiac catheterization laboratory, and has the potential to be used for dosimetry of brachytherapy, particularly in the use of β-sources. There is most likely a dose of β-radiation at which an adequate inhibition of restenosis (at least initially) may be seen with any coronary lesion. However, not to use IVUS may result in an overdose of a significant number of patients, at a time when long-term effects of this new therapy are basically unknown. Besides the potential application of IVUS for dosimetry (particularly β-emitting sources), IVUS is the ideal technique for the evaluation of the mechanisms of restenosis reduction by brachytherapy and its potential adverse consequences (eg: edge effects).[98]

Summary

IVUS is a catheter-based technique, which provides high-resolution cross-sectional images of both the coronary lumen and the vessel wall, far beyond the projection-dependent 'silhouette technique' of coronary angiography. The potential to meticulously evaluate coronary lesions of angiographically-uncertain severity and to perform serial IVUS examinations for guidance, device selection, and endpoint assessment of catheter-based interventions including brachytherapy, makes IVUS a practical clinical tool which significantly augments the information provided by standard angiography. Longitudinally reconstructed views, from the three-dimensional IVUS data set, can now be used in clinical practice. The combination of IVUS imaging and physiological data obtained from intracoronary Doppler or pressure measurements is practical and may further enhance the scope of IVUS.

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22

Physiological measurement of coronary blood flow

Andrew L McLeod and Neal G Uren

oduction

In the human heart, the ability of the resistance vessels to dilate or to constrict can only be assessed indirectly from measurement of coronary blood flow. The presence of epicardial coronary disease contributes additional resistance to blood flow and, with progressive obstruction, the ability of the vasodilated resistive vessels to accommodate this at times of hyperaemic stress is reduced.[1] The anatomical significance of epicardial coronary artery disease may be documented by analysis of coronary arteriograms. However, large intra- and inter-observer variability exist with visual inspection of arteriograms, and despite the use of computer-assisted edge-detection methods,[2] to reduce the error and inaccuracy of visual assessment,[1,3] poor correlations still exist with post-mortem evaluation of coronary stenoses.[4] Furthermore, there is a poor correlation between anatomical estimate of the severity of a coronary stenosis and any physiological measurement of the functional significance of the stenosis,[5,6] particularly with lesions in the range of diameter stenoses 50–90%, that is those of most interest in determining functional significance.[1]

Many of the problems relating to anatomical assessment occur because of the limitation of arteriography in reconstructing a three-dimensional lesion. Thus, the orientation of the vessel to the X-ray planes, stenoses at curvatures of the native vessel and asymmetrical narrowing lead to inaccuracy.[7] Because the effective resistance at the site of the stenosis is proportional to the fourth power of the radius, small changes in radius beyond the resolution of arteriographic assessment may cause larger changes in resistance, particularly in more severe stenoses. Problems also arise when describing the stenosis as a percentage of normal, as many adjacent 'normal' segments are affected by diffuse disease leading to an underestimation of stenosis severity. The use of intravascular ultrasound to document early atherosclerotic changes may indicate such disease in adjacent segments, but the problem still remains of predicting the functional significance of lesions. The eccentricity and irregularity of a lesion will determine the transtenotic pressure drop for a given luminal diameter due to flow separation and shear stress,[8,9] causing much variability for the same absolute diameter. With conventional arteriography these problems are compounded by variables which, with epicardial coronary diameter, determine myocardial perfusion such as mean aortic pressure (perfusion pressure), venous pressure, collateral blood flow, resistive vessel function in the distal vascular bed and intra-ventricular wall stress.[10]

For a true functional assessment of a coronary stenosis, measurement of its haemodynamic effect on a dynamic function such as coronary flow or pressure is required.

The determinants of coronary blood flow

Coronary blood flow was first measured by Benchimol in 1971 using a catheter based Doppler system,[11] and has since become widely incorporated into both diagnostic and interventional cardiac catheterization studies. The coronary flow reserve has been proposed as an objective measurement of the vasodilator capacity of the coronary resistive vessels, which regulate myocardial perfusion modulated by neural and metabolic influences. This was defined as the ratio of maximal coronary blood flow to basal coronary blood flow, ideally for a given perfusion pressure, by Gould in 1974.[12] Its validity has been confirmed and applied using different techniques such as coronary sinus thermodilution,[13] Doppler catheterization,[14] and positron emission tomography using pharmacological stress.[15]

The coronary vasodilator (flow) reserve has been widely used as a physiological measurement of the severity of a coronary artery stenosis, including all of its geometric characteristics.[10] The ultimate effect of a coronary stenosis depends on the degree to which the increased impedance to flow is compensated for by vasodilatation at the level of the resistive vessels. Thus, the coronary flow reserve (CFR) may be seen in terms of autoregulation: the ability of the coronary vascular bed to maintain coronary flow at a constant level in the presence of a potential decrease in coronary perfusion pressure at a constant myocardial oxygen demand.[12] Because of the non-linear relationship between translesional pressure gradient and stenosis severity, a progressive non-linear reduction in CFR is seen (Fig. 22.1).[16] In man, with the development of a 40% diameter stenosis or more, the coronary vasodilator reserve starts to diminish such that with a 85% diameter stenosis, the reserve is exhausted, that is the point at which autoregulatory vasodilatation is maximal.[17,18]

There are three variables which need to be taken into further consideration when measuring the CFR at a given point in time:

1 The coronary perfusion pressure,
2 The basal flow, which is largely dependent on myocardial oxygen demand (a product of heart rate, contractility and myocardial wall tension), and
3 The pressure–flow relationship during maximal vasodilatation, which is modulated by hypertrophy, loading conditions and heart rate (Fig. 22.2).

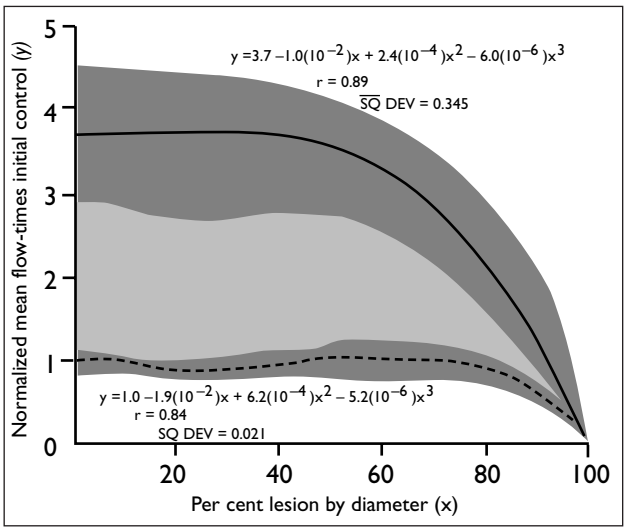

Figure 22.1
The relation of percent circumflex arterial constriction by diameter to resting mean flow (--) and hyperemic response (—) after intracoronary injection of Hypaque in 12 consecutive dogs. Flows are expressed as ratios to control resting mean values at the beginning of each experiment. The shaded area indicates the limits of the relation plotted for individual dogs. r = correlation coefficient. $\overline{SQ}$ DEV = mean square of deviations. Reproduced with permission from Gould et al.[12]

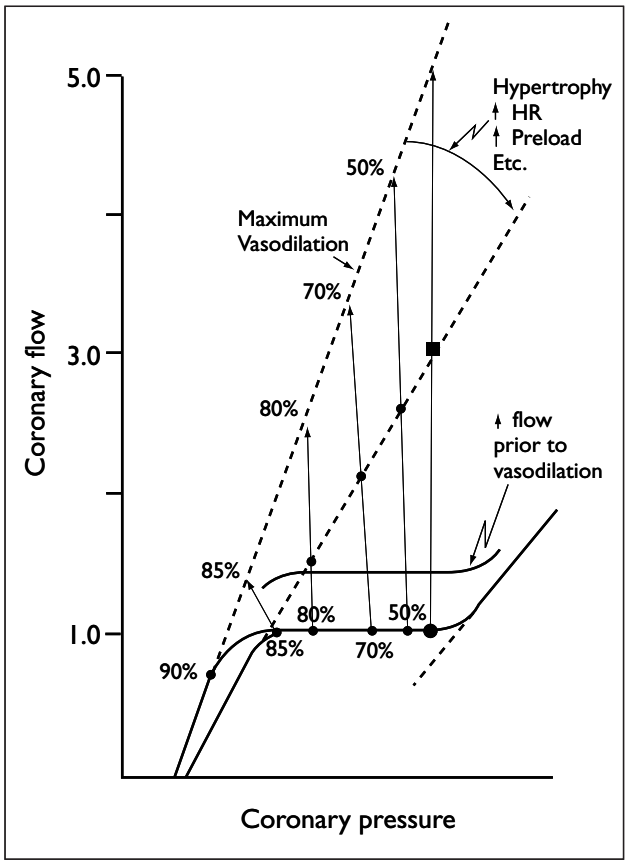

Figure 22.2
Complexities of the flow reserve concept. See text for details. Although some features of this figure would differ if coronary flow were expressed in absolute rather than relative terms,[4,5] the present formulation is more helpful for illustrating the points of greatest interest for techniques currently used in man. Reproduced with permission from Klocke.[1]

Other factors affecting coronary vasodilator reserve through an effect on maximal vasodilatation are blood viscosity and the extent of collateral flow which is difficult to quantify but which may be recruited by pharmacological agents.[10] Given the variability in the normal value of CFR because of these different determinants, a similar variability exists in deciding the threshold above and below which ischaemia may not or may occur.

In one study investigating the haemodynamic determinants of the CFR, atrial pacing led to a rate-related increase in basal flow but with no reduction in maximal flow at a rate of 120 beats/min.[19] A similar increase in basal flow was seen with volume expansion (an increase in preload), but with no effect on maximal flow. Increasing mean arterial pressure with handgrip caused a proportionate rise in basal and vasodilator flow and a maintenance of CFR. This confirms the importance of interpreting CFR measurements taking into account the haemodynamic conditions at the time of study.[20]

Measurement of coronary blood flow

Many different stimuli have been used to achieve maximal coronary vasodilatation in order to assess the CFR. Using atrial pacing,[21] intracoronary hyperosmolar contrast media or intravenous isoprenaline,[22] values of between 2 and 2.5 have been achieved, which is well below maximal vasodilatation.[1] With maximal exercise, coronary blood flow increases from 2 to 4 times control values.[1] However, such an increase in flow may not be maximal as it is possible to increase flow by another 35% in dogs after maximal exercise with dipyridamole.[23] This is evidence of the dissociation between vasodilatation due to an increase in myocardial demand and that due to a pharmacological stimulus.

The maximal coronary flow possible is probably the hyperaemic flow seen after a 20 second occlusion of an epicardial coronary artery at surgery which leads to a CFR of up to 6.3.[24] The CFR of 3.0 to 5.0 seen following pharmacological dilatation with intravenous dipyridamole,[25] with the addition of isometric handgrip, give the most easily obtainable maximal values in the non-invasive environment.

Methods for measuring myocardial and coronary blood flow in man are less accurate than in controlled animal models. However, in clinical terms, the major derivative is often what relative changes there have been in flow or perfusion, rather than absolute measurements of coronary flow. Until the development of the Doppler flow wire, measurement of coronary blood flow involved coronary sinus thermodilution,[2] and videodensitometry,[26,27] as methods to allow the estimation of regional coronary flow. However, significant technical limitations restricted their use to the research environment. The use of an intracoronary Doppler catheter to measure coronary blood flow velocity was developed at the University of Iowa in the mid 1980s.[3] The catheter consisted of a 20 MHz piezo-crystal reflecting ultrasound from red blood cells mounted at the top of a steerable 3F gauge catheter inserted over-the-wire into a coronary artery.[8,14] Using the Doppler equation, this allowed selective and repeated measurement of coronary flow and, like epicardial probes, these catheters had an excellent frequency response.[14,28] With this technique, the normal coronary vasodilator reserve was 5.0, with no difference reported with gender, age or study vessel.[28]

There was a small risk of injury to the coronary artery under study, compounded by the relatively unstable free-floating tip which could lead to a variable quality in the recordings. Another major limitation was the fact that measurements were taken proximal to any lesion of significance. This technology was thus superseded by the development of a Doppler wire which allowed successful measurement of the more representative distal coronary blood flow.

The Doppler flow wire

The 0.018-in and subsequent 0.014-in Doppler flow wire became available at the start of the 1990s.[29] The advantages of this wire were that coronary flow velocity could be measured both proximal and distal to a coronary stenosis, without significant interference in the cross-sectional area of the epicardial stenosis even in the presence a severe lesion. Because of its comparable handling characteristics to a regular floppy wire, the wire became established in interventional cases without the need for additional instrumentation.[30] The transducer positioned on the tip of the wire produces a 28° beam spread, range gated at around 5 mm from the tip, producing a sample volume area of 2.5 mm. The proximal end of the Doppler wire is connected to a rotary connector which connects to the Flowmap™ console (Cardiometrics, Mountain View, CA). Blood flow velocity is displayed with a predominant diastolic waveform and a smaller systolic waveform (in the left coronary artery). Coronary artery stenosis predominantly influences diastolic velocity parameters, whereas intramyocardial resistance mainly affects systolic flow. Good signals are dense, reproducible and regular shaped, with 'ghosting' and incomplete velocity envelopes indicating poor wire position (Fig. 22.3).

Blood flow is displayed on the Flowmap™ as maximal and average peak velocity (MPV and APV; in cm/s). Coronary flow velocity remains largely unchanged down the length of an

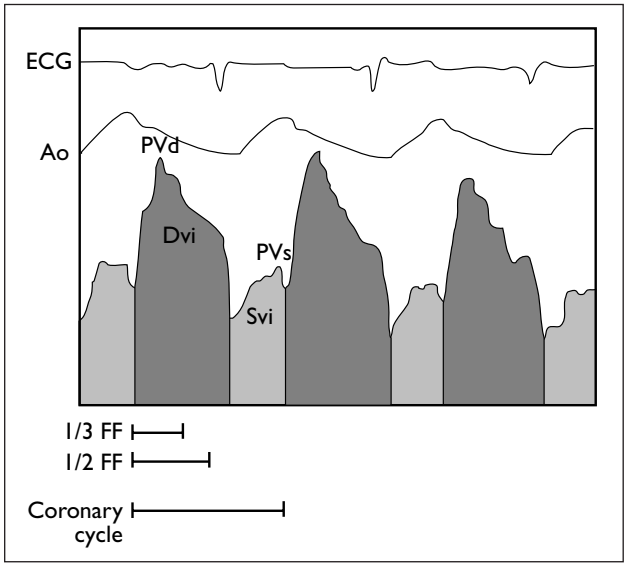

Figure 22.3
Schematic of digitized spectral profile. Ao = aortic pressure tracing; Dvi and Svi = diastolic and systolic velocity integral, respectively; ECG = electrocardiogram; $\frac{1}{3}$ FF and $\frac{1}{2}$ FF = first third and first half flow fraction, respectively. PVd and PVs = peak diastolic and peak systolic velocity, respectively. Reproduced with permission from Ofili et al.[31]

epicardial vessel although total blood flow will decrease according to the continuity equation.[31] During balloon occlusion, collateral blood flow can be identified by persistent antegrade or retrograde flow velocity signals. In the assessment of CFR in a diseased vessel, the distal wire tip should be at least 2 cm distal to the stenosis, minimizing post-stenotic turbulence. Baseline velocity is stabilized with intra-coronary nitroglycerine (200 μg) to reduce epicardial vessel spasm. Boluses of intracoronary adenosine (12–18 μg in the RCA, 24–30 μg in the LCA) or a steady-state intravenous adenosine infusion at 140 μg/kg per minute are used to achieve maximal hyperaemia.

The CFR (hyperaemic APV/baseline APV) indicates whether a stenosis is flow-limiting or not. A normal CFR, indicating a preserved capacity of resistance vessels to dilate, in patients with coronary risk factors and angiographically normal vessels is 2.7 ± 0.6.[32] A CFR2 suggests a flow-limiting lesion given the diminished ability of resistance vessels to vasodilate further. Several trials have compared directly measured coronary blood flow velocity using the Doppler flow wire with stress radioisotope perfusion imaging, concluding that distal CFR measurements have a predictive accuracy of 89% and above for an intermediate severity coronary artery stenosis.[33–36] The FACTS trial (Functional Angiometric Correlation with Thallium Scans) compared the flow wire, thallium scintigraphy and quantitative coronary angiography in assessment of lesion severity. The CFR was in agreement with thallium imaging 88% of the time, although quantitative angiography did not predict thallium imaging quite as reliably (57–63%).[37]

The distal diastolic to systolic velocity ratio (DSVR) may also be measured distal to a coronary lesion and should be greater than 1.8 in the absence of epicardial flow, although its postive predictive value for ischaemia is less than CFR. Significant stenoses are associated with distal DSVRs less than 1.3.[38–40] However, the predictive accuracy in determining lesion significance is less than with the CFR (85–88% concordance with thallium scintigraphy compared with 94–96%).[35,36] Another flow parameter, the Doppler-determined translesional velocity gradient is poorly predictive of SPECT thallium-201 imaging results with a 57% predictive value. [35]

Complications using the flow wire are rare but include dissection and vasospasm from the wire. Adenosine can cause transient AV block in approximately 2% of studies, which is usually asymptomatic, and steal-related angina in <1%. The CFR derived from APVs is sufficient for clinical decision-making without the need to calculate absolute coronary blood flow. However, given that changes in vessel diameter in this proximal segment may occur with vasodilatation, this diameter and thus the cross-sectional area of the so-called reference segment should be included in the estimation of coronary blood flow from coronary flow velocity.

The clinical application of Doppler flow measurement

After coronary angioplasty, the anatomical and functional success of the procedure may be difficult to assess due to plaque disruption and a loss of definition at the edges of the lesion dilated. Lesion dilatation improves the flow velocity parameters,[31,37,40–41] but a suboptimal CFR is observed in most patients, often despite a good angiographic result. This may be due to particulate microembolization or transient coronary resistive vessel dysfunction, but in many cases the reduced flow response reflects persistent abnormalities in vessel conductance. Intravascular ultrasound (IVUS) is a useful utility for accurately measuring the residual lumen area and documenting the presence of thrombus or unstable dissection. IVUS has demonstrated that the recurrence of symptoms in many cases after balloon angioplasty is not due to restenosis but results from an insufficient initial lumen enlargement.[42] Recent meta analysis of quantitative coronary angiography (QCA) after stent deployment has also demonstrated that residual minimum lumen diameter and per cent diameter stenosis are the strongest predictors of restenosis.[43] To quantify the flow-limiting implications of this anatomical disruption, Doppler flow-wire measurement may be used to determine the functional severity of the residual coronary stenosis and can be easily integrated into a standard interventional procedure (Fig. 22.4).

In the multicentre DEBATE I and II (Doppler Endpoint Balloon Angioplasty Europe)[44,45] and DESTINI (Doppler Endpoints Stent International Investigation)[46] studies, intracoronary Doppler during and after balloon angioplasty, with or without stenting, was used to determine the success of intervention. In the initial DEBATE study, the final per cent diameter stenosis and CFR after balloon intervention alone was compared with the clinical outcome at 6 months. A CFR of ≥ 2.5 coupled with a diameter stenosis of ≤ 35% (44 patients from 225) identified a population with a 6 month restenosis rate of 16% (compared to 41% in those with a suboptimal CFR and QCA) (Fig. 22.5).[44] Thus, flow-wire assessment coupled with QCA could predict a 'stent-like' result (similar to clinical restenosis of 14% in BENESTENT II)[47] compared to the converse, a higher incidence of recurrent angina or a positive exercise test at 1 month (47% vs 23%, $P < 0.01$) and target lesion revascularization at 6 months (34% vs 16%, $P < 0.05$). Furthermore, the absence of cyclic flow variations and the restoration of a normal CFR almost exclude the development of immediate complications after balloon angioplasty.[48]

The DEBATE I data were implemented into the design of the DEBATE II study which compared Doppler-guided balloon angioplasty with primary and bailout stenting, thus building on the evidence from the first study that a balloon angioplasty result with a CFR ≥ 2.5 with a diameter stenosis <35% may produce a stent-like result.[47] To date, 606

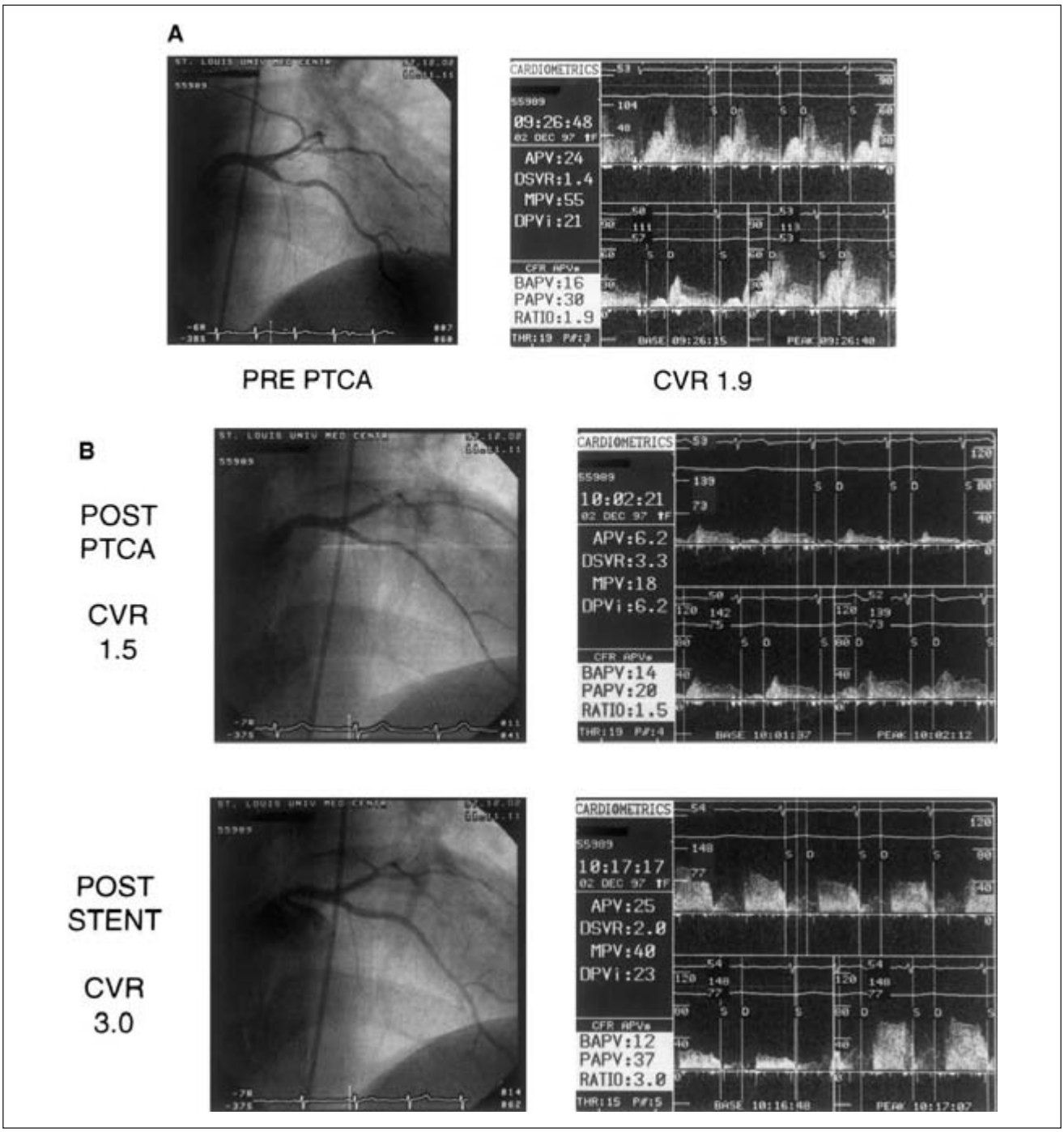

Figure 22.4

A, Absolute and relative coronary flow velocity data obtained during coronary stenting. Left, Pre-PTCA angiogram of left anterior descending artery (LAD) with a 60% proximal stenosis. Right, Flow velocity data obtained in LAD. Coronary flow reserve was 1.9. Basal average peak velocity (BAPV) was 16, peak hyperemic average velocity (PAPV) was 30. Velocity panel demonstrates continuous flow velocity signal (top) with the ECG and arterial pressure tracings. S and D demarcate systolic and diastolic periods based on the ECG. Heart rate (53 beats/min) and blood pressure (104/48 mmHg) are noted in the top left corner. The velocity scale is 0 to 90 cm/s. The lower section is split into the basal panel (left) and peak hyperemic panel (right). Numerical format as in the top panel. A reference vessel (ref, circumflex artery) coronary vasodilatory reserve was 2.9. rCVR was 1.9/2.9 = 0.66. DSVR indicates diastolic/systolic velocity ratio; MPV, maximal peak velocity; DPVi, diastolic peak velocity index. B, left, Angiographic frames demonstrating post-PTCA and poststent cineangiographic appearance. Right, Coronary flow reserve is 1.5 (rCVR = 0.52) after balloon angioplasty and 3.0 after stenting (rCVR = 1.0). Note that the BAPV remained relatively unchanged between 12 and 14 cm/s. Format for flow velocity data as in A. Reproduced with permission from Kern et al.[54]

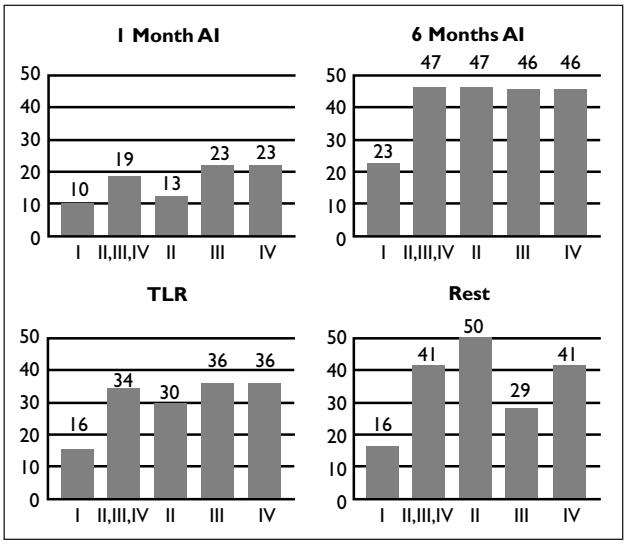

Figure 22.5
Percent incidence of recurrence of symptoms and/or ischemia (AI), TLR, and angiographic restenosis (Rest) in the four groups identified by predefined residual diameter stenosis and distal coronary flow reserve after PTCA. Values are percentages. Group I, n = 44, DS ≤35% and CFR >2.5; groups II+III+IV, n = 158, DS >35% or CFR ≤2.5; group II, n = 60, DS >35% and CFR >2.5; group III, n = 42, DS ≤35% and CFR ≤2.5; and group IV, n = 56, DS >35% and CFR ≤2.5. The percentage of events (1 month AI, 6 month AI, TLR, and rest, respectively), in patients with DS ≤35% or CFR >2.5 (combination of groups I, II, and III) is 15%, 39%, 26%, and 34%. Reproduced with permission from Serruys et al.[44]

tients have been randomized to the study with 95 undergoing direct stenting and 511 undergoing Doppler-guided balloon angioplasty after the first randomization. Of the latter group, 122 have required 'bailout' stenting with 376 having balloon angioplasty alone. The Doppler-guided patients fall into four separate groups depending on whether the CFR is ≥ 2.5 or <2.5 and diameter stenosis ≥ 35% or <35% (groups I–IV), and then undergo a second randomization to either stenting (186) or no further intervention (190). The 6 month rate for major adverse cardiac events (MACE; death, MI, target lesion revascularization) was 6% in the group having direct stenting in the first place. Of those having an initial Doppler-guided approach with second randomization, the additional stent subgroup of group I (CFR ≥ 2.5 + DS < 35%) had a 0% MACE, the additional stent subgroup of groups II–IV was 8%; the balloon subgroup of group I was 11% and that of groups II–IV was 21%. Thus, stenting lesions which are functionally optimal (CFR ≥ 2.5, DS < 35%) resulted in an even lower MACE rate. Stenting less optimal lesions after angioplasty (groups II–IV stent subgroup) gives a complication rate comparable to that of an optimal Doppler and angiographically-guided balloon result (group I balloon only).[45] These data argue strongly for provisional stenting where stents are used to improve on a functionally suboptimal result, achieving the same short-term clinical outcome as stenting as a primary strategy.

The DESTINI trial used a more liberal threshold of 2.0 and allowed for multivessel intervention compared to the single lesion approach of DEBATE II.[46] The preliminary results of the DESTINI study indicate that when optimal angiographic and physiological endpoints are achieved after PTCA, the early and late clinical outcomes are equivalent to those observed after elective stent implantation. However, only a minority (43%) of patients achieved the study endpoints, with the remainder requiring stenting. Despite this cross-over, a provisional stent strategy still has a lower cost than stenting all suitable lesions. The similarity of treatment outcome in DESTINI (contrary to the benefit of stenting in BENESTENT II,[47] for example) may be due to stents being implanted in all patients not meeting the QCA/CFR criteria (57% of patients stented), and not only in those patients requiring stenting as a bailout strategy (13% in BENESTENT II). Another reason could be the inclusion of bifurcation and longer lesions in DESTINI which may receive a smaller benefit from stenting.

Refining the coronary flow reserve

The use of the coronary flow reserve is limited by several variables already described. There is a technical limit to deriving reproducible coronary flow velocity measurements in all patients due to the tortuousity of vessels, the presence of side branches and diffuse coronary disease. In addition, there are several haemodynamic variables such as perfusion pressure, heart rate, left ventricular hypertrophy and collateral supply which result in a wide range of normal values and an uncertain threshold of definite normal and abnormal values (a CFR between 2 and 2.5). This has led to a greater current interest in the use of coronary pressure measurement and calculation of the fractional flow reserve as a more accurate measure of lesion-specific flow limitation.[20, 49–52]

For these reasons, and to allow the operator to control for the patient in question, the invasive equivalent of the relative flow velocity reserve has been proposed. The relative flow velocity reserve is the principle of myocardial perfusion imaging where hyperaemic flow (equivalent to isotope uptake during stress) in an area of myocardium subtended by a diseased vessel is compared with another area of myocardium assumed or known to be subtended by a vessel without a flow-limiting stenosis. On this basis, the relative coronary flow velocity reserve (rCVR) may also be calculated from the CFR as described above. The theoretical advantage of this is that it controls the index CFR value for the individual's 'normal' value in another vessel under the same loading conditions. This calculation is the same principle underlying

the fractional flow reserve (FFR), where the proximal coronary pressure acts as a denominator and control.

In one recent study, the rCVR was compared to the FFR and CFR in 24 target vessels using intracoronary adenosine, a pressure wire and a Doppler flow wire.[53] The correlation between rCVR and FFR was excellent ($r = 0.91$, $P < 0.001$) whereas the relationship between rCVR and CFR was poor ($r = 0.33$, $P =$ NS), perhaps indicating the refinement needed to improve the reproducibility of CFR but which requires additional instrumentation of another reference artery. This was confirmed in another study of 55 patients undergoing stenting where the rCVR increased from 0.64 ± 0.26 to 0.75 ± 0.23 after angioplasty to 1.00 ± 0.34 after stenting (CFR values in the intervened artery of 1.63 ± 0.71, 1.89 ± 0.55 and 2.48 ± 0.75, respectively).[54] In 17 patients with a $CFR_{stent} < 2.0$ (suboptimal by the DESTINI criteria), an increased basal flow was responsible. In eight patients with a $CFR_{stent} < 2.0$, a normal rCVR supported global resistive vessel dysfunction. In the remaining nine patients with a $CFR_{stent} < 2.0$ and an abnormal rCVR (16%), it was acknowledged that pressure-derived (lesion-specific) FFR was required to differentiate persistent obstruction from diffuse atherosclerotic disease or microvascular stunning.

Pressure wires

The evolution of pressure wires has included both fluid-filled (Grady™ (Schneider Europe, Bulach, CH) and Scived™ (Scimed Incorporated, Minneapolis, Minnesota) guidewire) and micromanometer-tipped (PressureGuide™ (Radi Medical Systems, Uppsala, Sweden), PressureWire sensor™ (Radi Medical Systems, Uppsala, Sweden)) designs. The fluid-filled guide wires have a diameter of 0.014 in, with slits just proximal to their radiopaque tip. The wire acts like a fluid-filled manometer, which transmits pressure to an external transducer. These were largely superseded in view of their tendency to overestimate pressure and the subsequent development of the high-fiedlity pressure monitoring systems (PressureGuide™, PressureWire™).

The 0.014-in PressureGuide™ has a micromanometer positioned just proximal to the radiopaque tip, and pressure measurements are obtained through fibreoptic transmission of energy. The more commonly used PressureWire™, also 0.014-in diameter, overcame the problems of torquability and detachability found with the PressureGuide™, with a high-fidelity, electronic sensor on a wire with handling equivalent to angioplasty wires. The signal transmits to an interface, which links with the Cath Lab monitoring system. The rival pressure wire (WaveWire™) and its interface (WaveMap™) is awaited.

The future holds for both combined flow and pressure measurements in a single angioplasty wire, of which designs are currently under development (Radi Medical Systems, Uppsala, Sweden and Cardiometrics Inc., Mountain View, CA).

Conclusions

The CFR is an attractive concept and not only allows a functional assessment of epicardial stenosis severity but also defines the vasodilator responsiveness of a coronary vascular bed, and thus coronary resistive vessel function. It is important to separate from the CFR the effects of other variables such as heart rate, loading conditions, contractility and hypertrophy. Several methodologies have been developed to measure coronary flow in the clinical environment, the best invasive technology validated being intracoronary Doppler catheterization. The development of a Doppler flow wire which has been incorporated into the cardiac laboratory for both diagnostic and interventional cases has improved the ability to measure functional lesion significance. The CFR may act as a more reliable predictor of long term interventional success and, furthermore, Doppler-guided angioplasty with additional stenting would appear to lead to the best clinical outcome when integrated into routine clinical practice.

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23

Transmyocardial and percutaneous laser revascularization and angiogenesis

Sarah C Clarke and Peter M Schofield

Transmyocardial laser revascularization

There are effective treatment options for patients with angina due to underlying coronary artery disease. In the vast majority of patients medication, coronary angioplasty/stenting or coronary bypass surgery can be used successfully. However, there is a growing number of patients who have severe angina which cannot be controlled by medical therapy and who are not suitable for conventional revascularization techniques due to the diffuse and distal nature of their coronary artery disease. It is for this group of patients that transmyocardial laser revascularization (TMLR) has been used in recent years.

Even before the introduction of coronary angioplasty and coronary bypass surgery, attempts at direct myocardial revascularization were made.[1] Needles were used to create transmural channels. This approach was developed with the background knowledge of the thebesian system and myocardial sinusoids in the hope that direct perfusion would occur with blood from within the left ventricular cavity. There was limited clinical benefit. Another approach was to encourage new vessel formation by the implantation of the internal thoracic artery directly into the myocardium.[2]

The mechanism of action of TMLR is still not clear. Suggested mechanisms include direct perfusion of the myocardium, angiogenesis, denervation and placebo effect. Currently, angiogenesis seems to be the most likely explanation for the symptomatic improvement.

Technique

Transmyocardial laser revascularization is usually carried out under general anaesthesia through a left anterolateral thoracotomy. The area of left ventricle to be treated is determined preoperatively from the coronary angiogram and myocardial perfusion scan (usually a nuclear scan, although positron emission tomography can be used). The laser probe is placed on the surface of the left ventricle and activated when the ventricle is maximally distended with blood (i.e. on the R wave of the ECG cycle) (Fig. 23.1). The density of the channels is usually about one every 1.0–1.5 cm^2. The original laser used was a high-energy carbon dioxide laser (the Heart laser, PLC Medical Systems, Massachusetts, USA) although more recently a holmium:YAG system (Cardiogenesis Corp, California, USA) has also been used. Bleeding from the channels stops either spontaneously or with finger pressure. The laser energy is absorbed by the blood within the left ventricle and this produces an acoustic image which can be seen on transoesophageal echocardiography. It is not necessary, however, to use this imaging technique routinely during the TMLR procedure.

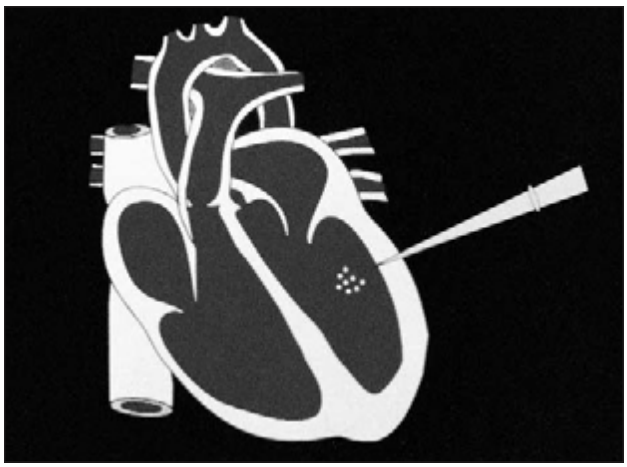

Figure 23.1
Transmyocardial laser revascularization. The laser probe is placed on the surface of the left ventricle and activated.

Results of trials

The early uncontrolled studies of TMLR suggested an improvement in symptoms of angina.[3] These patients had angina which was not controlled by medication, had evidence of reversible myocardial ischaemia and had disease which was not suitable for treatment using conventional revascularization techniques. They had a significant improvement in the Canadian Cardiovascular Score (CCS) for angina. Seventy-five per cent experienced a decrease of at least two CCS classes. However, there was a perioperative mortality of 9%. In a registry report from several European and Asian centres, again using a carbon dioxide laser, there was an operative mortality of 9.7%.[4] Around 50% of patients had an improvement of at least two angina classes.

Details of randomized controlled trials of TMLR using both the carbon dioxide and holmium:YAG laser systems have now been published. Prospective randomized trials using the carbon dioxide laser have been reported from the United States[5] and the United Kingdom.[6] In both trials, patients were randomized to either continued medication or TMLR plus medication. In the US trial, there was an improvement of at least two angina classes in 72% of the TMLR group as compared to 13% of the control group. However, there was a high cross-over rate from medical therapy to TMLR and the 12-month data only included 64 patients in the TMLR group and 23 in the control group from the 198 patients who were randomized. The results for the UK trial were less favourable. At 12 months, there was an improvement in two angina classes in 25% of the TMLR group as compared to 4% of the control group. Exercise capacity measured using treadmill exercise time and 12 minute walking distance, improved slightly in the TMLR group, although the difference between the two groups did not reach statistical significance. In this trial, there were no cross-overs and follow-up data collection was complete. The operative mortality was 5% and there was significant procedural morbidity. Wound or respiratory infection occurred in 33% of patients undergoing TMLR; 15% experienced transient arrhythmia (usually atrial fibrillation) and 12% developed left ventricular failure requiring increased diuretic treatment.

The ATLANTIC study randomized 182 patients to either continued medication or TMLR using the holmium:YAG laser plus continued medication.[7] At 12 months, there was a fall of at least two angina classes in 61% of the TMLR patients as compared to 11% of the control group. There was also an improvement in exercise tolerance test times. At 12 months exercise tolerance improved by a median of 65 seconds in the TMLR group compared to a 46 second decrease in the control group, and this was statistically significant. In this study, the operative mortality was only 1%. A further study using the holmium:YAG laser randomized a total of 275 patients.[8] Once again, there was symptomatic benefit following TMLR. A decrease in two angina classes occurred in 76% of patients treated with TMLR as compared to 32% of those treated with medication alone. The operative mortality in this study was 5%.

In summary, therefore, TMLR has been shown to produce symptomatic benefit in patients with angina which was not controlled by medication and who have coronary artery disease which is not suitable for treatment using conventional revascularization techniques (Table 23.1). There is usually an improvement in exercise capacity, although this is not always statistically significant (Table 23.2). These benefits must be weighed against the morbidity of the procedure as well as the perioperative mortality of 5–10% which has been reported in most of the studies (Table 23.3). There are therefore reservations regarding the widespread introduction of TMLR into clinical practice.

Table 23.1 Improvement by at least two Canadian Cardiovascular Score for angina classes at 12 months.

Reference	*TMLR group %*	*Control group %*
Horvath et al[3]	75	—
Burns et al[4]	50	—
March[5]	72	13
Schofield et al[6]	25	4
Burkhoff et al[7]	61	11
Allen et al[8]	76	32

Table 23.2 Improvement in exercise capacity at 12 months.

Reference	*TMLR group (secs)*	*Control group (secs)*
Burns et al[4]	+110	—
Schofield et al[6]	+70	+12
Burkhoff et al[7]	+65	–46

Table 23.3 Perioperative mortality with transmyocardial laser revascularization.

Reference	*Type of laser*	*No of patients*	*Mortality (%)*
Horvath et al[3]	CO_2	200	9
Burns et al[4]	CO_2	967	9.7
March[5]	CO_2	97	8
Schofield et al[6]	CO_2	94	5
Burkhoff et al[7]	Ho:YAG	92	1
Allen et al[8]	Ho:YAG	132	5

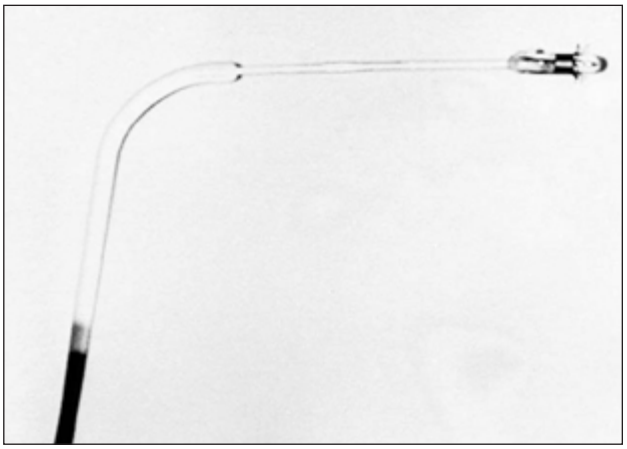

Figure 23.2
The equipment used for percutaneous myocardial laser revascularization: the aligning catheter (guiding catheter), the laser catheter, and the laser fibre.

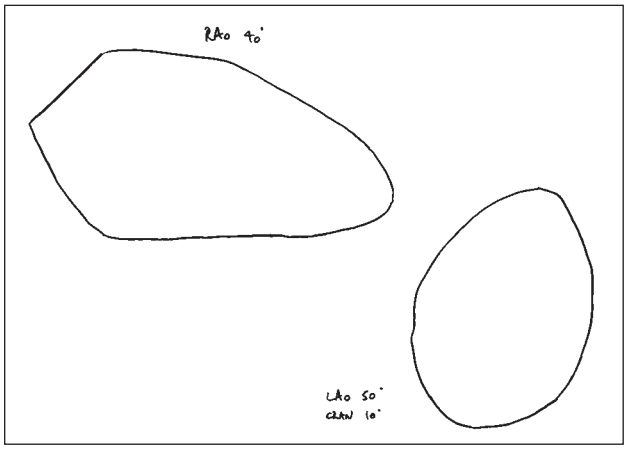

Figure 23.3
Tracings of the left ventricular outline at end diastole prior to the PMR procedure. The 40° right anterior oblique view and the 50° left anterior oblique view with 10° of cranial angulation are utilized.

Percutaneous myocardial revascularization

It is now possible to perform myocardial laser revascularization using a percutaneous, catheter-based approach. A holmium:YAG laser has been developed which enables laser energy to be delivered to the endocardial surface of the left ventricular cavity. From the patient's viewpoint, this approach is much more attractive. It does not require a general anaesthetic and there is no thoracotomy, with a reduction in the length of stay in hospital. After TMLR, the patients often need to stay in hospital for up to 10 days, whereas patients can normally be discharged from hospital 24 hours after percutaneous laser therapy.

Techniques

There are currently two systems available for catheter-based holmium:YAG laser therapy. Firstly, percutaneous myocardial revascularization (PMR, Cardiogenesis) and secondly, direct myocardial revascularization (DMR, Biosense, California, USA).

With the Cardiogenesis PMR system, access to the left ventricular cavity is gained using a 9F sheath introduced into the right femoral artery. There is a 'guiding catheter' that is advanced into the left ventricle. A 'laser catheter', which has a right angle bend towards its tip, is advanced through the guiding catheter. A 'laser fibre' can then be advanced through the laser catheter to make contact with the endocardium of the ventricular cavity (Fig. 23.2). While a biplane X-ray facility has advantages, the procedure can be easily carried out on single-plane equipment. It is important that the patient and the radiographic equipment do not move once the positions in which to work have been determined. The two views typically selected are the 40° right anterior oblique and the 50° left anterior oblique, usually with 10° of cranial angulation.

Once the guiding catheter has been advanced through the aortic valve into the left ventricular cavity, a left ventricular angiogram is taken in the two selected views. The outline of the left ventricular angiogram at end-diastole is traced onto acetate sheets which have been fixed over the viewing screens (Fig. 23.3). These outlines then act as 'maps' during the procedure. The region to be treated by PMR is determined prior to the procedure from the coronary angiogram and myocardial perfusion scan (usually by a nuclear scan or possibly using positron emission tomography). Using the Cardiogenesis equipment, it is possible to access the anterior, inferior or lateral walls of the left ventricle as well as the apical and septal regions. The guiding catheter is available in a variety of curves and the one selected depends on the size and shape of the left ventricular cavity as well as the area to be treated. The laser catheter, with its angled tip, is advanced through the guiding catheter into the left ventricular cavity. By manipulating the guiding catheter and/or the laser catheter, the region to be treated is accessed. The laser fibre is then advanced to make contact with the left ventricular wall. Contact can usually be felt, but can also be seen since the laser catheter is 'pushed back' from the endocardial surface of the ventricle. The right anterior oblique view is used to show contact with the inferior and anterior walls, and the left anterior oblique projection for contact with the lateral and septal walls.

Once contact with the endocardial surface is made, the laser is activated. This produces a channel approximately 3 mm deep into the myocardium. The laser fibre is then advanced slightly and reactivated, which results in a channel of around

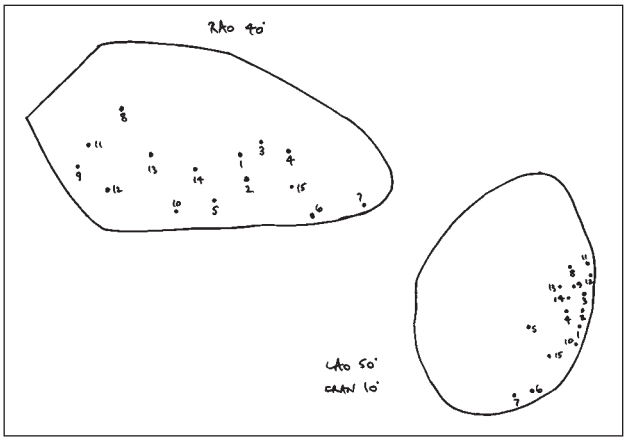

Figure 23.4
A map of the 15 channels created during the PMR procedure. The lateral wall of the left ventricle has been treated.

6 mm in total. The laser fibre is then withdrawn into the laser catheter and a different site selected by further manipulation. It is important to ensure, prior to the procedure, that the area to be treated is at least 8 mm thick using transthoracic echocardiography to reduce the risk of left ventricular perforation. In most patients, the apex of the left ventricle is thinner than the rest of the ventricle and most operators will use just one 'burst' of laser energy rather than two when treating the apical region. Once a channel has been created, the site is marked on the acetate sheets in the two views. Channels are usually created at about 1 cm intervals. When treating the anterior and inferior walls, the 'map' of the channels is usually best demonstrated in the left anterior oblique view, whereas for the lateral and septal regions the right anterior oblique view is preferable. In total, 10–15 channels are usually created in each of the areas which have demonstrated evidence of reversible myocardial ischaemia (Fig. 23.4).

The patient is given a bolus of intravenous heparin, usually 10 000 units prior to the procedure and the ACT is monitored to confirm adequate anti-coagulation. It is common to induce ventricular ectopics and non-sustained ventricular tachycardia during manipulation of the guiding catheter and laser catheter, although this is corrected by repositioning the catheter. Left bundle branch block can be induced during catheter manipulation and therefore a temporary pacing wire should be positioned prior to the procedure if the patient has pre-existing right bundle branch block. Currently, contraindications to PMR include the presence of left ventricular mural thrombus, severe peripheral vascular disease and significant aortic stenosis. The latter two exclusions cause problems with access into the left ventricular cavity. If the area to be treated by PMR is less than 8 mm thick, then caution should be exercised and two laser bursts should not be utilized.

The other catheter-based equipment which is currently in use is the Biosense DMR system. This technology enables left ventricular endocardial mapping and catheter-based intramyocardial treatment. The mapping system utilizes an ultra low magnetic field energy source and sensor-tipped catheter electrodes to locate the exact catheter position in three-dimensional space. The electromechanical maps generated by the system can be used to identify viable target zones for laser therapy based on the integration of endocardial electrical and mechanical signals. The system may also be used for the intramyocardial delivery of recombinant genes or growth factors directly into the ischaemic myocardium. Therefore, the endocardial mapping and guidance system integrates the identification of target zones (by electromechanical maps), catheter guidance (by location sensors) and intramyocardial therapeutics (by laser energy and/or local delivery of pharmacological therapy).

An electromagnetic field is generated from a triangular location pad, which is interfaced with a 7F deflectable tip catheter containing a miniature location system to provide a real-time three-dimensional electrical and anatomical map of the endocardial surface of the left ventricle. The system uses firstly a triangular location pad with three coils generating an ultra low magnetic field that decays as a function of distance from the coil and that codes the mapping space around the chest with both temporal and spatial distinguishing characteristics. Secondly, there is a stationary reference catheter with a miniature magnetic field sensor which can be located either within the right heart or externally on the body surface and thirdly there is a 7F navigation mapping catheter which has a deflectable tip and electrodes that provide unipolar and bipolar endocardial signals when inserted into the left ventricle. There is also a miniature passive location sensor within the mapping catheter and a work station (the NOGA unit) which processes the information from the mapping catheter and constructs the three-dimensional left ventricular image.

The location of the mapping catheter is gated to end-diastole and recorded relative to the location of the fixed reference catheter at that time, thus compensating for patient or cardiac motion. By moving the mapping catheter tip to multiple left ventricular endocardial sites, the NOGA system is able to reconstruct the left ventricular anatomy. Intracardiac electrical signals are acquired simultaneously and superimposed on the three-dimensional map. In sites where electrical activity is preserved, but mechanical activity is impaired, there is typically severe ischaemia associated with hibernating myocardium (Fig. 23.5). Endocardial zones with low electrical activity and impaired mechanical activity usually represent previously infarcted areas. Normal regional myocardial function is characterized by high electrical and mechanical activity.

The Biosense DMR laser system is currently undergoing clinical evaluation. The electromechanical maps can be used to help identify viable target zones for DMR laser therapy and the navigation system may be useful for catheter guidance during DMR. The distal laser catheter-tip location and orientation are detected in real time in order to achieve

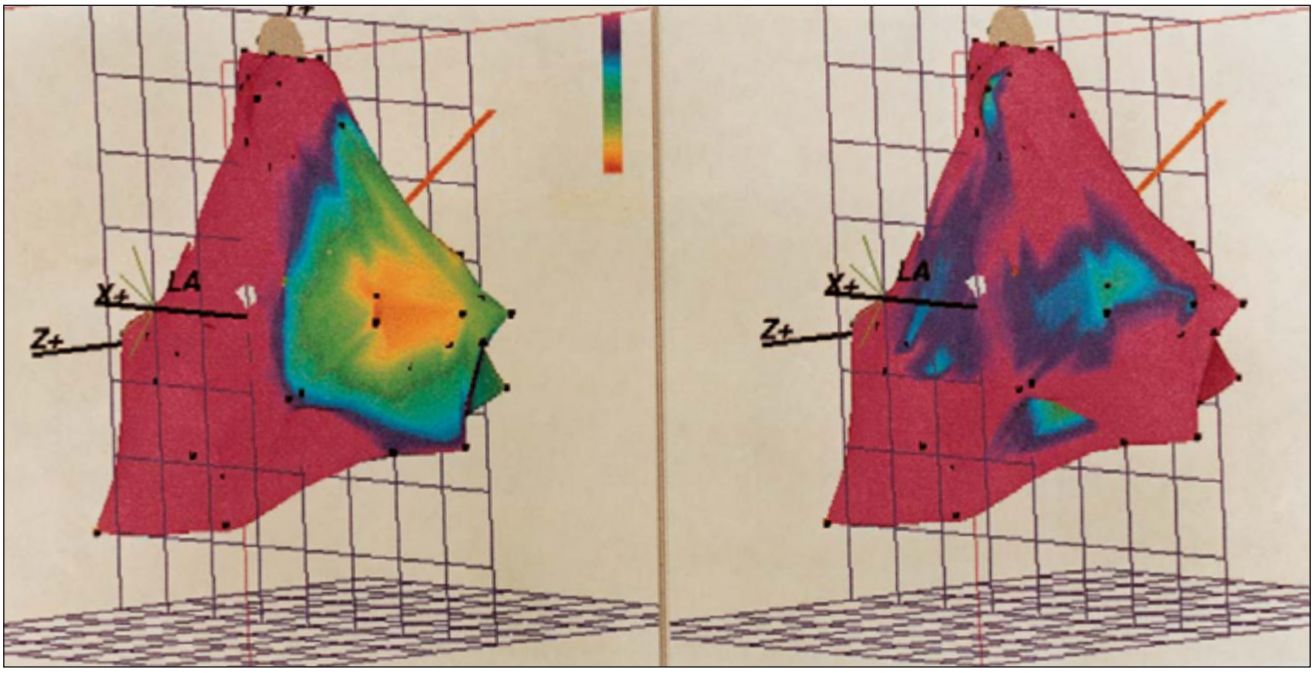

Figure 23.5
Electrical and mechanical maps taken prior to laser therapy. Graded from normal (purple) to abnormal (orange). There is a region of impaired mechanical activity affecting the basal part of the lateral wall of the left ventricle, which has preserved electrical activity. This region was the site for laser therapy.

optimal laser–tissue contact and guidance for viable treatment sites (ischaemic or hibernating myocardium). The exact location of the laser channels which have been created are indicated in real time on the electromechanical map. The endocardial mapping and guidance concept for DMR therefore integrates the identification of target zones (by electromechanical maps), catheter guidance (by location sensor) and the delivery of ablative laser energy (by laser system) with minimal X-ray radiation exposure.

Result of trials

A multicentre randomized prospective trial of PMR (Cardiogenesis) has now been completed—The PACIFIC trial.[9] The study recruited a total of 221 patients from 12 US sites and one UK site. All patients had angina which was refractory to medical therapy and had coronary artery disease which was not suitable for conventional revascularization techniques. Of the 221 patients, 111 were randomized to medication alone and 110 to PMR and continued usual medication. At 6 months of follow-up, there was a mean reduction of 1.4 CCS angina classes in the PMR group as compared to 0.125 in the control group ($P = 0.001$). There was also a 30% increase in treadmill exercise time at 6 months in the PMR group as compared with 5% in the control group, from baseline values of a little over 400 seconds ($P = 0.001$) (Fig. 23.6). There were no perioperative deaths in the PMR group, which is encouraging in light of the experience with TMLR. The morbidity associated with PMR was also low. Of the 110 patients who underwent PMR, one developed cardiac tamponade requiring percutaneous drainage and one developed atrioventricular block which required permanent pacing. Patients can usually be discharged from hospital the day after the PMR procedure, whereas the mean hospital stay for the TMLR procedure may be up to 10 days. The 12 month results from the PACIFIC trial have shown that the improvements in CCS angina class and exercise capacity noted at 6 months are maintained.[10]

There are further studies of PMR in progress, including a randomized prospective trial in which the control group undergoes a 'sham' procedure. The results of trials using the Biosense DMR system are also awaited with interest.

The preliminary results of a trial using the Biosense DMR system have been presented, but are as yet unpublished. The DIRECT trial randomized a total of 298 patients with refractory angina who were not suitable for conventional revascularization to one of three groups: placebo (mapping procedure only), low dose laser therapy (10–15 channels per zone) and high dose laser therapy (20–25 channels per

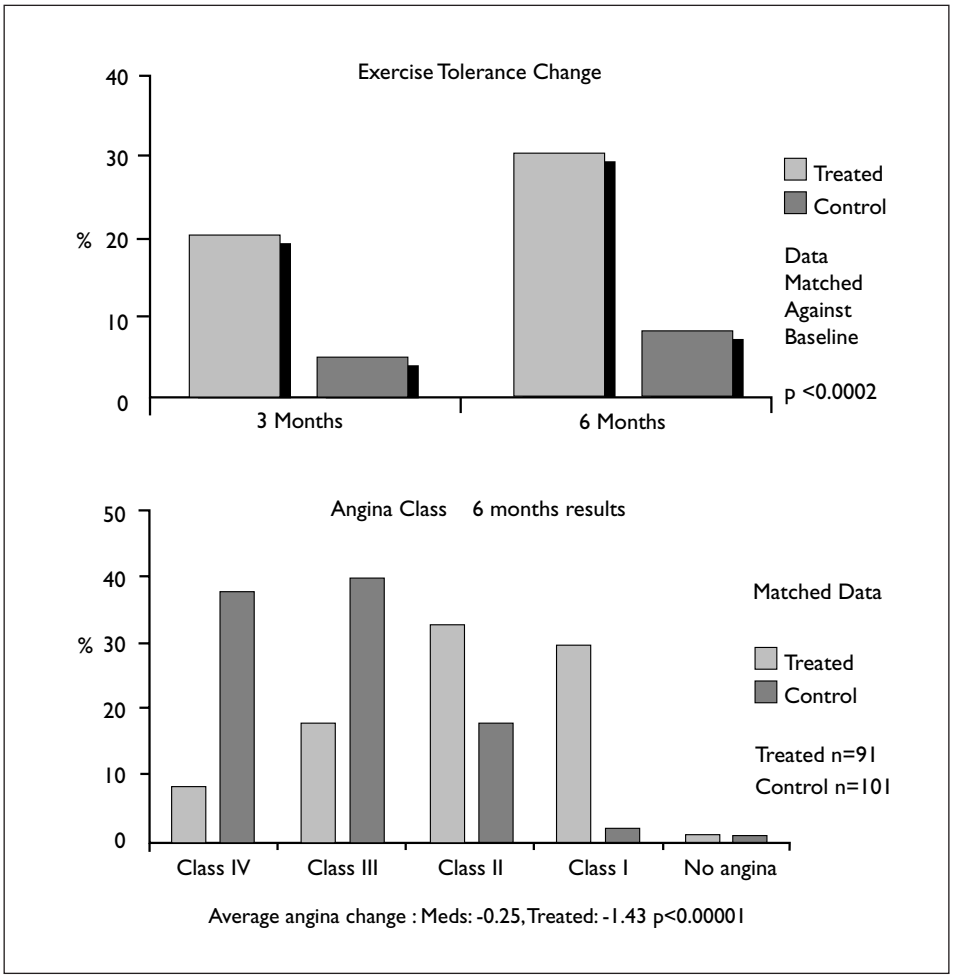

Figure 23.6
Results from the PACIFIC study. At entry, all patients had class 3 or class 4 angina. The angina class at 6 months is shown, demonstrating symptomatic benefit following percutaneous myocardial revascularization. The change in exercise tolerance at 3 months and 6 months is also shown. The baseline values in both groups was around 400 seconds.

zone). The patient was blinded to their treatment group. There was an increase in treadmill exercise duration at 6 months of 7% to 10% (baseline of 360–390 seconds), but no significant difference between the three groups. There was also an improvement in angina class at 6 months in all three groups, but again no difference between the groups. The authors have suggested that the changes demonstrated in symptoms and exercise capacity were due to the placebo effect. It is interesting to note that the increase in exercise duration on treadmill testing in the DIRECT trial (≤ 10%) was much less than that found in the PACIFIC trial (30%). There are substantial differences in the two techniques utilized for PMR and DMR.

If the techniques of PMR and DMR are proven to be effective, and the results of the PMR PACIFIC trial are most encouraging, then it is likely that the catheter-based approach will be preferred to TMLR in patients who have no other revascularization option. The techniques are much less invasive than TMLR and the early results suggest a much lower morbidity and mortality. TMLR may, however, still have a role to play—perhaps as an adjunct to coronary artery bypass surgery. There are many patients who have obstructed coronary vessels, some of which are suitable for bypassing grafting and some of which are not. In these patients, a combination of bypass grafting to some of the territories and TMLR to the remaining regions may be the preferred option. Similarly, PMR and DMR may be undertaken in conjunction with coronary angioplasty/stenting in the future—again with, for example, angioplasty/stenting to the left anterior descending artery and PMR of the inferior wall of the left ventricle since the right coronary artery had diffuse disease. It is likely that the use of PMR and DMR particularly, and possibly TMLR, will increase in the years to come.

Angiogenesis

Exogenous genes can be introduced into the heart muscle cells by the myocardial injection of plasmid DNA.[11] However, the efficiency of gene uptake and expression using this method is low. The potent angiogenic peptide vascular

endothelial growth factor (VEGF) could theoretically reduce heart muscle ischaemia by inducing new blood vessel formation (neovascularization). Its potency is such that even the small quantities produced following the injection of plasmid DNA encoding VEGF may be enough for a clinically useful biological effect. This approach has been used with apparent benefit in patients with severe peripheral vascular disease. More recently, myocardial injection of plasmid DNA encoding VEGF (via a thoracotomy) has been reported to improve anginal status and various parameters of myocardial blood flow in patients with ischaemic heart disease.[12] The requirement for thoracotomy precluded comparison with a placebo control group.

The process of angiogenesis is the growth of new vessels from pre-existing vascular structures. Angiogenesis allows the growth of new vessels from non-ischaemic to ischaemic tissue. The control of this process by pro- and anti-angiogenic factors is beginning to be understood. Furthermore, the differential effects of the known pro-angiogenic factors on the cells responsible for sprouting of new vessels—endothelial cells, smooth muscle cells and macrophages, have been well characterized. Gene therapy provides a new approach to initiate and sustain new vessel growth by altering the pro/anti-angiogenic balance by the expression of specific growth factors at the site of the ischaemia.

Vascular endothelial growth factor has attracted much interest as a potent angiogenic growth factor. It stimulates capillary formation and increased vascular permeability and its effects appear to be limited to endothelial cells. Hypoxia or ischaemia upregulate VEGF secretion but also increase VEGF receptor expression. These characteristics give VEGF an important theoretical specificity for therapeutic angiogenesis, since even if distant sites are exposed to VEGF DNA the risk of pathological revascularization is minimized.

Studies with VEGF proteins

Vascular endothelial growth factor protein has been used in animal models of chronic myocardial ischaemia and induced collateral growth into the ischaemic territory when given by direct injection into the coronary tree, myocardium or as surgically implanted coated beads. In the dog model of chronic myocardial ischaemia, Banai et al[13] demonstrated that VEGF 165 infused daily into the coronary artery increased collateral blood flow as well as the density of intramyocardial vessels 28 days after commencing therapy. Lazarous et al[14] compared fibroblast growth factor (FGF) and VEGF infusion into the left atrium of ischaemic dogs and found that only FGF was effective. The VIVA trial is the only clinical trial of VEGF protein to date. In this double-blind, placebo-controlled trial, intracoronary followed by intravenous VEGF 165 was infused in 178 patients with intractable angina. No significant differences occurred in treadmill exercise time or angina class. Treatment was not associated with increased mortality or carcinogenesis.

Studies using plasmid vectors

Although a number of vectors and routes are available to deliver and express genes in the myocardium, those receiving most attention at the moment are plasmid vectors given by intravascular and direct intra-myocardial injection. The advent of a plasmid vector to induce a sustained local production of VEGF at the site of delivery avoids the need for repeated administration. There have been uncontrolled clinical trials using naked plasmid DNA encoding VEGF 165, which did not have any form of control or blinding.

In the trial involving patients with ischaemic heart disease,[12] 125 μg of plasmid encoding VEGF 165 was injected into the myocardium of five patients with intractable angina via a thoracotomy. Two months later, there was a reduction in angina frequency in all patients. This was associated with an improvement in myocardial perfusion assessed by nuclear myocardial perfusion imaging and in the angiographic collateral score. There was no retinal neovascularization and no report of tumour development in this small group of patients.

Although the early reports show promise, there is clearly a need for well controlled prospective randomized trials of FGF and VEGF in patients with severe angina due to advanced coronary artery disease which is not suitable for conventional revascularization. The catheter-based systems used for PMR and DMR can also incorporate a 'delivery catheter' which permits the intramyocardial injection of angiogenic proteins or plasmid vectors. In animal models it has been shown that TMLR leads to local vascular growth as early as 2 weeks after treatment.[15] It is therefore possible that in the future PMR and DMR will be used in conjunction with the local intramyocardial delivery of angiogenic growth factors.

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24

Coronary intervention and the cardiac surgeon

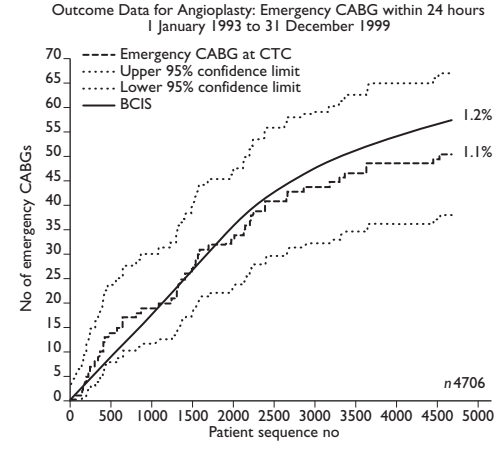
John AC Chalmers and David R Ramsdale

The ability to treat coronary artery disease has expanded incredibly in the last decade resulting in increased public demand and medical workload. Recent advances in interventional cardiology have had a substantial impact on cardiac surgery and many patients with coronary artery disease previously treated surgically now undergo percutaneous coronary intervention (PCI) including percutaneous transluminal coronary angioplasty (PTCA) and intracoronary stenting. Consequently, cardiac surgeons now see few elective patients requiring single or double grafts for discrete disease and accept that the disease process in patients now referred for coronary artery bypass surgery (CABG) is frequently more severe and diffuse in nature than previously.

Although PCI has developed dramatically over the last 20 years, the cardiac surgeon has continued to play an important role (albeit a changing one) in supporting the interventional cardiologist who may be performing elective coronary intervention or emergency procedures for acute coronary syndromes including primary PTCA/stenting for acute myocardial infarction. Moreover, close cooperation has become even more important when carefully planning complex procedures in high risk cases, in patients who have already undergone CABG surgery and in those undergoing hybrid procedures when minimally invasive cardiac surgery is combined with PCI. Finally, as new pharmacological agents have become available to reduce the incidence of thrombotic complications after PCI, the risk of severe bleeding must be overcome in the event of a complication during PCI which requires emergency CABG surgery.

Joint pre-operative assessment by cardiologist and cardiac surgeon

Given the importance of surgery in the management of PCI complications, how involved should surgeons be in the initial decision making and patient consultation?



STENTS (%)	1993	1994	1995	1996	1997	1998	1999
National	6	14	28	46	60	69	79
Local	3	9	13	40	77	75	75

Figure 24.1
Emergency CABG following angioplasty at the Cardiothoracic Centre, Liverpool and percentage of cases receiving stents during the period 1993–99. CTC, Cardiothoracic Centre Liverpool; BCIS, British Cardiovascular Intervention Society.

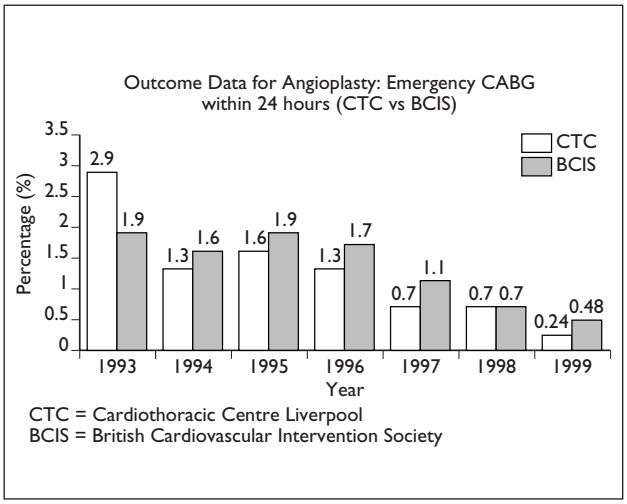


Figure 24.2
Reduction in urgent CABG requirement 1993–99 at the Cardiothoracic Centre, Liverpool.

In the early years, surgical consultation with all patients undergoing PTCA was considered both necessary and appropriate in view of the not insignificant (2–5%) requirement for emergency CABG surgery. However, with the advent of new improved technology such as modern stents and anti-platelet agents, experienced interventionists have very low complication rates and full surgical cover and consultation as a routine is no longer required. In our own institution (0.24% emergency CABG rate within 24 hours in 1999) (Figs 24.1 and 24.2), this is seldom now requested. The frequency with which cardiac surgeons need to be fully informed of the details of the case is as much dependent on the closeness of the working relationship and degree of trust between the interventionist and the surgeon as on the experience of the interventionist. Once this trust is established, it becomes accepted between parties that for high risk cases (for example, last remaining vessel, three-vessel disease and poor left ventricular function) appropriate consultation and agreement on treatment strategy between cardiologist and surgeon will take place in advance of the procedure and especially if full open theatre cover is requested (Table 24.1). In such cases, the details of this agreement on strategy and an assessment of risks of both PCI and emergency CABG surgery must be discussed with the patient and the next of kin before proceeding.

Important issues such as the presence of significant carotid or peripheral vascular disease, history of previous stroke, lack of conduits, co-existing comorbidity, blood cross-matching problems and the details of any previous CABG operation should lead to a pre-emptive discussion between cardiologist and surgeon (Table 24.2). It would be deemed unacceptable for inexperienced interventionists or those unfamiliar with the cardiac surgeon's skill and working practices simply to assume that emergency bail-out will be provided without prior discussion of the case. Indeed, patients may wrongly interpret the surgeon's involvement as indicating tacit approval of the intervention policy itself, which may not be the case and may result in potentially embarrassing legal and ethical problems.

Table 24.1 Cases to be discussed with surgeon prior to intervention.

Case considered high risk by cardiologist – request for cover: poor LV function, complex bifurcation stenosis involving large side branch
'Last vessel' – alternative surgical option? Cardiopulmonary standby?
Unprotected left main – cardiopulmonary standby?
Previous CABG where emergency salvage would be requested
Patients in whom clinical examination as in Table 24.2 is unsatisfactory (e.g. poor conduits)

How readily available should surgical cover be?

Despite technical advances in the 1990s, immediate surgical revascularization may still be required in 0.5–2% of cases (Figs 24.1 and 24.2). In recognition of the low incidence of complications and safer PCI with stenting, arrangements for surgical cover have become more informal between colleagues working closely together. A 'next available theatre' policy is now common practice in institutions with multiple operating suites – the majority of cases being referred only when emergency CABG surgery is required. This type of policy is pragmatic, recognizing the inefficiency and expense

Table 24.2 Pre-intervention assessment: important factors in the event of emergency CABG.

Adequate conduit? History of DVT; varicose veins; previous vein surgery; appropriate lower limb examination
Stroke risk – history of stroke; TIAs; carotid bruits – if +ve carotid doppler ultrasound study is indicated
Previous CABG – PVD*? Adequate femoral arteries for institution of emergency bypass
*PVD-peripheral vascular disease

of 'full formal standby' despite the apparent benefits for a small fraction of patients. However, as formal and flexible standby facilities have not been directly compared it is difficult to be certain whether any disadvantage may accrue from these more flexible arrangements. Ideally, the aim should be to achieve emergency revascularization within 90 minutes of irreversible acute vessel closure occurring as a complication of PCI. Careful audit should be performed in this situation in order to ensure best practice.

Who should have surgical cover for PCI?

Generally, access to emergency CABG should be available for all patients undergoing PCI other than for those individuals who have been prospectively agreed not to require surgical cover. These might include patients who are considered inoperable, those with severe comorbid conditions (e.g. malignancy), those in whom surgery is deemed inappropriate (e.g. severe cardiogenic shock post MI) or likely to be of little benefit (Table 24.3).

On-site versus off-site CABG surgery

The current low requirement for acute surgical intervention has led to calls for cardiologists to 'declare their independence from surgery'.[1] Although many centres in Europe and North America routinely perform angioplasty without on-site surgical back-up relying on transfer protocols, others transfer patients who are deemed to be at higher risk of complications to a unit with on-site cover.[2] Whether PCI is necessary in some of the remaining low risk patients, especially those with few symptoms, is questionable as there is little evidence of superiority over medical treatment. Nevertheless, a good correlation between the clinician's assessment of risk and outcome has been demonstrated.[3]

Currently, the majority of PCI in the UK and USA is performed in centres with on-site cardiac surgery and this should remain the gold standard despite reports of low complication rates in centres without that facility.[4,5] Although the incidence of emergency CABG following PTCA has steadily diminished over the last decade, the total potential burden of providing surgical cover and salvage for abrupt closure has not receded to the same extent due to widening indications for and access to PCI.[6–8] The application of PTCA (without stenting) to multivessel disease, for example, increased the risk of failure and it has been demonstrated that patients with multivessel disease have an increased mortality risk after CABG performed for failed PTCA. Wang et al reported a 21% operative mortality following failed PTCA in multivessel disease with an associated twofold increase in shock as compared to single vessel disease cases,[6] and multivessel disease has been shown to be an independent predictor of death[9] associated with an increased need for intra-aortic balloon counterpulsation and anti-arrhythmic therapy.[10]

It is important to plan for the worst outcome of PCI – cardiac arrest requiring cardiopulmonary resuscitation. The proportion of patients requiring cardiac massage until institution of bypass has increased over the years and these patients are unlikely to survive hospital transfer.[11–13] Carey et al reported a 25% incidence of such patients in their retrospective review of emergency surgery within 24 hours after PTCA.[11] Despite immediate on-site surgical intervention, these patients suffered a 32% operative mortality and 47% hospital mortality. Equivalence of theatre access times has been cited to support off-site PCI and although in the majority of patients this does not make an appreciable difference, in the event of cardiac arrest and massage resuscitation, the catheter laboratory can be used as an impromptu operating theatre. This option is not available without on-site surgery. If the decision is made to perform any PCI without on-site surgery, then the associated implications, risks and contingency plans should be made clear to the patient prior to obtaining consent for the procedure.

Table 24.3 No standby necessary.

Patient refuses surgery unequivocally: accepts consequences
Surgeon refuses case: unacceptable risk, vessel ungraftable
Non-surgical: comorbidity – cancer, chronic obstructive airways disease
Non-dominant RCA
Small territory at risk
Total occlusion of RCA with collateral flow into distal RCA from left coronary artery
Abrupt coronary artery closure considered less dangerous than coronary artery bypass surgery

Emergency CABG surgery following PCI

The principal risk of PCI is acute ischaemia progressing to acute myocardial infarction following vessel occlusion or

dissection. The decision to recommend surgical management is based on the realization that the situation cannot be rescued by catheter-based techniques and that emergency CABG is likely to restore coronary flow to ischaemic territory and thus prevent or limit myocardial damage. As the surgeon's role in patient selection is largely passive, it is imperative that patients deemed appropriate for PCI are all carefully assessed by cardiologists prior to intervention. Risk assessment should include conduit availability and the presence or absence of significant carotid and peripheral vascular disease or other systemic disease including significant pulmonary or renal impairment. Patients who have previously undergone CABG surgery are difficult cases to revascularize quickly and the strategy for dealing with an acute complication should have been discussed with a specific surgeon if at all possible.

The ability to prevent myocardial damage by emergency CABG is actually disappointing with myocardial infarction (MI) rates reported in 20–50% of cases depending on whether ECG or enzyme criteria are employed.[14–19] The success of any myocardial salvage strategy is directly related to ischaemic time prior to flow restoration. In a report from the Mayo Clinic, the median time to complete reperfusion (that is, from arrival in theatre to removal of the X clamp) was 135 minutes.[20] Bail-out stenting following acute vessel occlusion after PCI has been shown to reduce the rate of emergency CABG; however, the rate of Q-wave-MI is reduced only when successful stenting is achieved within 45 minutes of vessel closure.[21] All means available to protect the heart should therefore be instituted promptly in situations of angioplasty failure with on-going ischaemia and/or haemodynamic instability.[22–25] If severe stenoses become acute total occlusions without being crossed by a guidewire and acute myocardial ischaemia is evident, a surgeon should be requested to organize emergency CABG surgery immediately whilst attempts are continuing to cross the occlusion with different guidewires. In the event of a successful crossing, the case can usually be rescued by PTCA and stent implantation and the surgical team can stand down once the situation is stable again. Prolonged attempts to rescue the case before calling for surgical help are likely to compromise the patient further and only delay effective revascularization. In the pre-stent era, antegrade perfusion catheters were shown to be helpful in decreasing the extent of ECG changes and to result in more haemodynamic stability, but stent implantation has generally superseded perfusion balloons for dealing with acute occlusions as a result of dissection or bulky plaque prolapse or recoil. Just occasionally a deflated balloon catheter left across an occluded vessel can help maintain distal coronary flow until the vessel is successfully grafted as long as the blood pressure is adequately maintained. Every attempt should be made to maintain haemodynamic stability prior to emergency CABG surgery and intra-aortic balloon counterpulsation should be performed promptly, especially if acute ECG changes persist.

Table 24.4 Determinants of mortality in emergency CABG.

Unstable angina
Diabetes mellitus
Cardiogenic shock
Cardiac massage
Ongoing ischaemia
Time to reperfusion
Multivessel disease
Older age
Left ventricular function

Although a number of factors seem to be associated with a poor outcome after emergency CABG (Table 24.4), pre-operative haemodynamic instability and cardiogenic shock continue to be the major determinants of operative mortality.[6,24,26,27] Boylan et al reported an increase in mortality from 1.4% to 28% in patients with pre-operative shock.[26] Intra-aortic balloon counterpulsation (IABP) and/or percutaneous cardiopulmonary bypass[28] may allow stabilization of the patient's condition, although the former has little effect in reducing mortality in patients with hypotension or cardiogenic shock.[22,26,27] Prophylactic percutaneous cardiopulmonary bypass in high risk cases does not improve procedural success or reduce complications, except perhaps in patients with severely depressed left ventricular function, and morbidity in such cases may be increased over those afforded standby support.[28,29] However, although cardiopulmonary bypass does not reverse myocardial ischaemia in acute coronary occlusion, prompt mechanical support may nonetheless reduce mortality by 25%.[28,30–32]

Of course, not all patients with acute coronary occlusion will require emergency CABG, particularly if there is no myocardial ischaemia, the occluded vessel is very small or if the ischaemia is caused by distal embolization of friable material within old saphenous vein grafts. Some patients may have already been considered too high risk for surgical intervention and in these circumstances medically managed myocardial infarction may be calculated to be the lesser risk.

Surgical technique during emergency CABG for PCI complications

If emergency CABG is required the prime goal is prompt and complete revascularization. If necessary, bypass can be instituted and surgery performed in the catheter suite. The surgical technique and conduit selected will depend on the haemodynamic status, preference of the surgeon and the individual

circumstances of the case. Typically cardiopulmonary bypass will be required although more recently off-pump techniques have been used in haemodynamically stable patients.

Blood cardioplegic techniques represent the current state of the art, certainly for elective CABG.[33] However, during emergency CABG, there appears to be little benefit accrued by using any particular cardioplegic technique, and cross clamp time and the number of vessels bypassed do not appear to influence outcome either.[6,10,22,26,27] Confounding factors, however, may be small numbers in individual reports or non-reversibility of damage inflicted prior to surgery. More recent developments such as substrate-enhanced blood cardioplegia[33] and high-dose beta-blockade with Esmolol[34–36] may offer alternative strategies in the future.

Traditionally, saphenous vein graft use has been dominant in acute revascularization operations although the immediate mortality and long-term prognostic benefit by use of LIMA is well recognized.[37,38] Zapolanski et al reported zero mortality with use of LIMA to LAD in stable patients following failed PTCA.[39] This may simply reflect IMA use in patients who were stable with little ischaemia in whom a good outcome would be expected anyway. Analysis of the Society of Thoracic Surgeons' National Cardiac Surgery Database, however, has demonstrated a reduction in operative mortality with use of the IMA in all groups other than reoperative patients of more than 70 years of age.[40] LIMA harvest may, however, delay revascularization and prolong ischaemic time as may use of alternative arterial grafts. There may also be technical concerns about anastomosing small, thin-walled IMAs to dissected coronary arteries, although this may be overcome by use of a vein patch with subsequent IMA anastomosis to the patch. Clearly, surgical judgement is necessary when deciding if arterial grafts are appropriate in these patients and the degree of usage will reflect not only the urgency of revascularization but also the individual surgeon's philosophy. Cryopreserved homologous saphenous vein,[41] glutaraldehyde-treated homologous umbilical vein,[42] bovine IMA[43,44] and synthetic grafts[45–47] have all been used clinically for aortocoronary bypass. Although such 'off the shelf' conduits might seem valuable in an emergency situation, poor patency rates of approximately 50–60% at 1 year support the use of these grafts only when other conduits are unavailable.

Role of the cardiac surgeon during emergency PCI for acute myocardial infarction

Where facilities and resources allow, primary PTCA and stenting in association with GP IIb/IIIa inhibitors offer the best chance of reperfusion of the myocardium and best long-term outcome in patients presenting with an acute MI due to acute coronary artery occlusion.[48,49] Although emergency CABG surgery in acute MI is generally unavailable, has been shown to carry excessive morbidity and mortality and is even more unattractive in patients already treated with thrombolytic agents and or GP IIb/IIIa inhibitors who are undergoing rescue PCI for failed reperfusion, an emergency angioplasty program should only be commenced with the tacit approval of cardiac surgical, anaesthetic, nursing and paramedical colleagues. Here the closeness of the important working relationship between surgeon and interventionist is of paramount importance. Generally, PCI in this situation should be performed in high volume, well-equipped centres by experienced operators in well-staffed catheter laboratories where such good collaboration between the cardiologist and surgeon exists.

The cardiac surgeon should be called in the event of a major procedural complication such as left main coronary artery dissection associated with further haemodynamic compromise, although it may be decided after swift discussion to try and rescue the situation by coronary stenting in the first instance. The relatively uncommon no/slow reflow phenomenon (more common >3 hours after onset of pain) may be associated with a paradoxical impairment of left ventricular function and cardiogenic shock despite a fully patent infarct artery. It should probably be treated medically with inotropic agents, IABP and GP IIb/IIIa inhibitors initially, although emergency CABG or at least cardiopulmonary bypass should be considered if haemodynamic collapse cannot be rectified medically. The more aggressive use of mechanical LV assistance in this difficult situation requires further investigation.

The emergency investigation of patients presenting with acute MI with primary PCI in mind will inevitably turn up patients with extensive three-vessel disease, bad left ventricular function and/or left main stem disease who are poor subjects for PCI and more appropriate for surgical revascularization. Wherever possible, such cases should have an attempt to treat the culprit lesion by PTCA and stenting in order to stabilize the situation with a view to an urgent elective definitive surgical procedure within 4 to 6 weeks. Again a good understanding between cardiologist and surgeon will avoid frequent discussion over individual cases having to take place when time is of the essence.

Similarly, in patients undergoing urgent investigations because of severe unstable angina or non-Q-wave MI, those with significant LV dysfunction, diabetes, two-vessel disease plus severe proximal LAD disease, three-vessel disease or left main stem disease should perhaps be considered more suitable for CABG than PCI.

Effects of glycoprotein IIb/IIIa inhibitors

Patients with acute coronary syndromes currently undergoing PCI and especially stenting now commonly receive intra-

Table 24.5 Properties of intravenous GP IIb–IIIa inhibitors.

	Abciximab	*Tirofiban*	*Eptifibatide*
Compound	Antibody fragment	Non-peptide	Peptide
Reversibility of anti-platelet effect	Slow (≥12 hours)	Rapid (4 hours)	Rapid (4 hours)

venous GP IIb/IIIa inhibitors. Hence cardiac surgeons may expect to see a substantial increase in the number of patients presenting with profound platelet inhibition. All three currently available agents have a rapid onset of potent anti-platelet action, may cause thrombocytopenia and may increase the risk of bleeding should CABG be required. The three agents currently in use have differing properties (Table 24.5).

The use of abciximab with PCI has been shown to increase the red blood cell and platelet transfusion requirement,[50] although this effect can be reduced by adjusting heparin dosing at the time of PCI.[51] The risk of bleeding is more pronounced within the first 12 hours. Mediastinal blood loss following surgery within 12 hours of cessation of abciximab was >3 times that in patients operated upon after 12–24 hours in a study by Gammie et al.[52] More recent studies, although suggesting no incremental risk of increased bleeding, report increased platelet transfusion and a significant increase in re-exploration within 24 hours of abciximab administration.[53] In comparison, the shorter-acting eptifibatide does not appear to increase the bleeding risk of patients requiring emergency CABG and appears to improve clinical outcomes. Patients requiring CABG within 72 hours of randomization into the PURSUIT trial had a lower incidence of death or MI with eptifibatide than controls.[54–56] Clinical and bleeding events in patients undergoing CABG in the RESTORE and PRISM PLUS trials of tirofiban, however, were not reported.[57,58]

Table 24.6 Operative strategies in patients treated with GP IIb–IIIa inhibitors.

Agent	*Strategy*
Abciximab	Delay urgent surgery if possible for >12 hours Delay elective CABG for 1–2 days Prophylactic platelet transfusion ? On pump haemofiltration
Eptifibatide Tirofiban	No delay in emergency surgery necessary
All agents	Reduce anti-coagulation ± heparin-bonded circuits ?? 'Off pump' surgery

The management of each surgical case must be decided on clinical criteria at the time, including the type of GP IIb/IIIa inhibitor, the duration of the infusion and the time since the agent was last received (Table 24.6). Patients referred for CABG purely for an unacceptable angiographic result should be managed medically until the risks of surgical intervention are minimized. This would appear to be at least 24–48 hours after the last dose of abciximab. Patients requiring immediate intervention may benefit from prophylactic platelet transfusion either prior to or when 'coming off' bypass.[59] High dose aprotinin with platelet transfusion in patients treated with abciximab has been recommended, though this has yet to be fully evaluated,[60] as has haemofiltration on bypass.[61] Weight-adjusted heparin dosing has been shown to decrease the incidence of bleeding in patients undergoing PCI[51] and a similar approach may be useful in emergency CABG. However, intracardiac thrombosis has been described when reduced heparin doses were administered during cardiopulmonary bypass and is thus a cause of some concern.[62] Low dose heparin with heparin-bonded circuits has been used clinically with good results[63–67] and may be useful in this context. The use of clotting function monitoring by thromboelastography has reduced transfusion requirements in complex cardiac surgery[68] and off-bypass grafting might be considered in situations of haemodynamic stability. As a point of care measure of coagulation, platelet function, platelet–fibrinogen interaction and fibrinolysis, thromboelastography may prove useful in routine monitoring and allow the decision to administer platelets to be deferred until after cardiopulmonary bypass, reserving transfusions for patients who show evidence of bleeding. An excellent review of the pathophysiology, prevention and treatment of bleeding after cardiac surgery was published recently.[69]

Hybrid procedures

The introduction of minimally invasive CABG (MIDCAB) for left internal mammary artery (IMA) grafting to left anterior descending (LAD) coronary artery grafting has allowed the development of a combined strategy of MIDCAB and either PTCA or stenting to revascularize patients with multivessel disease.[70–73] The LAD graft may be performed either before

or after PCI depending on philosophy.[70,71] Initial LIMA anastomosis allows for angiographic verification of the anastomosis and a covering graft for left main stem angioplasty. Alternatively, initial PCI allows for CABG if PCI is unsuccessful. In a series of 434 successful MIDCAB procedures Calafiore et al reported a 97.1% survival at 29 months with an 89.4% event-free survival.[74] In the last 190 patients of the series a patent anastomosis was achieved in 98.9% and non-restrictive anastomosis in 97.4%. Other series have reported good clinical results with a low short-term angina recurrence rate.[75] MIDCAB intervention appears to be safe in experienced hands both in the short and medium term. Patients in whom this may be appropriate include the elderly, patients with excessive comorbidity, re-operative patients with poor vessels unsuitable for further surgery, grafting the circumflex artery via a left thoracotomy to avoid resternotomy and left main stem stenosis considered too high risk for conventional surgery. Although successful treatment of left main stem stenosis with the hybrid procedure has been reported,[76] Isomura and colleagues found that angina recurred in three out of five patients and a further died acutely.[77] Development of competitive flow may result in LIMA shut down with no capacity to recover should restenosis of the left main occur. Given the recognized long-term patency of the IMA, the long-term results of hybrid procedures will depend principally on the long-term patency of the stented vessel. Detailed evaluation in large multicentre trials is warranted to assess the future of hybrid procedures.

Conclusion

A good understanding and working relationship between cardiac surgeon and interventional cardiologist is essential for the success of a catheter-based coronary interventional program. For potentially high-risk or difficult cases, discussion between colleagues prior to the procedure is advisable and the strategy and risks should be discussed with the patient and next of kin. Access to emergency CABG should be available for all patients undergoing PCI other than those patients for whom it has been agreed that emergency CABG is not an option. In the event of a serious complication following PCI which cannot be rescued by the interventionist and especially in the situation of haemodynamic collapse requiring resuscitation, surgical revascularization will need to re-establish myocardial blood flow within the hour and no later than 90 minutes. This service can only realistically be provided where there is on-site surgery. Wherever possible, the left internal mammary artery should be used.

Newer pharmacological agents for reducing thrombotic risk during PCI carry with them an increased risk of bleeding in the event of emergency CABG and great care is necessary in monitoring platelet function, anti-thrombin and fibrinolytic activity by the cardiothoracic team before, during and after surgery. A full understanding of the differing effects of these powerful agents will help minimize further complications. Finally, although 'hybrid procedures' are carried out infrequently, the strategy can be extremely effective in certain difficult cases and success of the strategy is very much dependent on a team effort between cardiac surgeon and interventionist.

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The cardiologist and peripheral intervention

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Introduction

Peripheral vascular disease (PVD) is a major cause of disability, loss of work, and lifestyle limitations. Atherosclerotic peripheral arterial disease accounts for an age-adjusted prevalence of 12% in the United States.[1] Limb loss is a catastrophic event associated with severe physical and emotional disability. Cerebrovascular strokes account for 500 000 deaths per year in the United States. Furthermore, half of the patients that survive a stroke are permanently disabled.[2] Peripheral vascular disease has also been linked with an increased risk of mortality after coronary artery bypass graft surgery (CABG). A study of 2871 consecutive patients discharged after CABG indicated that even after successful revascularization, patients with PVD faced substantially higher mortality rates.[3] All these facts support the institution of aggressive strategies towards the prevention and treatment of PVD. With an aging population that is surviving coronary events, cardiologists will play a more global role in the management of vascular disease since patients seeking treatment for coronary disease may turn to them to direct the care for their PVD.

Conventional treatment of patients with newly diagnosed mild PVD has included medical management with agents like dipyridamole, pentoxifylline, ticlopidine, clopidogrel, and aspirin. In patients with more severe and symptomatic disease, surgical intervention has been the main method of therapy. The advent of catheter-based vascular therapy and recent advances in the field of interventional cardiology have revolutionized the therapeutic alternatives for patients with symptomatic PVD. Of these advances, stents have had the most significant impact. Results with stenting have quickly eclipsed those seen with laser and atherectomy procedures. Stents are also associated with lower restenosis rates when compared with balloon angioplasty alone.[4] New materials like nitinol (alloy of nickel and titanium) promise even better stent results.

In this chapter we discuss the evolution, current indications, technique, and complications of carotid intervention since this is perhaps the next arena of interest for interventional cardiologists beyond that of the coronary circulation.

Evolution in the treatment of carotid disease

Dr Michael E DeBakey introduced carotid endarterectomy (CEA) in 1953 as a therapy for the prevention of ischemic stroke due to distal carotid artery stenosis.[5] In spite of bad preliminary results,[6] the surgical techniques and complication rates for CEA improved. With improved surgical outcomes, the number of CEAs performed in the United States rose from 15,000 to 107,000 between 1971 and 1985.[7] Uncertainty from the neurologist's community about the safety and efficacy of CEA led to several large randomized trials. All these trials showed that CEA was better than conventional medical treatment for severe carotid disease in both asymptomatic and symptomatic patients.[8–10] However, they showed that the benefits of CEA were critically dependent on the surgeon's rate of perioperative complications. If the perioperative morbidity and mortality exceeded 3% in asymptomatic patients and 6% in symptomatic patients, the benefits of surgery were lost.[11]

Revascularization of carotid arteries has, until recently, been considered to be exclusively a surgical disease. After encouraging results obtained with angioplasty and stenting in the coronary, renal, and peripheral vascular systems, applications of these new technologies were made to the cerebrovascular system. Jacques Theron in France and Klaus Mathias in Germany reported the first significant experience with balloon angioplasty of carotid bifurcation lesions.[12–14]

Elective stenting of carotid bifurcation lesions was first reported in 1995 after a multidisciplinary collaboration at the University of Alabama at Birmingham that included a cardiologist, neuroradiologist, and a neurologist.[15] This collaboration was pivotal in the development of a percutaneous approach to treat carotid artery disease.

The technology for carotid angioplasty and stenting has been of particular interest since they offer several advantages over CEA that make them an attractive alternative in the treatment of carotid disease:

- Angioplasty and stenting are performed with the patient fully alert, facilitating close monitoring of neurological complications during the procedure; with CEA, complications are only apparent after the patient recovers from the anesthesia.
- Since the majority of patients with carotid disease also have coronary artery disease, avoiding general anesthesia translates into a safer procedure; the risk for myocardial infarction and cardiac death during general anesthesia for this population has a reported incidence of between 4% and 18%.[16]
- Carotid angioplasty and stenting are less invasive and traumatic, thus avoiding local wound problems, medical complications, cranial nerve palsies, and scars associated with surgery
- Patients can expect to leave the hospital in 24 hours and return to work with full activities after 72 hours.

Preliminary clinical series suggested that carotid angioplasty and stenting could be carried out with an acceptable degree of safety and with excellent angiographic results both immediately and at 6 months.[17–23] Although long-term follow-up is not yet available, the low morbidity and mortality associated with these procedures has led to the possibility that the less invasive percutaneous approach might be applied more widely for carotid artery disease in a select group of patients. Randomized prospective trials will ultimately define their precise role.

Validation and limitations of CEA

CEA became the 'gold standard' to which all other carotid interventions are compared on the basis of extensive studies on both symptomatic and asymptomatic patients. The North American Symptomatic Carotid Endarterectomy Trial (NASCET),[8] European Carotid Surgery Trial (ECST),[9] and Asymptomatic Carotid Atherosclerosis Study (ACAS),[10] are the main three trials that will be discussed. Of note, the NASCET and the ECST used different methods to measure stenosis, but a simple formula can be used to convert between the two methods.

The NASCET was designed to determine whether CEA reduces the risk of stroke among patients with a recent (less than 120 days) non-disabling cerebrovascular event and carotid stenosis.

- A randomized trial involved 50 clinical centers throughout the United States and Canada, in patients in two strata based on the severity of carotid stenosis: 30 to 69% and 70 to 99%.
- The subgroup with carotid stenosis >70% included a total of 659 patients.
- The cumulative risks of any stroke at 2 years were 9% for CEA and 26% for medical therapy, an absolute risk reduction of 17± 3.5% ($P < 0.001$).
- For a major or fatal stroke, the cumulative risk was 2.5% for CEA and 13.1% for medical therapy, an absolute risk reduction of 10.6 ± 2.6% ($P < 0.001$).
- The benefit of CEA was apparent at 3 months despite a risk of stroke and perioperative death of 5.8%.
- Benefits were greatest for patients with 90%+ lesions and less for 50–60% lesions.

The ECST was designed to determine the role of CEA in patients post non-disabling cerebral infarction, transient ischemic attack, or retinal infarct that presented with a stenotic lesion in the relevant carotid artery.

- For 374 symptomatic patients with only mild <30% stenosis, there was no benefit from CEA. For patients with stenosis between 30 and 69%, the benefit was uncertain.
- For 778 symptomatic patients with severe >70% stenosis the risks of surgery were significantly outweighed by the later benefits. Although 7.5% had a stroke (or died) within 30 days of surgery, during the next 3 years, the risk of stroke was an extra 2.8% for CEA and 16.8% for medical therapy, a 6-fold reduction ($P < 0.0001$). At 3 years the total risk of surgical death or stroke was 12.3% for CEA and 21.9% for medical therapy.
- The main concern was to avoid disabling or fatal events, and among patients with >70% stenosis, 3.7% had a disabling stroke (or died) within 30 days of CEA. After 3 years, an extra 1.1% for CEA vs 8.4% for medical therapy had a disabling or fatal stroke. The total 3-year risk of any disabling or fatal stroke (or surgical death) was 6.0% for CEA vs.11.0% for medical therapy.

The ACAS was designed to determine whether the addition of carotid endarterectomy to aggressive medical management reduced the incidence of cerebral infarction in patients with asymptomatic carotid artery stenosis.

- One thousand, six hundred and sixty-two asymptomatic patients with stenosis >60% were enrolled.
- NASCET angiographic criteria were used.

- The primary outcome measured was cerebral infarction occurring in the distribution of the study artery or any stroke or death occurring in the perioperative period.
- The aggregate risk over 5 years for stroke and any perioperative stroke or death was estimated to be 5.1% for CEA and 11.0% for medical therapy (aggregate risk reduction of 53% (95% confidence interval, 22% to 72%)).
- The perioperative stroke rate at 30 days was 2.3%.

In summary, CEA reduced the risk of disabling stroke or death for patients with symptomatic carotid stenosis exceeding ECST-measured 70% or NASCET-measured 50%, and asymptomatic carotid stenosis exceeding NASCET-measured 70%. These results are applicable only to surgically-fit patients operated on by surgeons with low complication rates.

It is important to recognize that although these studies validated CEA, they also showed its limitations. Patients in whom CEA was proved beneficial were very carefully selected and excluded high-risk patients:

- Age greater than 79 years.
- Heart, kidney, liver, or lung failure.
- Cancer likely to cause death within 5 years.
- Cardiac valvular lesion or rhythm disorder likely to be associated with cardioembolic stroke.
- Previous ipsilateral CEA.
- Angina or myocardial infarction in the previous 6 months.
- Progressive neurological signs.
- Contralateral CEA within 4 months.
- Major surgical procedure within 30 days.

Thus these trials do not adequately represent the entire spectrum of patients with carotid occlusive disease. Many of the patients evaluated for possible carotid angioplasty and stenting present one or more of these exclusion criteria. Despite these exclusions, there was a high risk of stroke and perioperative deaths with CEA: 7.5% in ECST, 5.8% in NASCET, and 2.3% in ACAS. These findings reveal that, although 'gold standard', CEA has its limitations. The limitation is further supported by the observation that although the published mortality in the NASCET series was 0.6%, during the same period, mortality among Medicare beneficiaries undergoing CEA was 3%.[24] Thus carotid angioplasty and stenting seem to have a place in the therapy of carotid disease.

Validation and limitations of carotid angioplasty and stenting

Carotid angioplasty and stenting offer many advantages over CEA. General anesthesia is avoided and no incision is required, making it a safer alternative in high risk patients. Low morbidity and mortality seen in early clinical series[25–27] suggest that they may have a role in the treatment of carotid disease. Nevertheless, the risks of vascular complications (ie, emboli, dissection, acute thrombosis) must not be underestimated. Although combined morbidity and mortality has been reported to vary from 2.8% to 9.6%, no rigorously controlled comparison with CEA has been published. To attain their place as a safe and effective alternative to CEA, randomized controlled trials are needed for validation. To date, the CAVATAS (Carotid and Vertebral Transluminal Angioplasty Study)[28] is the only trial that has been completed. Several projects are currently under way or in the planning stages (CAST[29] in Europe; CASET, CREST,[30] and SAPPHIRE in North America).

CAVATAS was an international multicenter prospective randomized controlled trial conducted in Great Britain through a collaborative effort between neurologists, radiologists and surgeons. The primary aims of the study were (a) to determine the risks and benefits of carotid and vertebral artery transluminal angioplasty and (b) to compare these with CEA or medical treatment.

- This trial included a high risk, symptomatic population with a high grade carotid stenosis.
- Inclusion criteria were much broader than in the NASCET.
- Interventions were performed at large medical centers by experienced surgeons. In contrast, the radiologists operated within their learning curves for carotid intervention.
- Only one-third of patients received a stent.
- The stents and technical approach used were suboptimal and now considered outdated (ie, stainless steel, self-expanding stents, 0.035" wires, no carotid sheath).
- The CAVATAS results were similar for both early and late outcomes:
  - The incidence for major stroke and death were 5% for both procedures.
  - The incidence of all strokes (disabling and non-disabling) was close to 11% for both procedures and follow-up events were also similar.

CAST is a multicenter trial that will evaluate the safety of percutaneous carotid artery stenting. Inclusion criteria will include symptomatic or asymptomatic patients >65 years of age, with internal carotid artery stenosis of >70% and <2 cm long.

CREST will be an NIH sponsored multicenter study. The study will recruit high risk patients with symptomatic stenosis >50% by NASCET angiographic criteria. Initial entry to the study will be based on carotid angiography or carotid duplex study if it shows disease of 70–99% severity. Newer stent technology (ie, nitinol self-expanding) will be used. The primary endpoint will be any stroke, myocardial infarction, or death.

The SAPPHIRE trial will randomize high risk patients, both symptomatic and asymptomatic, to either surgery or stent placement. It will combine the use of newer stent technology (ie, nitinol self-expanding) with an embolic protection device.

Indications for carotid angioplasty and stenting

On the basis of current knowledge derived from short term data, certain patient subgroups could benefit from carotid angioplasty and stenting. Included in these subgroups are patients with one or more of the following conditions.

Patients with significant medical comorbidity

Since this subgroup of patients were excluded from the CEA trials, the indications and results of surgery are not well established. When long term results of CEA in patients with clinically important coronary artery disease were reviewed, myocardial infarctions were the leading cause of death.[31] Conversely, patients with significant carotid disease undergoing coronary artery bypass grafting (CABG) have a risk for stroke from hypotension during general anesthesia.[32] Published reports on combined CEA and CABG suggest that the risk of stroke or death ranged from 7.4% to 9.4%, 1.5 to 2.0 times the risk of each operation alone.[33] In this subgroup of high risk patients, carotid angioplasty and stenting may represent a valid alternative to CEA.

Carotid restenosis

Surgery for recurrent carotid stenosis is technically challenging because of scar tissue surrounding the carotid bifurcation. Even with very experienced surgeons, the major complication rate of redo CEA approximates 10%.[34] Early results indicate that endovascular treatment of carotid restenosis can be safely achieved and that it represents a valid alternative to carotid re-exploration in this high risk group.[35,36]

High grade carotid stenosis with contralateral occlusion

The NASCET study showed that the perioperative risk of stroke or death in the presence of a contralateral carotid occlusion was 14.3%.[37] Carotid shunting was used in 67% to 83% of patients with contralateral occlusions, but there is no evidence that it reduces the perioperative risk of stroke. Carotid angioplasty and stenting obviate the need for carotid occlusion in the presence of reduced cerebrovascular reserve.

Radiation induced carotid stenosis

Patients with symptomatic carotid occlusive disease occurring as a result of cervical irradiation present surgical challenges because of both involvement of the distal common carotid artery and extensive scarring and fibrosis.[38] Infections and wound problems are increased by previous radiation. Carotid angioplasty and stenting offer potential risk advantages for these patients.

High cervical stenosis and tandem lesions

A very high bifurcation near the skull base, especially in patients with short or thick necks, or a long stenotic lesion extending high in the neck, are difficult to expose surgically. These high lesions are more likely to have less atherosclerosis and dense calcifications, and therefore are more suitable for the endovascular approach.[26] Tandem lesions present a high risk of postoperative occlusion from decreased flow velocity. These patients were excluded from the NASCET. Carotid angioplasty and stenting of tandem lesions can be done at the same time, so they represent a valid alternative to carotid surgery.

Necessary experience for a cardiologist

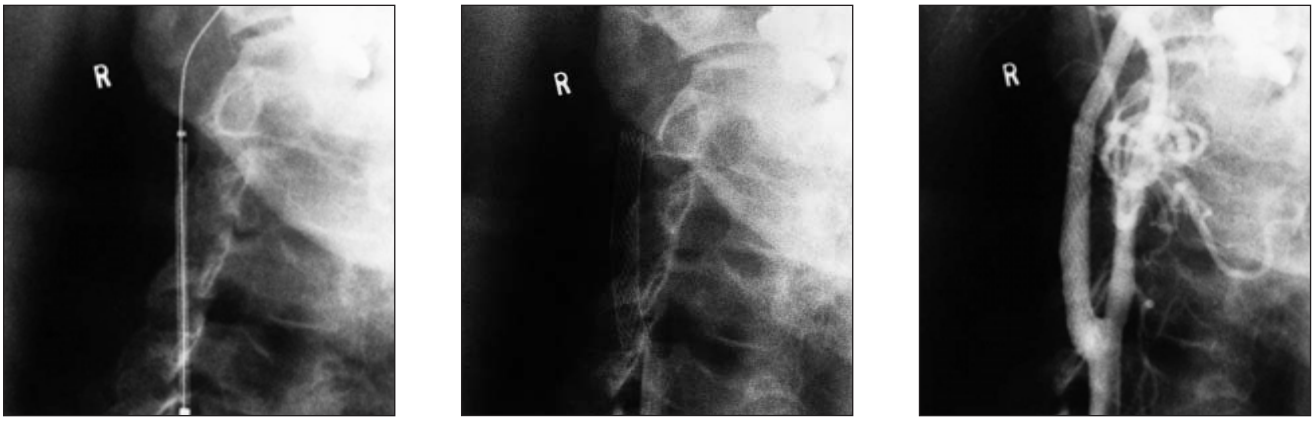
As a base minimum, an interventionist should have performed a minimum of 100 diagnostic four vessel studies. Prior to carotid intervention, a four vessel study should be performed by selective injection. This should include evaluation of the central circulation and ascertainment of the flow at the Circle of Willis. The bifurcation of the common carotid arteries is usually located at the level of C3 or C4 vertebral bodies but it can be located higher or significantly lower. If very low or very high, this presents problems for endarterectomy and favours stenting.

Clinical preparation of the patient

- All patients should undergo an adequate medical and neurological evaluation.
  - Patients with a history of stroke or symptomatic carotid disease should have a CT scan or MRI of the brain to document pre procedural anatomic deficits.
  - A neurologist should be consulted for a formal neurological assessment and completion of a National Institute of Health (N.I.H.) stroke scale pre and post procedure.
- Patients must understand the potential complications of the procedure and give consent.
- Complete cerebral angiography is done as a separate examination or immediately before carotid angioplasty and stenting. Knowledge of the status of the brachiocephalic arteries, circle of Willis and intracranial vessels is essential.
- Duplex ultrasound is required pre and post stenting and is used as a baseline for follow-up.
- Patients should be started on antiplatelet therapy, aspirin 325 mg and clopidogrel (Plavix) 75 mg or ticlopidine (Ticlid) 250 mg twice a day for 48 hours before the procedure.
- Same day admissions and 23-hour discharges are done when possible.

Equipment selection and technical approach

- The femoral access approach is the most commonly used.
- Femoral puncture is performed with insertion of a standard 5–9 French 12 cm arterial sheath; a 23 cm sheath for a diseased iliac artery; a 40 cm sheath in case of an abdominal aortic aneurysm.
- The patient is given heparin to obtain an activated clotting time of 200–250 seconds.
- A diagnostic catheter is advanced into the ascending aorta over a 0.035" wire. For difficult or anomalous anatomy, an aortogram of the arch vessels can be done and is used as a guide to selective cannulation.
- After angiography of the aortic arch and recognition of the anatomy, the diagnostic catheter is advanced into the common carotid artery using an over-the-wire technique. Prior to cannulation of the common carotid, a careful flush of saline should be performed to clear any debris or thrombus.
- Once the catheter is in the common carotid, the guidewire should be replaced with an exchange length 0.035" wire. In cases of vessel tortuosity, Amplatz type wires are used; otherwise standard or hydrophilic wires are used.
- The diagnostic catheter is then exchanged over the wire for a 7–9 French 90 cm sheath.
- The 90 cm sheath is advanced over the wire into its position within the common carotid artery below the carotid bifurcation.
- The 0.035" wire is removed to measure pressures and to inject contrast for angiography via the guiding catheter side port.
- After selective carotid angiography, a steerable 0.018" or 0.014" coronary guidewire is advanced through the stenosis. If a 0.035" compatible system is used, a tapered wire with 0.018" tip is preferred.
- An appropriately sized monorail or coaxial angioplasty balloon is then advanced to the lesion for predilatation at low pressures, 1 atmosphere above the disappearance of the waist.
- The balloon is exchanged for a stent system (Fig. 25.1).
  - The diameter of the stent should be approximately 1–2 mm larger than the largest segment to be covered.
  - Nitinol self-expanding stents are superior to both stainless steel balloon- and self-expanding stents since they are more pliable to accommodate tortuosities, and thus prevent straightening of vessels.
  - Although the internal carotid artery is 2–3 mm smaller than the common carotid artery, oversizing the stent in the internal carotid artery does not cause late problems (Fig. 25.2).
  - Covering the external carotid artery is safe and rarely causes patency problems (Fig. 25.3).
- Post stent deployment dilatations, if needed, should be performed at nominal pressure or lower to prevent vessel dissection. If the external carotid artery becomes significantly stenosed or occluded after post dilatation of the stent, this vessel can be approached through the stent mesh and reopened.
- The stent system is removed to perform carotid angiography to identify further lesions, dissections and embolic complications.
- Continuous monitoring of the heart rate, blood pressure, and neurological status throughout and post intervention is mandatory. A squeaky toy in the ipsilateral hand of the patient is useful during predilation, stent deployment and post dilation. It keeps the patient alert and interactive with the interventional team but it is imperative that a nurse communicates directly with the patient and continues to assess the neurological status of the patient during the procedure. Good hydration and maintenance of an appropriate blood pressure are important in the recovery period.
- The sheath is removed when the ACT is <180 s and the patient is discharged the next morning if no complications are encountered.



a b c

Figure 25.1
(a) Fluoroscopic image of a 0.035" to 0.018" tapered wire across an internal carotid stenosis with a stainless steel, self-expanding stent prior to deployment. (b) Fluoroscopic image after stent deployment. (c) Carotid angiogram after stent deployment.

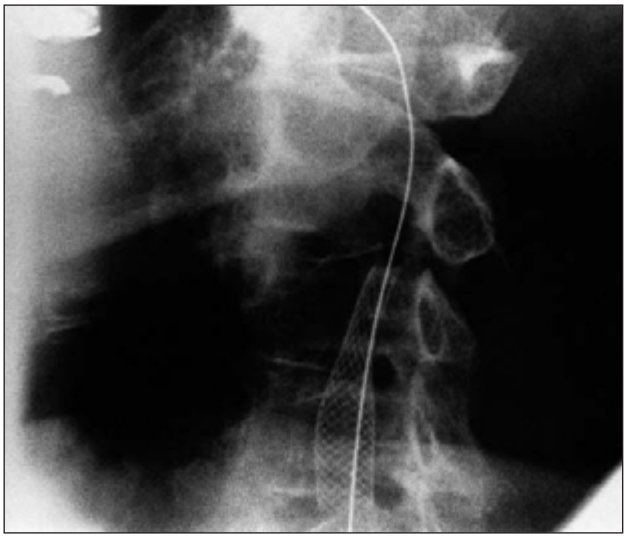


Figure 25.2
Fluoroscopic image of a stainless steel, self-expanding stent in the common carotid artery and tapered in the internal carotid artery.

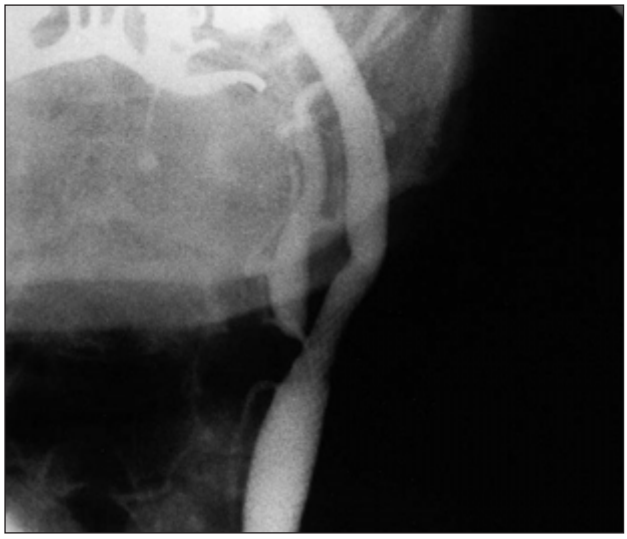


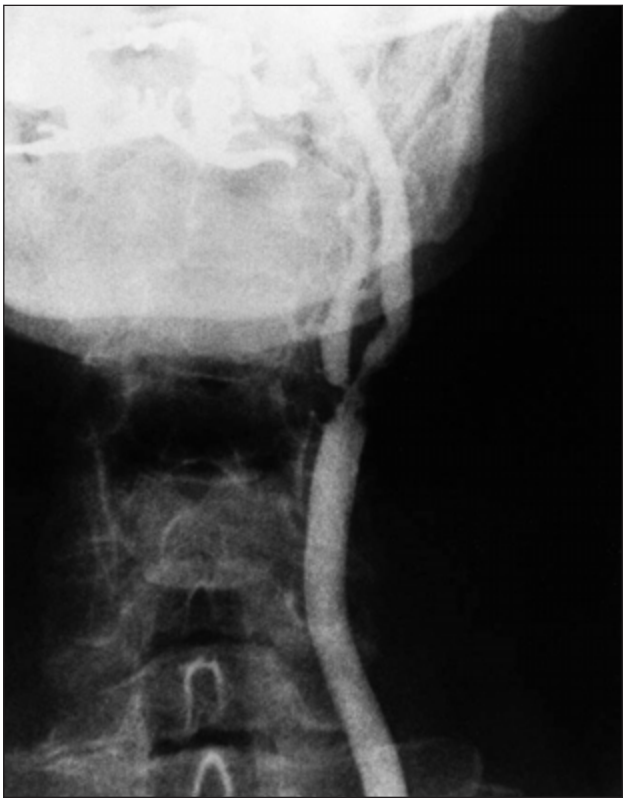
Figure 25.3
Patent external carotid artery after deployment of a stainless steel, self-expanding stent across the carotid artery bifurcation.

Complications of carotid angioplasty and stenting

Various clinical and angiographic variables can be used to identify patients at risk for neurological deficits after carotid angioplasty and stenting. Such variables may help identify patients who may benefit from pharmacological and mechanical preventive approaches.[39–41] Several risk factors have been identified:

- advanced age;
- prior CVA with a large neurological defect;
- unstable neurological symptoms;
- diffuse, severe peripheral vascular disease;
- severely tortuous, calcified and atherosclerotic arch and carotid vessels;
- co-existent proximal common carotid lesions;
- high grade-complex and sub-total lesions (Fig. 25.4);
- angiographic evidence of thrombus (Fig. 25.5);
- long, complex lesions extending into the distal internal carotid (Fig. 25.6);
- severe tortuosity just distal to the bifurcation;
- platelet or anticoagulation defects.

Although major complications can be encountered during the learning curve of carotid angioplasty and stenting, they are minimized by the use of meticulous techniques. The most commonly encountered complications will be discussed.



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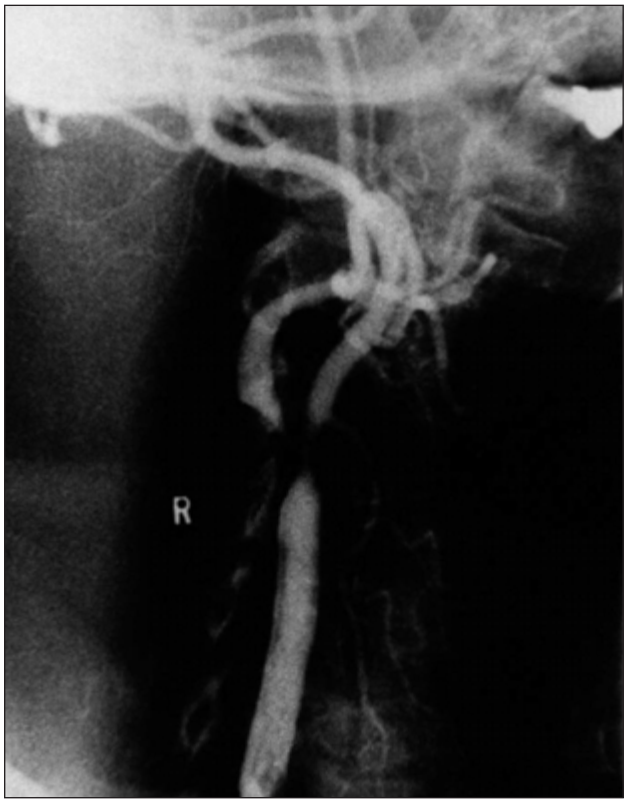

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Figure 25.4
Examples (a) and (b) of high grade-complex lesions involving the carotid bifurcation.

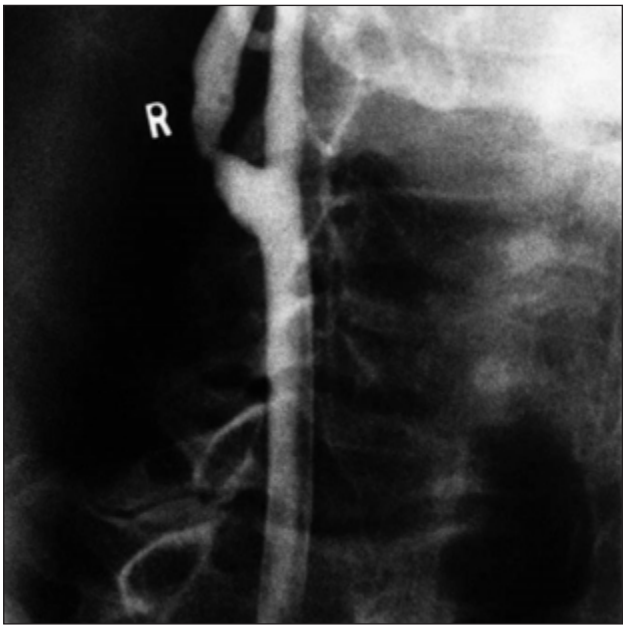


Figure 25.5
Angiogram showing evidence of thrombus in the internal carotid artery.

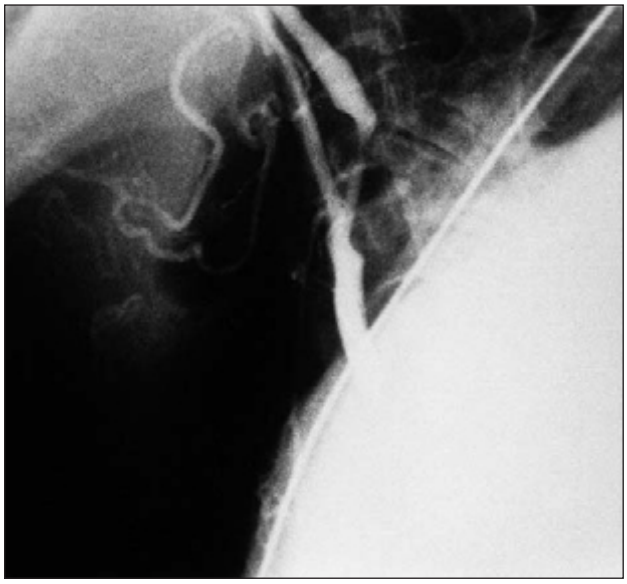


Figure 25.6
Angiogram showing a long stenosis of the internal carotid artery.

Thrombotic and embolic complications

These are the most feared complications of carotid percutaneous intervention. A recent survey on carotid artery angioplasty and stenting[42] revealed a 30-day minor stroke rate of 3.08%, and a major stroke rate of 1.32%. With an endovascular approach one has the ability to diagnose and treat these complications immediately; patients also are awake, allowing close neurologic monitoring. Pre treatment multiplane projections of the involved hemisphere should be available during the procedure. For acute thrombosis, local intra-arterial thrombolysis can be carried out using mechanical as well as chemical disruption of the clot.[43] Extreme care must be exercised to avoid vessel perforation, which would likely result in a major hemorrhage after thrombolysis. In order to prevent thrombotic complications, some investigators have advocated the use of glycoprotein IIb/IIIa platelet inhibition.[44] To prevent embolic complications, several types of distal protection devices (eg, filter, umbrella, balloon occlusion) have been developed.[45,46] Transcranial Doppler for evaluation of embolization during carotid work may have a role; however, virtually all studies have shown that during carotid intervention, small particulate embolization is uniform and universal.

There has been a fair amount of experience with Percusurge®, but it is a bulky device with some impractical aspects in the carotid anatomy. Filter devices such as the Angioguard™, Mednova™ and EPI filter are exciting prospects but only particulate debris >100μ are filtered. However, it is likely that such devices will become an essential component during this procedure. Newer stent designs will integrate these protection devices.

Carotid artery spasm

This is a guidewire-induced phenomenon and usually resolves after it is removed. The use of 0.014–0.018" wires minimizes its occurrence. It can be successfully treated with papaverine.[18]

Transient bradyarrythmias and hypotension

Bradycardia is common during PTA of the carotid bifurcation involving the area of the carotid baroreceptors. If encountered, the balloon should be immediately deflated. If persistent, atropine should be administered. Asystole is very rare, but if seen it is transient and resolves with balloon deflation.

Post stenting hypotension

This is common after carotid stenting and may last from hours to days. It is mediated by the stretch of the carotid baroreceptors and should be treated aggressively if the patient has severe distal or contralateral disease. Puncture site complications should be ruled out.

External carotid artery (ECA) occlusion

Acute occlusion of the ECA is tolerated well but in the absence of collateral circulation from the contralateral ECA, patients may experience jaw muscle angina. If the ECA supplies collaterals to the brain via the ophthalmic artery and pial branches, its patency should be re-established but not at the expense of embolic complications from excessive catheter manipulation.

Stent restenosis

Short term studies have shown that the restenosis rate for carotid stenting is 4.8% at 6 months.[45] If encountered, it is simply treated with balloon dilatation at the restenosis area.

Carotid perforation

This can be seen after excessive balloon sizing prior to or after stent placement. Treated vessels should not be overdilated to optimize their luminal appearance. If encountered, the procedure should be immediately terminated and anticoagulation reversed. Low level balloon inflations can be performed to seal the perforation. Covered stents can be used if there is no compromise of major side branches.[47]

Carotid dissection

This can be seen at the stent edges after post deployment dilatation, or secondary to guiding sheath trauma. Dissections are mainly seen in areas of vessel tortuosity. Stented segments should not be dilated as long as the stent is 1–2 mm larger than the reference vessel. Balloon inflation at the stent edges should be done at low pressures to avoid dissection of the vessel. Further stenting may be necessary to avoid flow disruption in the area of dissection.[48]

Cerebral hemorrhage

This is usually fatal, but fortunately rare. It is associated with a combination of excessive anticoagulation, poorly controlled hypertension, intracranial vessel manipulation, and stenting in the presence of a recent stroke (<3 weeks). If suspected, the procedure should be immediately terminated, anti-coagulation reversed, and hypertension controlled with medication. An emergency brain CT scan should be performed.

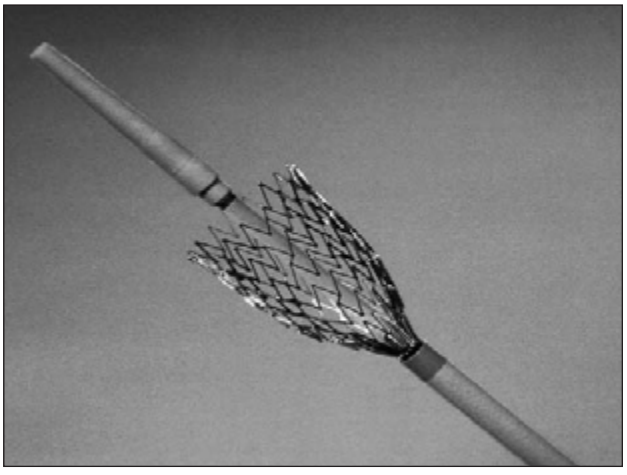
Neurovascular rescue

The concept of neurovascular rescue for neurologic events is something beyond the approach of most interventionists. A low dose of heparin (5000 U or less), wise utilization of other agents such as tPA and urokinase, as well as the only judicious use of glycoprotein IIb/IIIa platelet inhibition would hopefully result in there being no need for neurovascular rescue. However, the interventionist should be well skilled in small vessel angioplasty in case there is a tear, particularly above the carotid syphon or smaller vessels, which usually cannot be stented. The presence of intracranial lesions, aneuryms or A-V fistula would probably exclude the patient from carotid intervention. These most likely would be in the purview of a neurologist and not appropriate for an interventional radiologist or interventional cardiologist. In summary, problems that occur with carotid stenting are usually best taken care of by the interventionist and not necessarily a neurosurgeon, vascular surgeon or neuroradiologist. However, the problems above the bifurcation, particularly in the small cerebral vessels are best tackled by a neuroradiology interventionalist

Conclusions

Results of a recent worldwide survey on carotid artery angioplasty and stenting that included placement of a total of 5074 stents on a majority of symptomatic patients, revealed that the 30-day death and stroke rate for the entire group was 6.3%.[45] In analyzing the data, investigators found that interventionists who had completed <50 cases had a higher rate of procedural complications. Restenosis for the entire cohort was 2.4% at 1 year. Centers that performed <100 procedures had restenosis rates of 3% to 5%, whereas centers where >200 procedures had been performed reported restenosis rates of <2%. Worldwide, 62% of the physicians placing stents were cardiologists, followed by radiologists (21%) and surgeons (17%). These data reveal that endovascular stent treatment of carotid artery atherosclerotic disease is growing as a viable alternative to CEA, especially for high risk patients. This subgroup of patients is at risk for carotid clamping (contralateral carotid occlusion, prior cerebral infarction, or tandem lesions), has significant medical comorbidities, and has lesions difficult to access surgically. The endovascular technique is well tolerated and is performed with minimal sedation, allowing assessment of neurological status. Patients are usually discharged after 24–48 hours.

The catheters, balloons, and stents used in preliminary studies were all adapted from coronary, renal, or peripheral vascular applications. None of these technologies were specifically developed for carotid use. Future developments will include better nitinol self-expanding, non-shortening, low profile stents (Fig. 25.7). New materials like platinum, which is biologically inert, will be used. Tapered stents are being developed to accommodate for size mismatch



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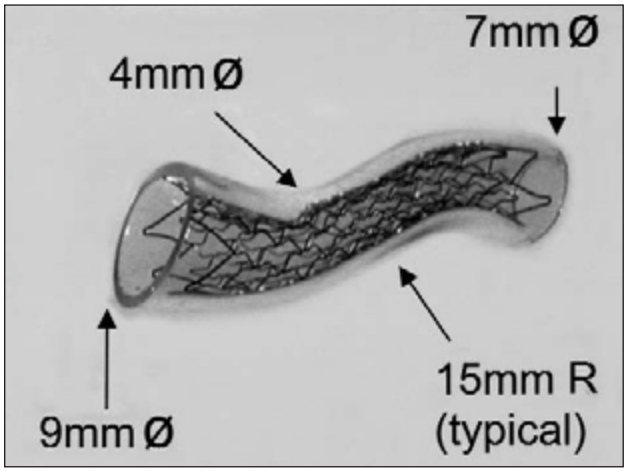

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Figure 25.7
Nitinol self-expanding stents (a) SMART stent (Cordis Corporation, Miami, FL): (b) Endotex stent (Endotex, Menlo Park, CA).

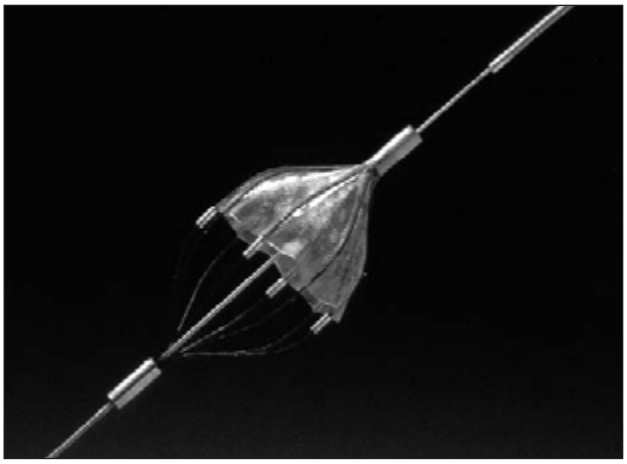

Figure 25.8
Angioguard embolic protection device (Cordis Corporation, Miami, FL).

between the proximal and distal carotid artery. Embolic protection devices will also be integrated into the newer stent designs (Fig. 25.8). All these new developments will produce devices suitable for the endoluminal treatment of carotid artery disease, which may translate into reduced complication rates and better short- and long-term outcomes.

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26

Transcatheter closure of ventricular septal defect post myocardial infarction

W Lindsay Morrison and Kevin P Walsh

Introduction

Myocardial infarction complicated by ventricular septal rupture carries a high mortality. Without surgery, only 50% of patients survive the first week, and fewer than 20% survive for one month.[1] Hospital mortality following emergency repair is high and ranges from 10 to 60% depending on the pre-operative clinical characteristics of the patient population.[2,3] Insertion of sutures into acutely infarcted myocardium is fraught with difficulties, and despite successful initial repair, ventricular septal defects (VSD) recur in up to 20% of patients as a result of patch dehiscence, development of a new VSD, or an overlooked second VSD (Fig. 26.1). This may result in a significant haemodynamic shunt or haemolysis requiring re-intervention. General anaesthesia and cardiopulmonary bypass following acute myocardial infarction further depress myocardial function when it is already compromised.

The option of percutaneous transcatheter closure of VSD post MI is therefore an appealing alternative to emergency surgical repair. Following experience of catheter based closure of atrial septal defects we have undertaken transcatheter closure of post MI VSDs using the Amplatzer septal occluder. The Amplatzer atrial septal defect occluder is self-centring and repositionable after deployment and has a low profile. It is constructed of 0.004 inch (0.01 cm) Nitinol wires, tightly woven into two self-expanding flat round discs with a 3 mm long connecting waist corresponding approximately to the thickness of the atrial septum (Fig. 26.2). Dacron fabric is

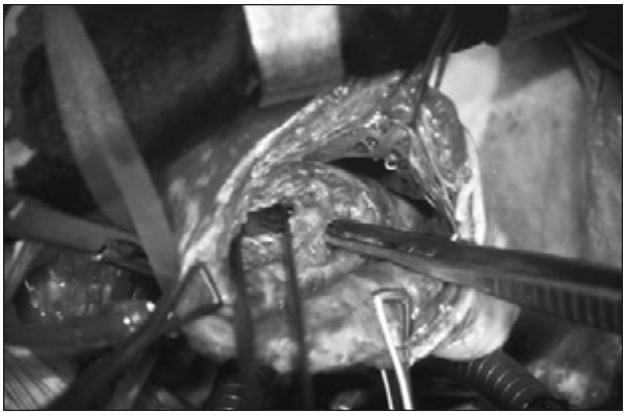

Figure 26.1
Two VSDs post MI at surgery.

Figure 26.2
Amplatzer occluder in profile showing the two retention discs and central waist.

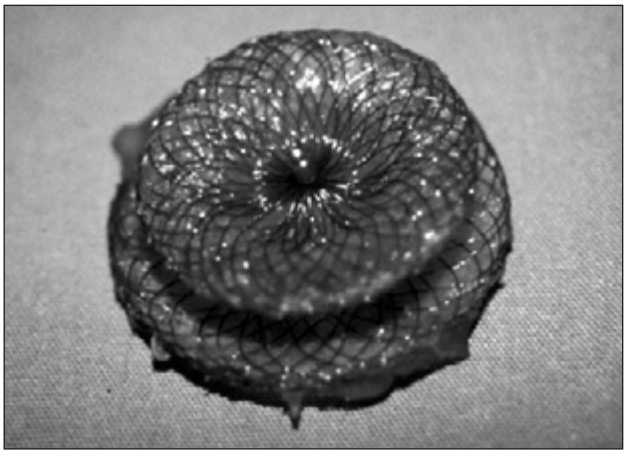

Figure 26.3
Amplatzer device removed after 5 weeks in patient who subsequently had surgical closure.

sewn into both retention discs as well as into the waist (Fig 26.3). Waist diameters vary from 4 to 38 mm. The device is securely attached onto a delivery cable by a recessed screw and loaded into a delivery sheath.

Technique

General anaesthesia for transoesophageal monitoring throughout the procedure is required to ensure correct positioning and alignment of the device.

Intra-aortic balloon counter-pulsation and inotropic support should be considered to stabilize the situation. The right femoral artery and vein and right internal jugular vein are cannulated. Intravenous heparin and prophylactic antibiotics (eg: cefotaxime) are administered. Coronary angiography, left ventriculography and oximetry to estimate shunt size are performed (Fig. 26.4). The VSD is then crossed retrogradely using a Judkin right coronary catheter or multipurpose catheter (Cordis, Bracknell, UK) using an angled exchange length 0.035 inch guidewire. It is usually possible to loop the guidewire in the right ventricle and then prolapse it into the right atrium and thence into the superior vena cava. If this is not successful the guidewire can be passed into the pulmonary artery. The end of this wire is then snared with a 25mm Amplatz goose-neck snare (Microvena; Vadnais, Minnesota, USA) and then extruded via the right internal jugular vein, thereby creating an arteriovenous guidewire loop. Alternatively a femoral artery–femoral vein loop can be created, which may allow an easier curve for the delivery catheter. Heparin 10 000 iu is given. A 7 F balloon catheter with a precalibrated balloon (Meditech, Boston Scientific Corporation, Watertown, Massachusetts, USA) is then passed across the VSD, and the balloon volume producing VSD occlusion on transoesophageal echo is noted.

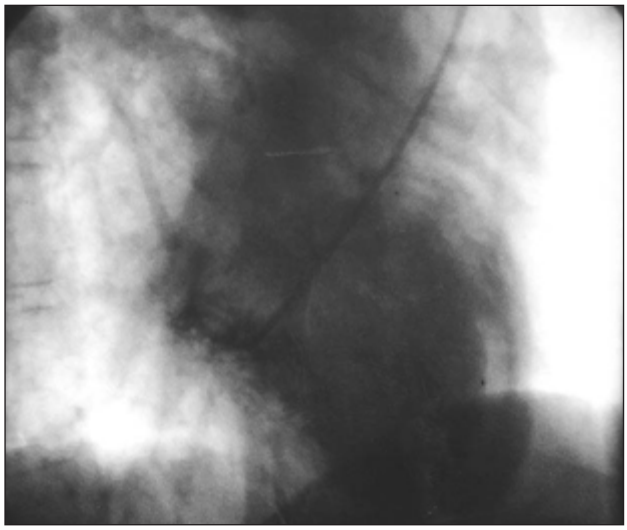

Figure 26.4
Left ventriculogram in RAO projection showing VSD and late filling of RV.

The Amplatzer delivery catheter (Aga Medical Corporation, Minnesota, USA) is then passed over the exchange guidewire loop via either the jugular vein or femoral vein. If any significant resistance to passage of the sheath over the exchange guidewire is felt then encirclement of a tricuspid valve chordae/papillary muscle by the guidewire should be considered. Continuing to apply force by pulling on both ends of the AV guidewire loop may result in avulsion of a papillary muscle.

The Amplatzer septal occluder is then screwed onto the delivery cable, compressed into the loader and introduced into the long delivery sheath. The distal disc is extruded and pulled back onto the left ventricular side of the septum under TOE guidance. Once septal alignment is confirmed, the prox-

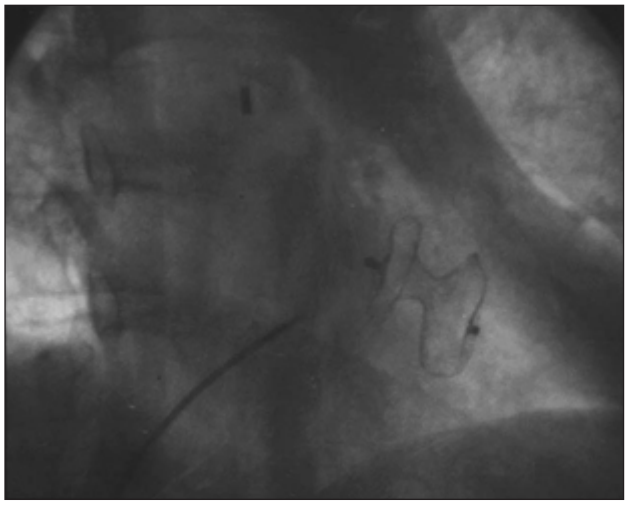

Figure 26.5
Amplatzer device released from cable during delivery.

imal (right ventricular) disc is then deployed; the device is then released by counter-clockwise rotation of the delivery cable (Fig 26.5). Repeat left ventriculography and oximetry is then performed to check for closure.

The main difficulty with the delivery is that the sheath can easily be kinked. This can be avoided by precurving the sheath to match the guidewire loop configuration. It is also very helpful to pull the guidewire out via the arterial end very slowly with the tip of the guidewire remaining in contact ('kissing') with the device throughout its introduction.

Very occasionally an armoured sheath (Arrowflex™) 2 French sizes larger than the Aga™ delivery sheath may have to be used to avoid kinking of the sheath. In this situation the device is front loaded in the Aga™ delivery sheath prior to insertion of the entire system into the Arrowflex™ sheath. The patient remains on aspirin long-term.

Early experience

Six males, in the age range 50 to 85 years, have been treated to date. Five had anterior and one inferior MI; three were acute and three had recurrent or residual VSDs post surgery. All three acute MIs were on IABP and inotropes, and the three recurrent VSDs had continuing heart failure. Two patients had multiple VSDs. The median Qp/Qs calculated on oximetry was 3:1 (range 1.8 to 5.9) and median mean PA pressure was 28 mm. Hg (range 12 to 39). The device sizes ranged from 10 to 26 cm.

All patients are alive and well (6 months to 3 years follow-up). Procedure times varied from 90 to 216 minutes. Median shunt fell from 3:1 to 1.3:1. Device placement was successful in all patients. Follow-up echocardiogram demonstrated complete closure in two, a trivial to small residual defect in three and a large residual defect in one. The patient with a large residual shunt had a second device implanted 10 days later, but still continued to have a large residual shunt; he underwent successful surgical repair of a 5 cm diameter VSD 5 weeks after his myocardial infarction (Fig. 26.6). Complications consisted of one episode of transient complete heart block, two episodes of VF (in one patient) and avulsion of the tricuspid septal leaflet in one patient.

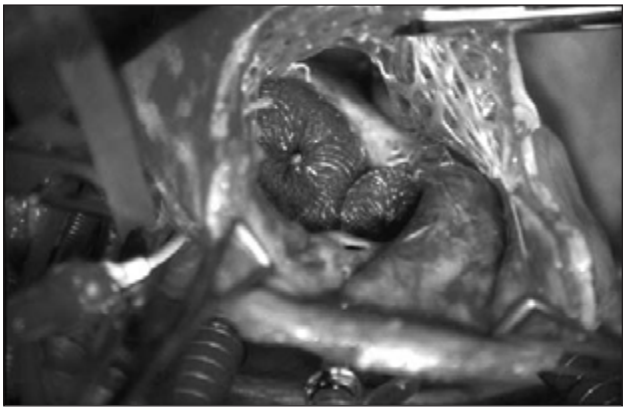

Figure 26.6
Amplatzer occluder × 2 in situ in patient with residual shunt who subsequently underwent surgical repair.

Transcatheter closure is an established method of treating selected congenital heart defects.[4–6] Devices used to close congenital VSDs to date include the Rashkind double umbrella and the clamshell occluder.[7,8] Congenital muscular VSDs have a good rim of tissue to anchor the device, whereas post acute MI tissue is bruised and tears easily, and the VSD is often irregular and serpiginous post MI.

Clinical experience of early closure of VSDs post MI is limited so far.[9] The Amplatzer septal occluder has been used to close a late residual VSD post surgical patch repair (10 months from the original MI).[10] The avoidance of cardiopulmonary bypass is a clear advantage in a sick patient.

Multiplane transoesophageal echocardiography is a valuable adjunct to fluoroscopy in patient selection, device positioning/deployment and shunt assessment.[11]

Potential complications are device migration due to inaccurate sizing, inaccurate deployment, inadequate rim for tissue deployment or device malfunction. This results in inadequate defect closure, residual shunting, device embolization or encroachment into the surrounding structures. Trapping of tricuspid or mitral chordae may lead to valvular regurgitation. Dysrhythmias such as complete heart block or ventricular tachycardia are usually transient. Thrombo-embolism and prosthesis endocarditis are rare. Apical defects may result in squashing or distortion of the disc.

The Amplatzer septal occluder may improve outcome in transcatheter closure of VSD post MI. It has a single unit construction, allows easier deployment and retrievability and may reduce device migration. Its smaller rounded discs are less likely to result in damage to surrounding structures than devices with struts or sharp corners. Our experience has been using the Amplatzer device; the Cardia Star™ device (up to 16 mm) as an alternative device which is marketed for closure of PFOs or small ASDs.

Even if complete closure of the VSD post acute MI may not be possible, this often allows time for the patient to be stabilized, healing of the infarct to take place and the development of scar tissue to develop and if necessary surgical repair can then be undertaken at a later date when surgical risks are considerably reduced.

Transcatheter closure of VSD post MI shows potential as an alternative to late re-operation in recurrent post infarction VSD following patch repair, but more exciting still is the possibility of primary closure of VSD following acute myocardial infarction. However, more experience is necessary to assess its role as a primary closure technique or as a bridge to subsequent surgery which can then be planned electively and performed with, it is hoped, reduced risk to the patient.

Future directions

The development of a new Amplatzer device designed for post MI closure of VSDs with a 1 cm long stent and with more dacron should soon be available which should allow easier deployment. Intracardiac echo imaging from the RV rather than TOE would prevent the need for general anaesthesia during the procedure which is an advantage in sicker patients.

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27

Non-surgical septal reduction in hypertrophic cardiomyopathy

Rodney H Stables and Ulrich Sigwart

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disease characterized by hypertrophy of the left ventricle (LV), with markedly variable haemodynamic consequences and clinical manifestations.

In a subset of patients, the site and extent of cardiac hypertrophy results in obstruction to the left ventricular outflow tract (LVOT). This may be present at rest, but in others, significant obstruction occurs only under conditions that tend to reduce ventricular preload (dehydration, sudden adoption of the upright posture and the Valsalva manoeuvre) or increase ventricular afterload, particularly exercise.

In the classic form of hypertrophic obstructive cardiomyopathy (HOCM), patients manifest asymmetric septal hypertrophy (ASH), systolic anterior motion (SAM) of the anterior leaflet of the mitral valve and in most cases, mitral regurgitation (Fig. 27.1). The inward movement of the hypertrophied septum during systole further narrows the LV outflow tract, resulting in high LVOT blood velocities that pull the mitral valve leaflet toward the interventricular septum (Venturi effect). The SAM of the mitral valve with valve–septal contact is in many patients the most important determinant of the severity of LV outflow obstruction and the cause of the mitral regurgitation.

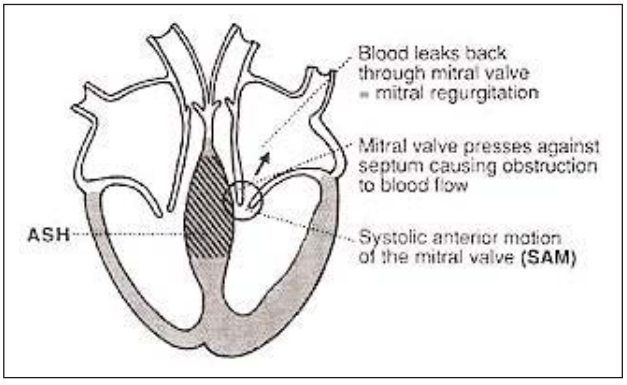

Figure 27.1
Schematic diagram of hypertrophic obstructive cardiomyopathy illustrating asymmetric septal hypertrophy (ASH), systolic anterior motion of the mitral valve leaflet (SAM) and obstruction of the left ventricular outflow tract. Mitral regurgitation may also be present.

A number of variants of obstructive HCM have been characterized:

- Mid-cavity obstructive hypertrophic cardiomyopathy—due to the systolic apposition of hypertrophied papillary muscle and LV wall at the level of the mid-LV, producing two distinct LV chambers.
- Complex obstructive HCM—consists of obstruction at the level of both the papillary muscle (mid-LV cavity) and the aortic valve leaflets.
- Obstructive HCM in the elderly—associated with calcification of the mitral valve annulus and anterior displacement of the mitral valve.

Although patients with these variants may manifest high LVOT gradients and limiting symptoms, current experience with the non-surgical septal reduction is restricted to the classical form of HOCM.

Treatment options in classical HOCM

Many patients with HOCM eventually develop one or more of the following symptoms: dyspnoea, chest pain, syncope, palpitations and fatigue. Symptoms are variable and not

exclusively related to left ventricular outflow tract obstruction, with which there is a poor correlation. Other mechanisms include:

- impaired myocardial function in the absence of obstruction;
- arrhythmia or conduction delay;
- impaired filling due to diastolic dysfunction.

Drug therapy with beta blockers or other negative inotropes can be effective, but a number of patients are intolerant of these agents or remain symptomatic despite treatment. Right ventricular contraction immediately following atrial systole reduces LV outflow tract gradients without adversely affecting systemic arterial pressure. This observation provided the rationale for the evaluation of dual chamber (DDD) pacing for the treatment of HOCM. Randomized controlled trials (RCT) have demonstrated only very limited haemodynamic and clinical improvement with DDD pacing and the inability to predict response in an individual patient means that this is rarely used as routine therapy.[1]

Patients with resistant symptoms have traditionally been considered as candidates for cardiac surgery. Left ventricular myectomy, performed in the septal area and sometimes combined with mitral valve replacement, eliminates or improves symptoms in most patients and significantly reduces LV outflow tract pressure gradients. The long-term efficacy of this procedure has been demonstrated in a number of reports, although there is an associated procedural mortality of around 5% and considerable morbidity including complete heart block, ventricular septal defect formation and cerebrovascular accident.[2,3]

Non-surgical septal reduction

Percutaneous methods of septal reduction have been developed as an alternative to open surgical therapy. A number of terms have been used to describe these procedures including 'percutaneous transluminal septal myocardial ablation '(PTSMA)', 'the Sigwart procedure', 'alcohol septal ablation' and 'transcoronary ablation of septal hypertrophy' (TASH).[4-6] We prefer the more generic description 'non-surgical septal reduction' (NSSR), which encompasses the variety of techniques that can be employed in this setting.

Initial observations in this field have demonstrated that transient occlusion of a septal artery with an angioplasty balloon resulted in a reduction in the LVOT gradient. In 1994 Ulrich Sigwart extended this approach, introducing a small volume of absolute ethanol by selective injection into a septal vessel to create an area of localized myocardial infarction in the area of the left ventricular outflow tract.[7] This technique has been adopted by a number of groups worldwide and several hundred procedures have now been performed. As with all new interventions there has been a process of rapid evolution in patient selection and operative technique. This chapter describes our current approach and identifies aspects that are the subject of ongoing evaluation.

Patient selection and initial investigation

Subjects should exhibit symptoms despite medical therapy or have proven intolerance to drug agents. Patients with previous surgical myectomy or DDD pacemaker implantation can be treated.

Echocardiography confirms the anatomical diagnosis. Magnetic resonance imaging provides comprehensive diagnostic information in almost all patients and may be an alternative when echocardiography is suboptimal. The patient should manifest classical HOCM with SAM, as described in the introduction. Although we have performed a small number of procedures in patients with the mid-cavity obliteration variation of HOCM, experience in this clinical setting is limited.

Doppler examination can be used to measure the LVOT gradient at rest and under conditions of exercise or pharmacological stress. A resting gradient of >50 mm Hg or a stress gradient of >100 mm Hg are commonly used thresholds for intervention although highly symptomatic patients with less significant findings may benefit from the procedure. Exercise testing is safe in HOCM and for research purposes we document exercise capacity with measurement of maximal oxygen uptake.

Diagnostic cardiac catheterization provides important information. Left ventriculography can demonstrate LV outflow obstruction, SAM and mitral regurgitation. Coronary angiography is performed to exclude co-existing significant coronary disease and to identify the anatomy of the blood supply to the septum

We measure the LV outflow tract pressure gradient with simultaneous recordings from a Brockenbrough catheter in the left ventricle (placed via a trans-septal approach) and a coronary angioplasty guide catheter in the ascending aorta. Other units use bilateral femoral artery puncture for retrograde cannulation of the LV cavity and aorta with separate catheters. It is best to employ an end-hole catheter in the LV since the level of obstruction can be very localized. The pressure gradient may also be measured with a double lumen catheter or by withdrawing an end-hole catheter slowly from the apex of the LV to the ascending aorta (Fig. 27.2). These methods do not allow continuous examination of changes in the gradient over the course of the procedure.

Manoeuvres designed to detect provoked obstruction are indicated when the gradient at baseline is less than 30–50 mm Hg. The stimulation of ventricular premature beats may reveal a gradient in the post extra-systolic cycles. Ectopics can

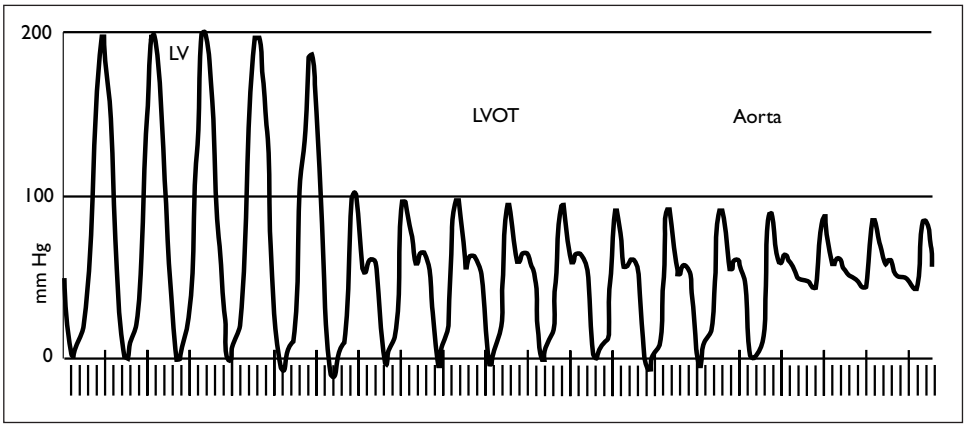

Figure 27.2
Pressure recording from a catheter pull-back from the left ventricular cavity (LV), through the LV outflow tract (LVOT) and into the aorta. The level of obstruction is seen to lie in the LVOT.

be induced with manipulation of the ventricular catheter or using a single paced beat from a temporary wire. The most reliable method of gradient provocation is to use a slow infusion of isoprenolol at an initial rate of 1 μg/min. The rate is then increased until the heart rate reaches 100–110 beats per minute or the LV outflow pressure gradient reaches diagnostic values. Operators should note that there is often a delayed heart rate response with a lag time of up to a minute and close control of the infusion is essential.

A significant systolic pressure gradient often develops between the ascending aorta and femoral artery during isoprenolol infusion, particularly in young patients. This may give rise to an exaggerated estimation of the provoked LV outflow obstruction if pressures are recorded from the femoral sheath.

Performing the non-surgical septal reduction procedure

Preparation

The procedure is performed under local anaesthetic with light premedication (eg: temezapam 10–20 mg). An intravenous cannula should be placed in a peripheral vein. The right groin is prepared in the usual manner and venous and arterial sheaths placed. The first venous sheath is used to introduce a temporary pacing electrode at the apex of the right ventricle. This is essential, as heart block (usually transient) is very common following alcohol injection. In our unit, a second venous sheath is used for the trans-septal puncture (TSP) equipment. An alternative strategy is to perform an arterial puncture (perhaps at the left groin) and use this to position an end-hole catheter at the apex of the LV.

The third sheath is placed in the femoral artery and is used to introduce the left coronary guide catheter. This can be selected from routine stock and sized for optimal access to the left coronary system. We favour the Judkins left short tip, but patient anatomy and local preference will influence the choice. After the TSP has been performed, systemic anticoagulation is induced with a bolus of heparin (7500–10 000 units as dictated by body weight) and diagnostic evaluation of the LVOT gradient performed (see above).

Identification of the target vessel

Angiographic images are acquired to identify the anatomy of the blood supply to the septum. The vessel pattern is variable and can be confusing. Multiple angiographic projections may be required to distinguish between septal and diagonal vessels

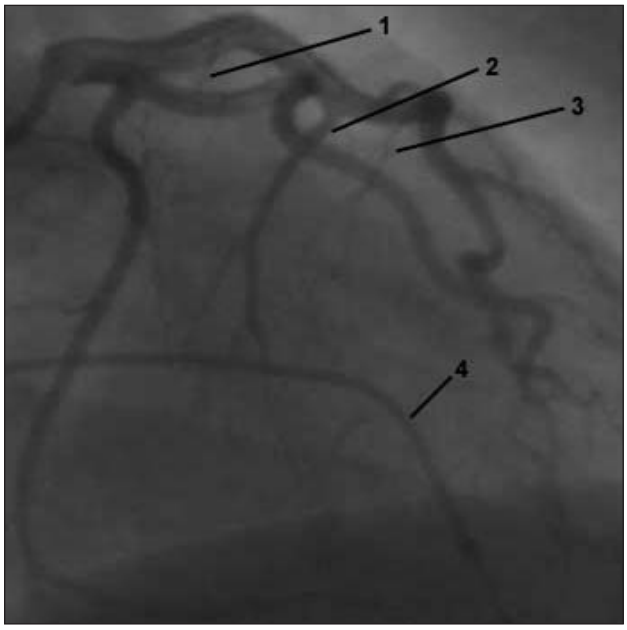

Figure 27.3
Selective coronary injection of the left coronary system in a right anterior oblique projection. Potential target septal vessels are identified (1, 2, 3). A temporary pacing wire has been placed at the apex of the right ventricle (4).

(Fig. 27.3). The ideal target vessel is a proximal septal artery of diameter 1.0–2.0 mm. If more than one potential target is identified then additional techniques (described below) are required to identify the most suitable vessel. These methods, using intra-coronary echo contrast agents, are also of value in the very rare circumstances when the blood supply to the proximal septum is derived from the circumflex or an intermediate coronary trunk.[8]

A 300 cm angioplasty guidewire is introduced into the selected septal vessel. A flexible, low trauma wire is the first choice, although sometimes a stiffer shaft (intermediate or standard) may be needed to ensure balloon access to a septal arising at an acute angle from the main left anterior descending (LAD) vessel. An over-the-wire (OTW) angioplasty balloon catheter is advanced over the wire and positioned in the proximal part of the septal vessel. Any semi-compliant, OTW balloon system is acceptable but it is best if the balloon is of short length (maximum 10 mm). Longer devices mean that the alcohol will be delivered into a more distal portion of the target vessel, limiting its myocardial distribution, particularly if the balloon tip lies distal to a branch in the septal vessel. If the septal artery has an early bifurcation, each distal branch can be approached as if it were an individual vessel.

The balloon diameter should be sized to ensure complete occlusion of the septal artery at low or nominal inflation pressure. A two-marker balloon allows more precise positioning. The entire length of the balloon must be within the septal to eliminate the possibility of LAD barotrauma or the balloon 'melon-pipping' back into the LAD vessel (Fig. 27.4). Sometimes balloon occlusion of the vessel reduces the resting gradient. This is a very favourable sign that an appropriate target septal vessel has been identified, but the positive and negative predictive value of this observation is limited and does not obviate the desirability of a contrast echo study (see below).

With the balloon inflated, two injections of radiographic contrast are performed. In the first of these a standard, selective left coronary injection through the guide catheter demonstrates that the target septal vessel is sealed to the antegrade flow of dye and hence, by presumption, any subsequent retrograde leak of alcohol. In the second injection, contrast is introduced through the central lumen of the OTW balloon into the target vessel (Fig. 27.5). This is to ensure that there is no major collateralization that takes dye (and hence, in due course, alcohol) to the LAD or other major epicardial vessel. The ideal image seen at this stage is a septal myocardial blush.

Additional anatomical confirmation is provided with a myocardial echo contrast study. Trans-thoracic images in the para-sternal long axis or apical four chamber views are used with recording for immediate play-back analysis. An echo contrast agent is injected through the central lumen of the OTW balloon. Suitable agents include Levovist™ (manufactured by Schering) or Optison™, although the latter has a very short dwell time in the myocardium. The region of myocardial distribution is then visible as a bright area on the echo images. The ideal target region is the hypertrophied muscle at the point where the SAM of the mitral valve touches the septum. If the septal vessel selected is too distal then contrast illuminates the septal muscle in mid-cavity or

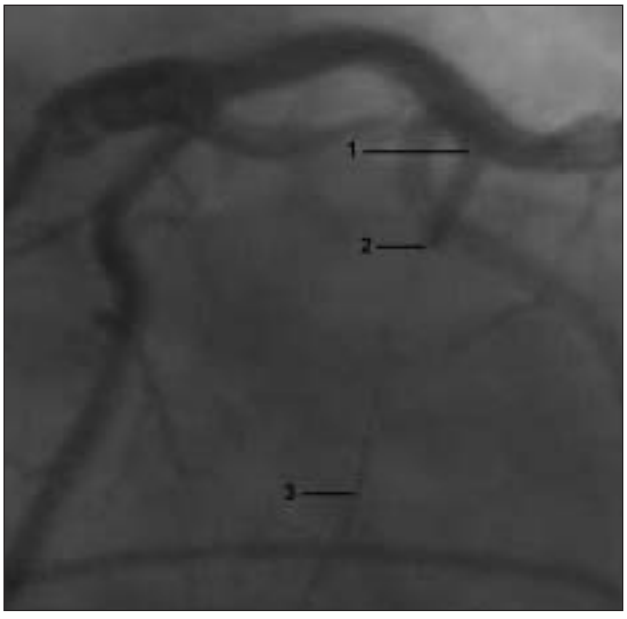

Figure 27.4
An over-the-wire angioplasty balloon is inflated in the proximal portion of the septal vessel. The margins of the balloon are illustrated (1, 2). An angioplasty guidewire marks the course of the septal vessel (3)

Figure 27.5
The angioplasty balloon is inflated in the proximal portion of the septal vessel. An injection of radiographic contrast has been made through the central lumen of the over-the-wire balloon. The contrast distribution in the septal vessel and its branches is clearly seen (2).

near the apex. Contrast appearance in the left or right ventricular free walls identifies that the target vessel is a diagonal branch rather than a septal.

Alcohol injection

After final angiographic confirmation of balloon positioning and septal occlusion, a small volume of absolute alcohol is injected through the OTW system. The dose depends on the size of the septal artery and the extent of myocardial run-off. There has been a trend towards the use of reduced alcohol doses and typical injection volumes now lie in the range 0.5–1.5 ml. We favour the use of a single bolus injection rather than a slow infusion. We believe that this will promote dispersion in the perfusion bed without the risk of selective distribution caused by small vessel thrombus and occlusion in the early phase of the injection. The alcohol should be followed by 1–2 ml of saline to clear the dead space of the OTW balloon.

The patient will experience immediate pain and should be warned to expect this symptom. If required, diamorphine can be administered before the injection, but we do not do this as a routine as the pain eases after 30–45 seconds and is rarely severe. ST segment change and ventricular ectopic activity are routine. Transient heart block is common but the heart rate is supported by the temporary pacemaker, which is set to initiate capture if the native rate falls below 40 beats per minute.

The balloon is kept inflated for 5–7 minutes after alcohol injection. After this time the guidewire can be re-introduced into the distal septal although this is not essential. Deflation of the balloon and withdrawal into the guide catheter should be performed in a rapid and positive fashion to limit the possibility of any residual alcohol entering the LAD circulation.

It is possible to repeat this process with a second, third or even fourth septal vessel. Multiple vessel injection was our norm in the early series and may still be indicated in cases when the septal territory is supplied by a leash of small vessels or two proximal septal perforators. Other groups have adopted a policy of single-vessel injection with the option to perform a subsequent staged procedure on a second vessel if the patient does not demonstrate a good clinical response at medium term follow-up.

Repeat diagnostic evaluation

A coronary angiogram usually reveals occlusion of the target septal with a no-reflow appearance. A repeat resting or stress gradient study can be performed, often with gratifying results although, as discussed below, myocardial remodeling and hence the full benefits of the intervention may take many months to become apparent.

Efficacy and complications

Like all new surgical and interventional procedures, NSSR has undergone a period of rapid evolution and refinement. Coincident with this a number of operators and centres have gained their initial experience with the technique. Consequently, it may be expected that the results from the earliest cases may be less good than in current practice. Certainly the use of myocardial contrast echocardiography has allowed more precise targeting of the alcohol injection and the trend towards the delivery of smaller alcohol volumes into fewer septal vessels has reduced the immediate procedure-related complications, in particular complete heart block.

Follow-up data have been published describing short-term results in around 200 patients and medium-term data in less than 100 cases. The longest reported follow-up period is a mean of 30 months in 25 patients.[9] All outcome data were recently reviewed by Knight,[4] who observed that the mortality rate was low (2%) both at the initial procedure and in subsequent follow-up. It must be remembered that early cases were often performed in patients with significant co-morbidity and involved more aggressive dose regimes. The current procedural mortality rate is probably well below this value.

The main complication of the procedure is the induction of permanent atrio-ventricular conduction block necessitating permanent pacemaker implantation. The presence of trifasicular or complete heart block persisting at 48 hours post procedure is an indication for implantation of a dual chamber pacing device. To date this has occurred in around 20% of cases, although with better myocardial targeting we may expect this to fall to 10%.

Some observers have been concerned that the induction of septal infarction may result in a range of adverse effects.[10] To date there have been no reports of late ventricular arrhythmia or induced ventricular septal defect. Another concern relates to the impact of the procedure on ventricular function, both systolic and diastolic. The natural history of HOCM can involve progression to a phase of poor ventricular function and this may be hastened or exacerbated by the infarction of healthy muscle. Fortunately, follow-up studies have not demonstrated any trend to increasing ventricular cavity dimensions or reduced systolic performance, although the current observation period is too short and involves too few patients to draw any firm conclusions in this respect.

There is little doubt that NSSR is effective in the reduction of LVOT obstruction. Echocardiographic studies have observed that the procedure results in thinning of the basal septum with reduced SAM and mitral regurgitation. Left atrial size may also be reduced. Serial follow-up has revealed that the magnitude of the gradient continues to fall as the myocardium remodels with scar formation. The benefits of the procedure may take up to 3 months to become apparent and may continue to develop over the first post-operative

year. In the German series with 2–3 year follow up, the stress LVOT gradient was reduced from a pre-procedure mean of 147 mmHg to a mean of 12 mmHg at final assessment. All patients experienced a greater than 50% reduction in gradient and there was complete elimination in over 70% of subjects.[9]

The technique also results in an improvement in left ventricular diastolic function with improved relaxation and compliance.[11] In addition there is consistent alteration of septal activation with secondary incoordination of contraction—similar to that seen with dual chamber pacing.[12] These factors could play a significant role in gradient reduction and subjective functional improvement.

The assessment of symptomatic benefit is complicated by the potential for a placebo effect. Nevertheless, follow-up reports suggest a substantial and sustained improvement of greater than 1 New York Heart Association functional class. Objective tests of functional capacity have also shown increases of around 40% in exercise performance at medium term follow-up.

Future directions for NSSR therapy in HOCM

Developments in technique, principally the use of myocardial contrast echocardiography, have refined the procedure and hold the prospect of reduced complication rates. Questions concerning the selection of single- or multiple-target vessels, the total alcohol dose and its rate of administration may be subject to further evaluation. We suspect that there will be an increase in the use of single-vessel procedures with the option of repeat intervention if medium term maturation of the infarct area fails to bring the desired clinical benefit.

The elegance, simplicity and apparent efficacy of this procedure have led to its rapid dissemination within the cardiology community. Maron has observed that the number of NSSR procedures performed over the last few years is ten times that predicted by the historic activity of the best surgical units offering the surgical myectomy procedure.[6] NSSR is a promising therapeutic option for the management of a selected group of patients with symptomatic HOCM, resistant to medical therapy. The procedure may be best performed in specialist centres with a developed interest in the management of HOCM. All cases should be documented for inclusion in collaborative registries and other research ventures. Its long-term efficacy has yet to be evaluated and its value compared to intensive medical therapy or traditional surgery has not been assessed in prospective randomized trials. Such studies are now indicated but may be difficult to complete given the very disparate nature of the treatments under consideration.

Conclusions

- Non-surgical Septal Reduction (NSSR) is a promising new therapy for the treatment of classical hypertrophic obstructive cardiomyopathy (HOCM).
- Patients should have symptoms related to a significant left ventricular outflow tract (LVOT) gradient that have proven resistant to conventional medical therapy.
- The procedure involves the selective injection of absolute alcohol into the hypertrophied basal septum via the epicardial coronary vessels.
- This results in localized infarction with septal thinning and other changes that tend to reduce the LVOT gradient.
- The procedure is well tolerated with low mortality. The principal complication is the development of heart block, which demands pacemaker implantation in around 20% of patients.
- Haemodynamic and functional improvement can take some time to become evident and may continue to improve for several months after the procedure.
- Emerging medium-term follow-up data suggest that the benefits are sustained with no late morbidity.
- The long-term outcome of the procedure is not known and its value has never been compared to other therapeutic options in randomized controlled trials.

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28

Percutaneous transvenous mitral commissurotomy

Kanji Inoue, Kean-Wah Lau and Jui-Sung Hung

Introduction

Rheumatic mitral stenosis continues to be a major health concern in many less developed countries. Previously, the only mechanical therapy for selected symptomatic patients with significant mitral stenosis was either open or closed surgical commissurotomy. Percutaneous transvenous mitral commissurotomy (PTMC) introduced in 1984 by Inoue et al[1] provided a new dimension in the treatment of patients with mitral stenosis. Extensive clinical studies have established this minimally invasive, non-surgical procedure to be a safe and effective therapeutic modality in selected patients with mitral stenosis.[2–8] This chapter provides an overview of the technical aspects and clinical outcome of the procedure, and attempts to place the clinical use of PTMC in its proper perspective.

Technical aspects of PTMC

Besides the original Inoue technique using size-adjustable, self-positioning balloon catheters, various other techniques using fixed-size balloon catheters have been developed for performing PTMC. These include the antegrade (transvenous) approaches with one or two balloon catheters through one or two inter-atrial septal punctures[5–12] or the retrograde (transarterial) approaches with or without transseptal access.[13,14] However, the Inoue balloon catheter and the double-balloon catheter systems via the transvenous approach have remained the two principal PTMC techniques used today.

Although both techniques are effective, the Inoue method is more extensively applied for several reasons. Firstly it is technically less demanding and clearly simpler to perform than the double-balloon approach, thereby engendering a shorter procedural and radiation time.[15] This advantage is vital in pregnant patients where the hazard of radiation to the fetus is of paramount importance, and for patients in pulmonary edema in whom swift and expeditious PTMC is clearly desirable.[16]

Secondly, the Inoue balloon system has a short balloon and a flexible catheter tip. It does not require placement of guide wires within the left ventricle, as does the longer, stiffer Mansfield balloon, which requires left ventricular wiring. These favourable characteristics have avoided left ventricular perforation in the thousands of Inoue PTMC procedures performed.[3] In contrast, left ventricular perforation with or without tamponade, especially in the presence of a small left ventricle, has been reported in up to 8% of double-balloon procedures.[15] Thirdly, the ability to control the balloon catheter tip afforded by the Inoue balloon assembly enables the operator to prevent entrapment of the balloon within the chordae tendineae, thus avoiding rupture of the chordal structures during full balloon inflation. It also allows the catheter tip to be steered away from the left atrial appendage – thereby preventing systemic embolization in patients with left atrial appendage thrombus undergoing the procedure.[17] Thrombus confined to the left atrial appendage is not considered a contraindication in our institutions.[4,18] Furthermore, the Inoue balloon system is designed for stepwise dilatation and also for left atrial hemodynamic assessment after each inflation–deflation cycle. The procedure can thus be terminated immediately whenever there is a suggestion of increasing mitral regurgitation.[17] This salutary feature is crucial during PTMC in high-risk situations such as grossly distorted mitral valves and/or coexisting baseline moderate (grade 2+) mitral regurgitation, where the risk of incurring severe mitral regurgitation is increased.[4,19–22] Nevertheless, the Inoue balloon system suffers from one major drawback: it is significantly more expensive than the double-balloon system.

Equipment

Inoue balloon catheter

The Inoue balloon catheter (Fig. 28.1) is a novel single-balloon catheter. The balloon is made of a double layer of latex rubber, with a synthetic micromesh inserted between the layers for reinforcement. In addition, the central region of the mesh is wound with a rubber band. The shape of the balloon changes in three stages, depending on the extent of inflation: a small spherical shape with inflation of the distal half (Fig. 28.1d), an hourglass shape with inflation of the proximal half (Fig. 28.1e), and a barrel shape of the fully inflated balloon (Fig. 28.1f). The balloon catheter has a 12 Fr polyvinyl chloride tube shaft with a coaxial double lumen. The inner lumen of the catheter permits pressure measurements, blood sampling, and insertion of a metal tube, a guidewire or a stylet. The Inoue balloon catheter does not easily slip from the stenosed mitral valve orifice during its inflation. It allows for a short inflation–deflation cycle of 5–6 sec and the diameter of the balloon can be varied.

Auxiliary instruments (Fig. 28.2)

In addition to the Inoue balloon catheter (Fig. 28.1), a number of auxiliary instruments are provided.

- Metal tube (18-gauge, length 80 cm)
- Dilator (14F polyethylene tube, length 70 cm)
- Stainless steel guidewire (diameter 0.025 inch, length 180 cm)
- J-tipped spring wire stylet (diameter 0.038 inch, length 80 cm)
- Syringe (30 ml) with connecting tube
- Ruler

Selection of the balloon catheter (Table 28.1)

It is important to select the balloon catheter size properly for each individual patient. In selecting the catheter size, the patient's height is used as a first guide (Table 28.2). The catheter size is then modified according to the following factors:

- valvular condition;
- age;
- gender;
- occupation;
- degree of surgical risk.

Table 28.1 Selection of balloon size.

Patient height
Other determinants
Valvular condition
Age
Gender
Occupation
High surgical risk
Stepwise dilatation technique
Diameter at initial inflation 4 mm below maximal diameter
Diameter at subsequent inflations increased by 1 or 2 mm
Determining the need for further dilation
Degree of increase in mitral regurgitation
Degree of commissure separation
Degree of persistence of constriction in the inflated balloon
Increase in mitral valve area

Table 28.2 Patient height.

Catheter	*Diameter range (mm)*	*Patient height (cm)*
PTMC-30	26–30	>180
PTMC-28	24–28	>160
PTMC-26	22–26	>147
PTMC-24	20–24	≤ 147

Patients with severe valve deformity have a high risk of developing significant mitral regurgitation following the procedure. Therefore, a balloon catheter one or two sizes smaller than that dictated by the patient's height should be selected.

Preoperative and postoperative management

Premedication

Patients in atrial fibrillation or those with a history of paroxysmal atrial fibrillation should be anticoagulated with warfarin for at least 6 weeks.

Heparin during PTMC

A total dose of 100 U/kg body weight of heparin should be given to patients already receiving warfarin; 150 U/kg body weight of heparin is given to those not receiving warfarin. Half

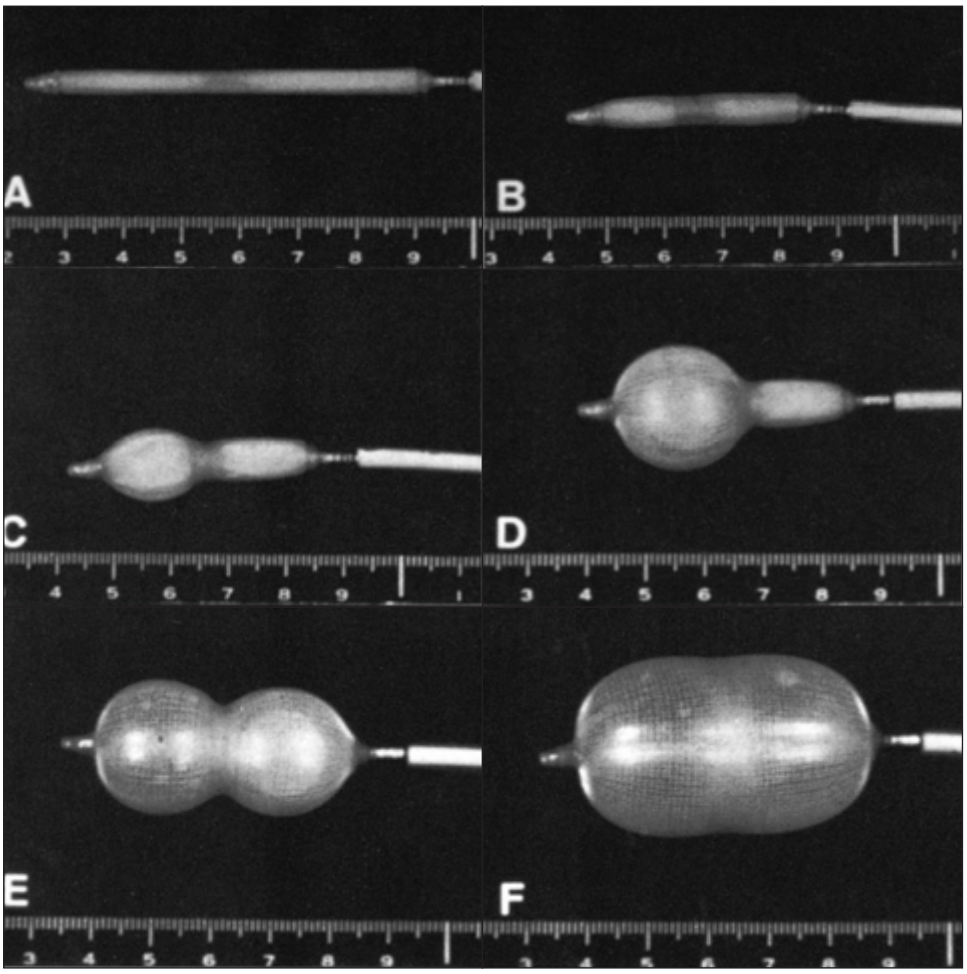


Figure 28.1
Various stages of inflation of the Inoue balloon catheter. (a) Stretched deflated balloon. (b) Unstretched deflated balloon. (c) Partially inflated distal end, enables crossing of the mitral valve (MV) orifice. (d) Inflation of the distal end of the balloon to anchor the balloon to the ventricular aspect of the MV. (e) Proximal and distal ends partially inflated across MV. (f) Inoue balloon fully inflated.

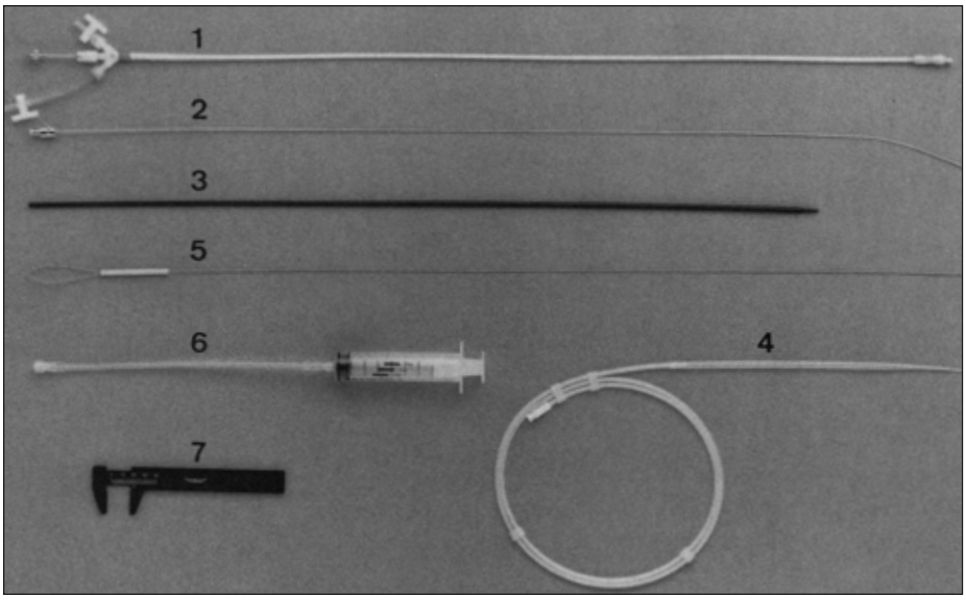


Figure 28.2
Inoue balloon catheter and auxiliary instruments. (1) Inoue balloon catheter (2) Metal tube (3) Dilator (4) Guidewire (5) Stylet (6) Syringe (7) Ruler.

of the dose is given at the beginning of the procedure, and the rest is given after successful atrial septal puncture. In elderly patients or patients with hepatic dysfunction, the amount of warfarin should be reduced to avoid serious hemorrhagic complications.

Postoperative management

Patients remain at rest for 24 h after PTMC. Doppler echocardiography is performed to confirm the absence of cardiac tamponade 4–5 h after PTMC. When patients show an uncomplicated course after the procedure, they are usually discharged from the hospital after 1–3 days. Patients in atrial fibrillation remain on warfarin therapy.

Atrial septal puncture

After left ventriculography, right atrial angiography is performed to determine the trans-septal puncture site (Fig. 28.3), using the following techniques. Right atrial angiography is performed under normal respiration in the frontal view until the aorta is visualized. On the right atrial stopped-frame image at systole, the position of the upper end of the tricuspid valve is regarded as point A. On the left atrial stopped-frame image, a horizontal line is drawn from point A to the point where it intersects with the right lateral edge of the left atrium (regarded as point B). A vertical line is drawn from the mid-point of line AB, and the point where it intersects with the lower edge of the left atrium is regarded as point C. The puncture site is on the vertical line about two-thirds of the vertebral body height above point C. Trans-septal puncture is performed using a Brockenbrough needle and a Mullins dilator (USCI, Bellerica MA) without its sheath and under local anesthesia. After right atrial angiography, the position of the fluoroscopic device should be kept as stable as possible.

Initially, a J-shaped 0.032-inch guidewire is inserted via the right femoral vein into the superior vena cava. The dilator is inserted over the guidewire into the superior vena cava, the guidewire is removed, and the Brockenbrough needle is inserted into the dilator to a point about 5 mm from the dilator tip. The direction indicator is rotated clockwise to the 3 o'clock position, and the dilator with the concealed needle is pulled downward until near the target point. In this process, the catheter tip sometimes moves, as if falling into the left side near the target point. This shows that the dilator tip has fallen into the fossa ovalis. To put the needle tip perpendicularly to the atrial septum, the arrow direction is rotated further clockwise until strong resistance is felt. The arrow direction varies according to the left atrial size: between 4 and 5 o'clock in a mildly or moderately dilated left atrium, and between 6 and 7 o'clock in a large left atrium. When the dilator tip is at the target point, the dilator with the concealed needle is pushed slightly, and the dilator tip is fixed against the atrial septum. The needle is then pushed forward with the right hand, while

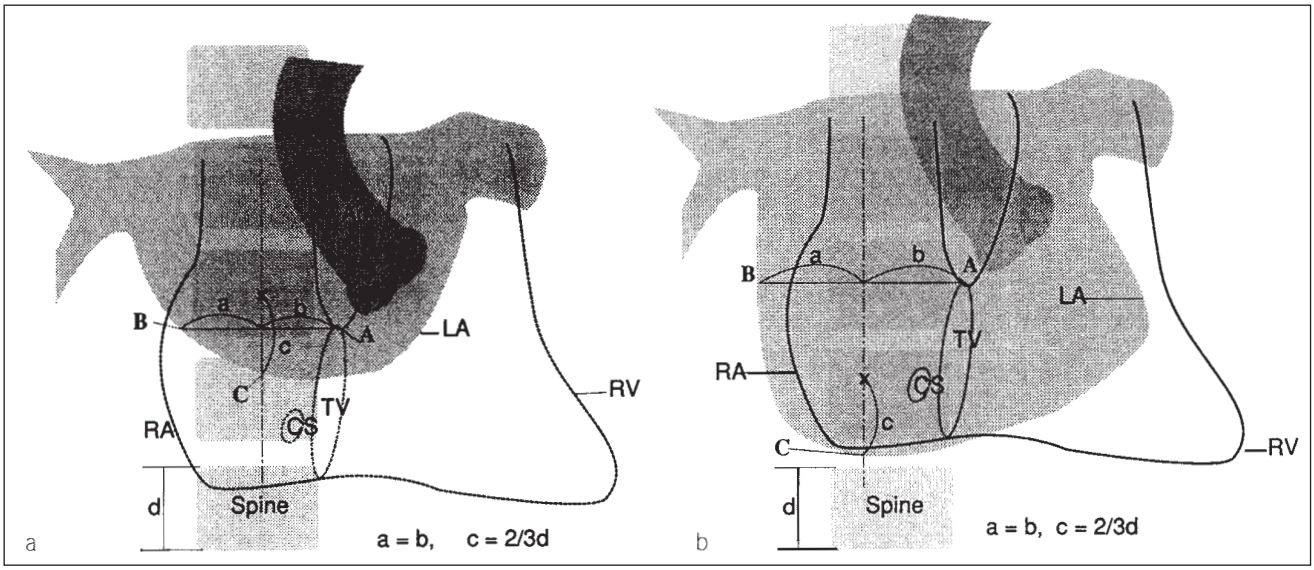


Figure 28.3
Landmark for atrial septal puncture from right atrial angiography. (a) Moderately enlarged left atrium: (b) Giant left atrium. On the right atrium image, the position of the upper end of the tricuspid valve at systole is regarded as point A. On the left atrial image, a horizontal line is drawn from point A, and the point where it intersects with the right lateral edge of the left atrium is regarded as point B. A vertical line is drawn from the mid-point of line AB. The point where it intersects with the lower edge of the left atrium is regarded as point C. The puncture site is on a vertical line at a point approximately two-thirds of the vertebral body height above point C.
Ao, aorta; LA, left atrium; RA, right atrium; RV, right ventricle; TV, tricuspid valve; CS, coronary sinus.

fixing the dilator with the left hand. Entry into the left atrium is confirmed by injection of contrast media. The indicator arrow is directed toward 3 o'clock and both the needle and dilator are simultaneously advanced 2 cm into the left atrium. Then, only the dilator is advanced 2 cm further with the needle held fixed. Finally, the needle is withdrawn, immediately thereafter, the required heparin is administered.

PTMC procedure

Balloon preparation

After confirmation of the balloon diameter, the balloon is prepared for insertion. A metal tube is inserted into the inner tube of the balloon catheter, and locked in place. The inner tube with the locked metal tube is pushed forward until its pin is locked into the slot. In this position the balloon is fully stretched.

Insertion of balloon catheter into left atrium (Fig. 28.4)

After the Mullins dilator is carefully pulled back 1–2 cm so that its tip does not touch the left atrial wall, a 0.0025-inch stainless steel guidewire is passed through the dilator and advanced until its coiled loop touches the roof of the left atrium. The Mullin dilator is then removed and a 14 Fr dilator is inserted into the left atrium over the guidewire to dilate the puncture site of the femoral vein and atrial septum, and then

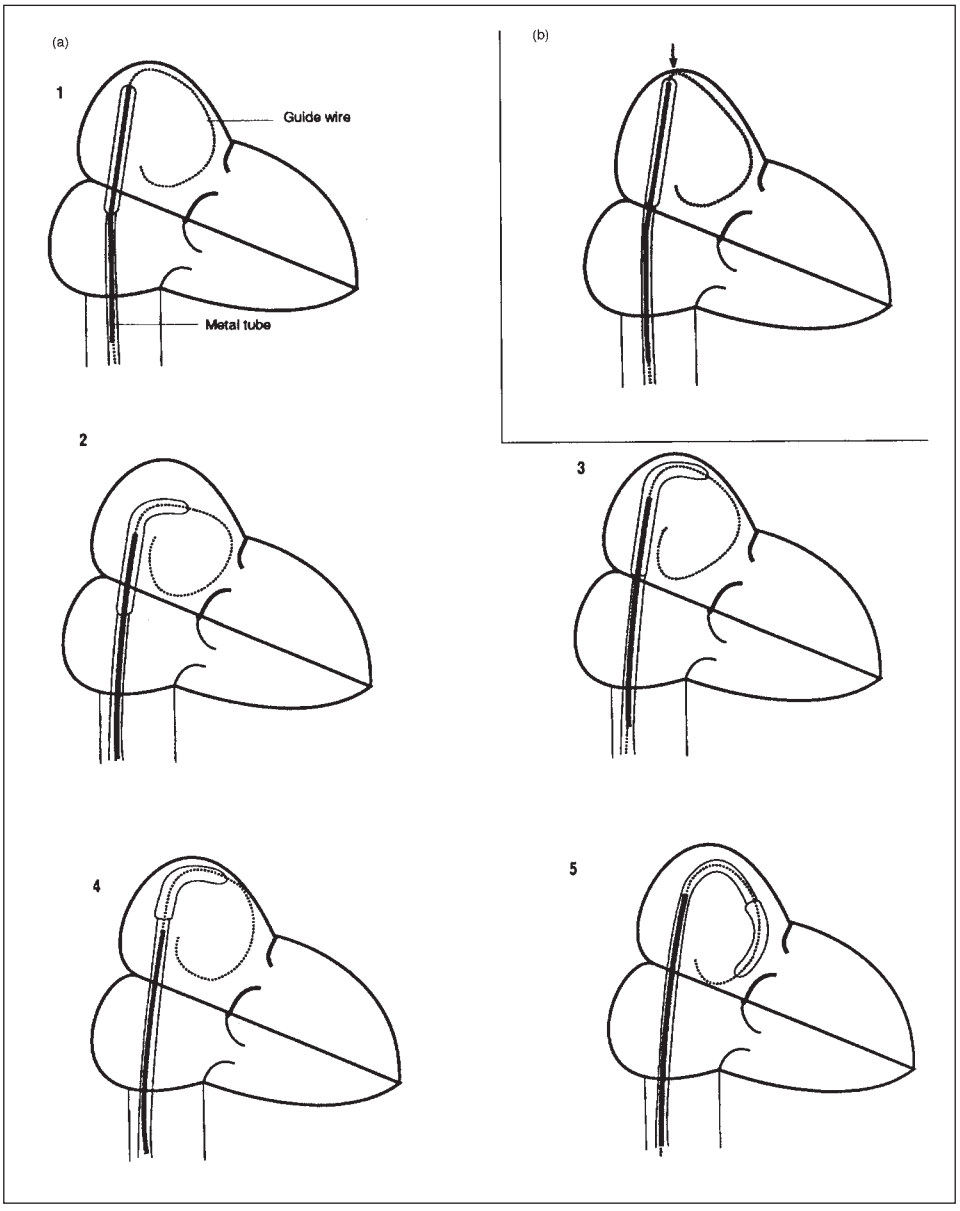


Figure 28.4
Insertion of the balloon catheter into the left atrium (a1). After the tip of the balloon catheter passes across the atrial septum, the catheter is inserted into the left atrium, leaving the proximal part of the balloon within the right atrium. (b) If the catheter tip is pushed forcefully against the upper edge of the left atrium, the guidewire will bend at an acute angle. (a2) The metal tube is withdrawn 2–3 cm from the inner tube. (a3) Both the balloon catheter and the metal tube are advanced further until the balloon section passes completely through the atrial septum. (a4) The stretched balloon is returned to its original length. (a5) The balloon catheter is advanced further until it is near the mitral orifice.

the dilator is removed. The balloon catheter with its balloon segment stretched is passed over the guidewire across the atrial septum and advanced until its tip approaches the roof of the left atrium, with the proximal part of the balloon remaining within the right atrium. Pushing the balloon catheter forcefully against the roof of the atrium should be avoided, as this would bend the guidewire into an acute angle, making subsequent manipulation difficult.

After the balloon tip is advanced near the roof of the left atrium, the metal tube is released and withdrawn 2–3 cm from the inner tube, and then both the balloon catheter and metal tube are advanced. The balloon is inserted along the guidewire until the entire balloon is within the left atrium. Next, the inner tube is released and pulled back until resistance is felt; thus the stretched balloon is returned to its original length. Only the balloon catheter is advanced further over the coiled guidewire until the balloon tip is near the mitral valve orifice. Finally, both the metal tube and guidewire are removed simultaneously.

Crossing the mitral orifice (Fig. 28.5)

After the balloon catheter is inserted into the left atrium, the fluoroscopic projection is changed from frontal to 30° right anterior oblique view. The distal portion of the balloon is partially inflated to a diameter of 10–15 mm with about 1 ml of diluted contrast material. This allows the balloon to easily pass through the mitral valve orifice into the left ventricle, and ensures that the balloon will not stray among the chordal structures in the left ventricle.

There are two different methods of inserting the balloon catheter from the left atrium across the mitral valve orifice into the left ventricle. In the direct method, the spring wire stylet is inserted into the balloon tip. The balloon catheter and the stylet are moved together while twisting the stylet counterclockwise, so that the balloon tip is directed toward the mitral valve orifice and the balloon is aligned with the long axis

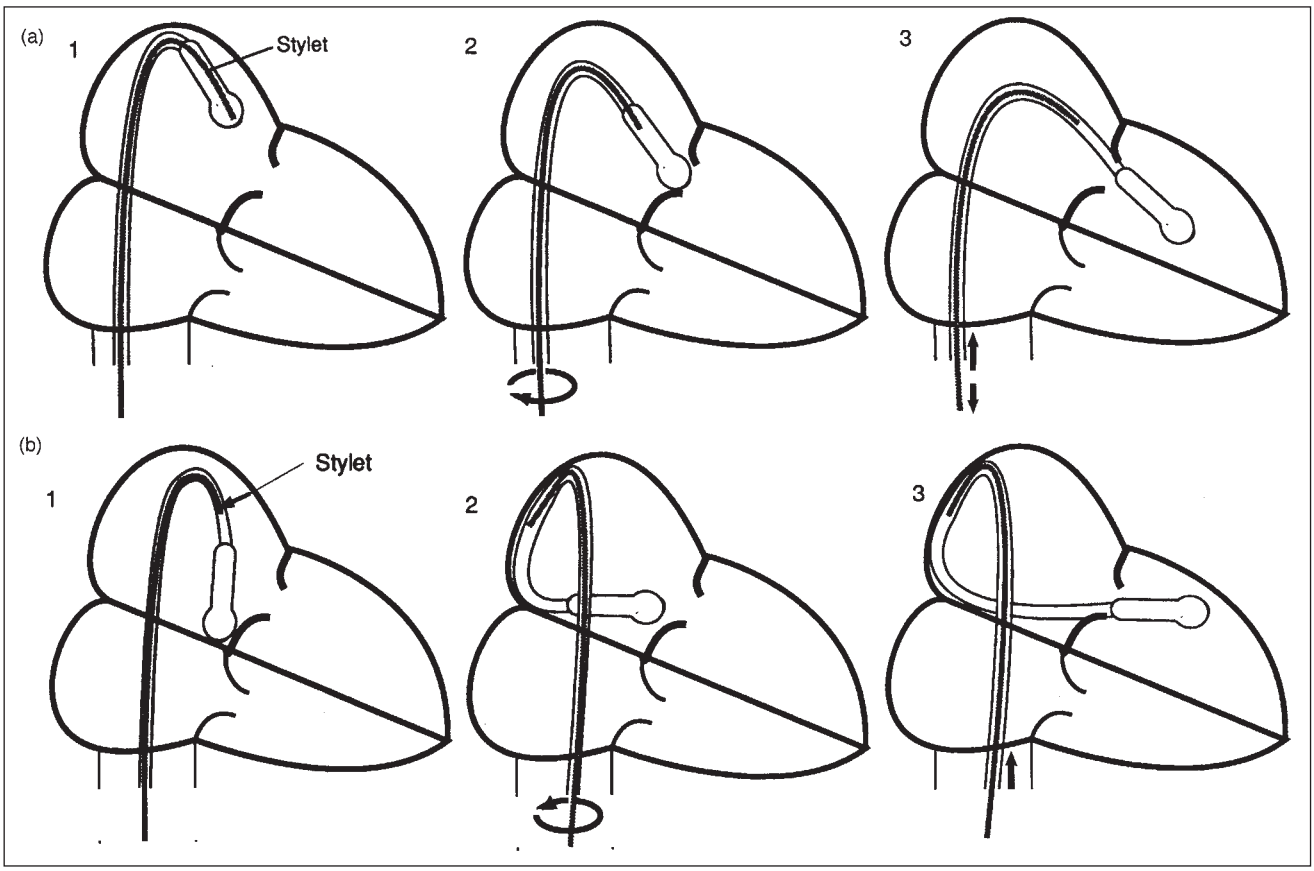


Figure 28.5
Method of balloon insertion across the mitral orifice. (a) Direct method. A stylet is inserted into the end of the balloon catheter. While rotating the stylet counterclockwise by approximately 180°, the balloon catheter and stylet are moved together to direct the balloon tip toward the mitral orifice (a1). When the stylet is pulled back 4–5 cm with the balloon catheter held fixed or the balloon catheter is advanced with the stylet held fixed, the balloon catheter passes through the mitral orifice to the left ventricle. (a2–3). (b) Loop method. The balloon catheter is inserted deeply into the left atrium. The stylet is inserted into the balloon catheter to a position 3–4 cm from the balloon base (b1). When the balloon catheter is rotated clockwise by approximately 360°, the balloon catheter forms a loop (b2). With the stylet held fixed, only the balloon catheter is advanced, allowing the balloon catheter to cross the mitral orifice into the left ventricle (b3).

of the left ventricle. Next, with the balloon catheter held fixed in the position, the stylet is withdrawn 4–5 cm while being twisted counterclockwise by approximately 180° or, with the stylet held fixed, the balloon catheter is advanced toward the valve orifice. Insertion is easier when the stylet is withdrawn 4–5 cm while being twisted counterclockwise and the balloon catheter is advanced forward 4–5 cm at the same time. In the loop method, the balloon catheter is inserted deeply into the left atrium and the stylet is inserted into the balloon catheter to a position 3–4 cm from the balloon base. By rotating the stylet clockwise by approximately 360°, a loop is formed at the catheter section in the left atrium and the balloon tip is brought toward the mitral valve orifice. While the stylet is held firm, only the balloon catheter is advanced. The balloon catheter can be inserted easily across the mitral valve orifice to the left ventricle. This method is best when the atrial septal puncture site deviated upward or leftward from the target point.

Dilation of the mitral orifice

After the balloon catheter is inserted into the left ventricle, the balloon catheter is moved back and forth two or three times inside the left ventricle to confirm that the balloon has not strayed among the chordal structures. When properly inserted, the balloon catheter can be moved freely between the apex and the mitral valve within the left ventricle.

Inflation of the balloon at the mitral orifice is performed by two individuals under fluoroscopic guidance. The operator manipulates the balloon catheter and the assistant handles the syringe. After the assistant has partially inflated the distal portion of the balloon, the operator pulls the catheter back until resistance is felt. Immediately after gently pressing the catheter against the valve orifice, the assistant inflates the balloon fully. As soon as the entire amount of dilute contrast material contained in the syringe is injected rapidly, the assistant deflates the balloon rapidly by applying a negative pressure to the syringe. The change of the balloon shape is observed on the right anterior oblique view under fluoroscopy. Figure 28.6 shows the sequence of steps in the PTMC procedure using the Inoue balloon catheter.

Assessment of efficacy

After each dilatation, the balloon catheter is withdrawn into the left atrium and the stylet is removed. The transmitral gradient, left atrial pressure and cardiac output are measured. The efficacy of valve dilatation is assessed by mean transmitral gradient, auscultation, and two-dimensional color Doppler examination. If necessary, the left ventriculography is repeated to assess the degree of mitral regurgitation. The balloon dilatation procedure is performed using a stepwise dilatation technique described in the next section. The stepwise process is repeated until the pressure gradient is reduced as much as possible without creating significant mitral regurgitation (Fig. 28.7). After the dilatation procedures hemodynamic and cardiac output measurements as well as left ventriculography are repeated (see Fig. 28.6).

Removal of the balloon catheter

When the balloon catheter is withdrawn, the balloon segment is stretched to avoid injury to the atrial septum and right femoral vein. This is accomplished by reusing the guidewire and the metal tube. The guidewire is inserted into the metal tube until it protrudes approximately 10 cm from the tube tip. After completion of the dilatation procedure, the catheter is gently pulled until resistance is felt at the atrial septum puncture site. The metal tube with the guidewire hidden inside is inserted into the balloon catheter, and then the guidewire is advanced and coiled in the left atrium. The metal tube is advanced to the balloon tip and the balloon segment is stretched. Finally, the balloon catheter is withdrawn through the atrial septum and the femoral vein.

Stepwise dilatation technique

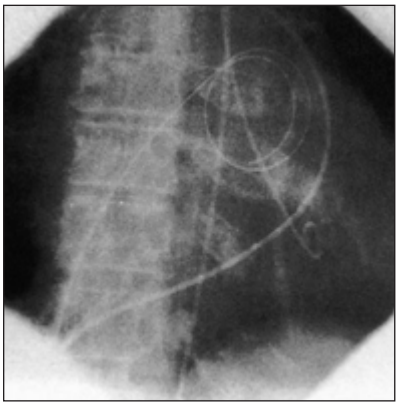
To prevent severe mitral regurgitation, the dilatation procedure is performed in a stepwise process. The balloon is first inflated to a diameter of 4 mm below the maximal balloon diameter and the sequential inflations are repeated with stepwise increments in the balloon diameter. On each inflation, the balloon diameter is increased by 1 or 2 mm. The following parameters are important in deciding whether to dilate further. The balloon size may be changed during stepwise inflations.

Commissure split

The most important factor affecting the immediate results of PTMC is the separation of fused commissures. After each dilatation procedure, the degree of commissure separation is assessed by two-dimensional echocardiogram on the parasternal short axis view. Figure 28.8 shows the method of stepwise dilatation.

The morphology of commissure separation is divided into three types. It can be predicted early in the stepwise dilatation procedure:

- splitting of both commissures;
- splitting of either commissure;
- no splitting of either commissure.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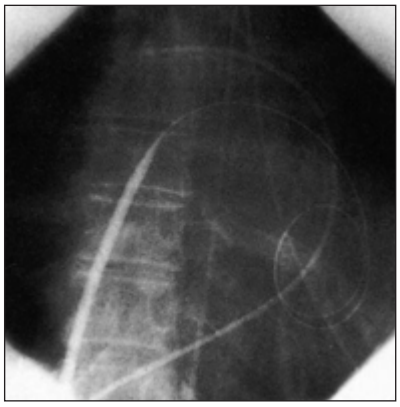
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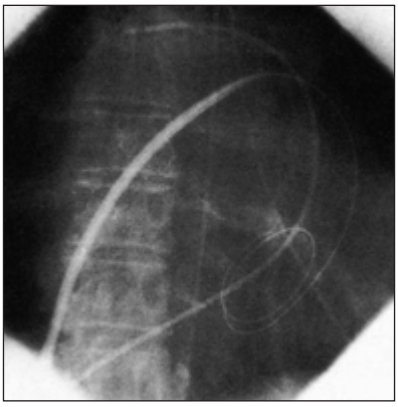
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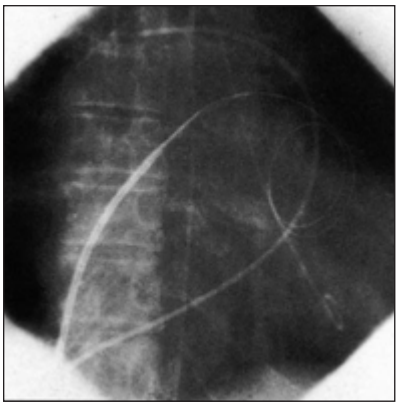
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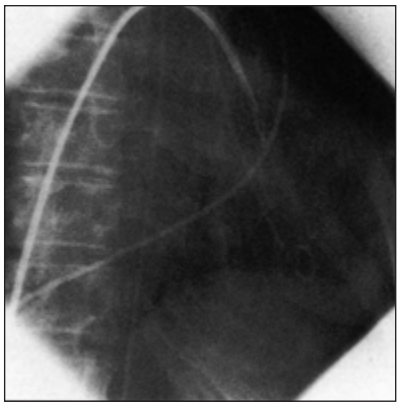
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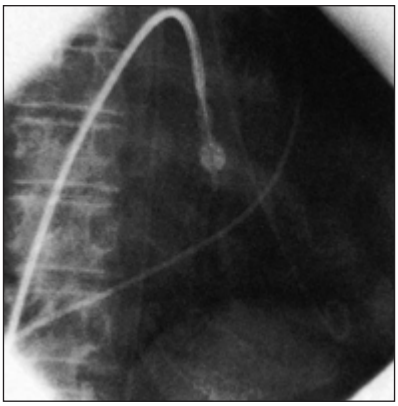
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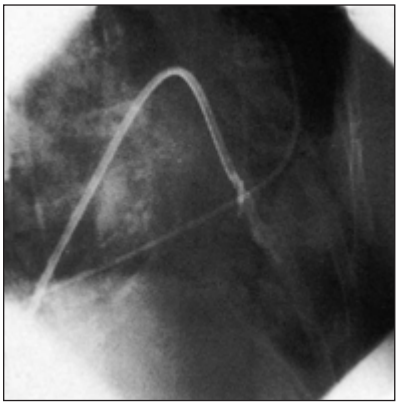
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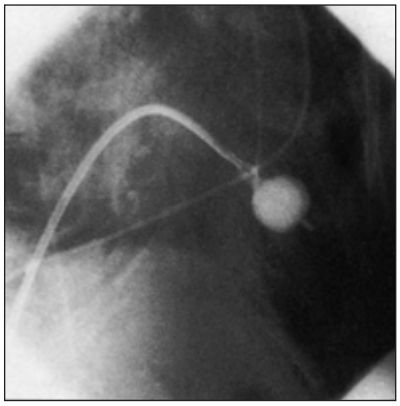
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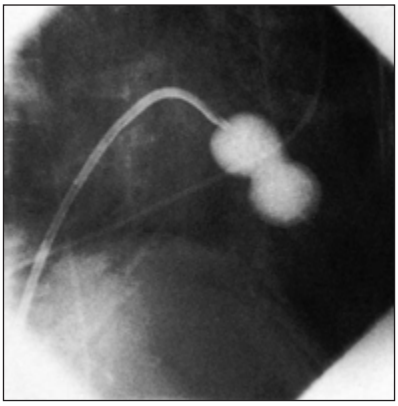
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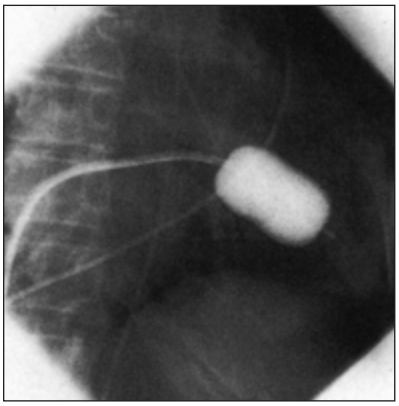
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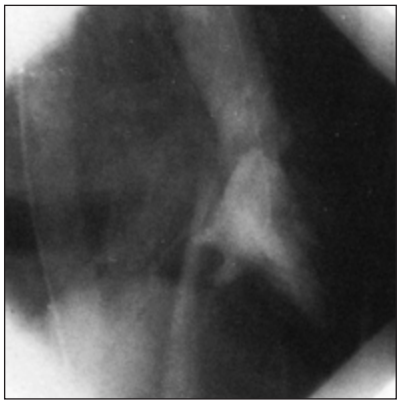
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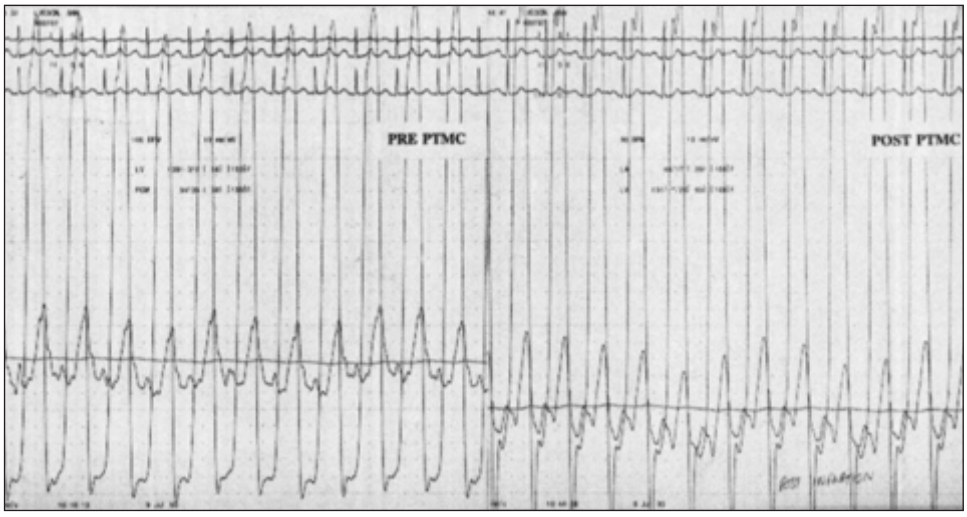

Figure 28.7
Simultaneous left ventricular and left atrial pressure traces showing abolition of mitral valve gradient following PTMC with the Inoue balloon. (Courtesy of Dr DR Ramsdale.)

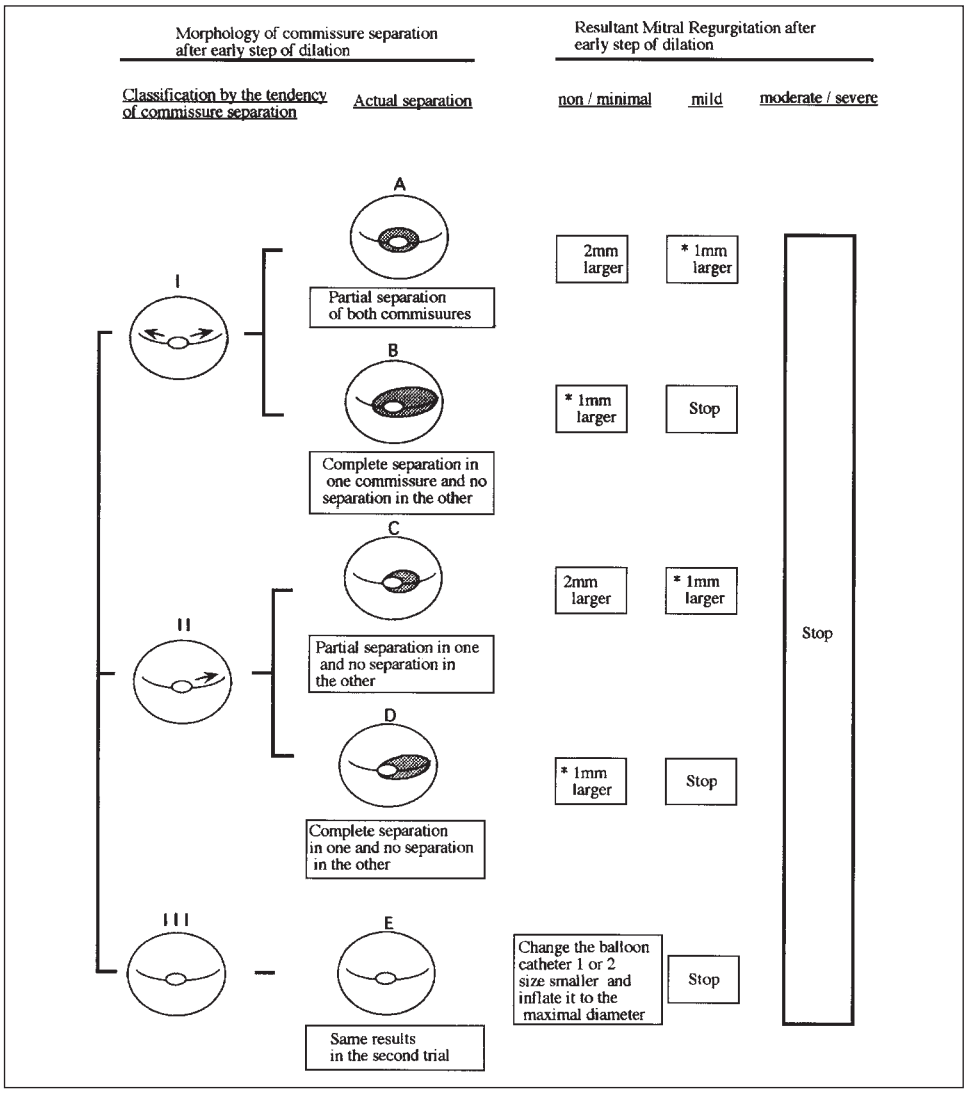

Figure 28.8
Decision whether to further dilate the orifice using the stepwise dilatation technique. When the mitral orifice acquired is adequate for the working condition of the individual patient, further dilatation should be stopped. *In case of severe valve condition or very old patients, further dilatation should be stopped.

Figure 28.6 (opposite page)
PTMC procedure using the Inoue balloon catheter. (a) Coiled guidewire is placed into left atrium using trans-septal technique. (b, c) Teflon dilator is passed over the guidewire across the interatrial septum. (d) Stretched Inoue balloon advanced into left atrium over coiled guidewire. (e) Stretching metal tube removed and balloon catheter tip is dipped towards mitral valve. (f) Distal end of balloon is partially inflated to aid crossing of the mitral valve. (g) Inoue balloon catheter crosses mitral valve with aid of stylet. (h) Distal half of balloon is inflated and pulled onto ventricular surface of mitral valve. (i) Proximal and distal halves of balloon inflated across mitral valve, giving a champagne cork appearance. (j) Inoue balloon fully inflated across the mitral valve. (k) After the mitral valve gradient has been abolished, a left ventricular angiogram is performed via the pigtail catheter and confirms the absence of mitral regurgitation in this case. (Courtesy of Dr DR Ramsdale.)

The range of the remaining fused commissure is observed after each dilatation procedure, commissure morphology is classified from A to E, and the need for further dilatation procedure is finally determined by assessing the degree of mitral regurgitation.

Mitral regurgitation

The degree of mitral regurgitation is assessed by left atrial pressure and Doppler echocardiography immediately after each dilatation. Left ventricular angiography should be performed if Doppler assessment is inconclusive. Color Doppler assessment is useful to determine the severity of new or increased mitral regurgitation, and to detect the site of mitral regurgitation. A regurgitation signal should be thoroughly sought using several views. When a significant increase in mitral regurgitation is detected, the dilatation procedure is generally terminated. When tearing of mitral leaflet is suspected, even though the development of mitral regurgitation is mild, further dilatation should be terminated. In the case of patients with pre-existing grade I mitral regurgitation, if a tendency to increase is detected, it is advisable to stop further dilatation. If grade I mitral regurgitation is detected following valve dilatation, further dilatation is performed only when both commissures remain fused, as in A or C. In this case, it is desirable to inflate the balloon diameter 1 mm more than in the previous dilatation. If only one commissure is completely split, further dilatation may be continued in an attempt to separate the remaining fused commissure only when the degree of mitral regurgitation is negligible or non-existent.

Constriction of inflated balloon

A decrease or disappearance of constriction during inflation of the balloon is observed under fluoroscopy. Persistence of a marked constriction in the inflated balloon indicates the presence of severely fused commissures and that the internal pressure of the inflated balloon is insufficient. In such a case, the balloon diameter is increased by using a large volume of dilute contrast medium, thus elevating the internal pressure. Alternatively, the balloon catheter is replaced with a smaller one, and then maximally inflated to produce sufficient internal pressure.

Increase in valve area

A mitral valve area can be obtained from two-dimensional echocardiography using the Doppler pressure half-time method or hemodynamic measurement using Gorlin's equation. The pressure half-time method provides an inaccurate estimate during this procedure. Therefore, the mitral valve area should be assessed by Gorlin's equation or planimetry from two-dimensional echocardiography. However, Gorlin's equation is not always reliable either, because it is affected by the accuracy of cardiac output determination. Although planimetry is considered to be the most reliable during this procedure, accurate measurement may be difficult when the mitral valve is extensively distorted or markedly calcified, or both.

Acute outcomes of PTMC

The technical success (defined as successful transseptal access and completion of balloon dilatation of the mitral valve) rates of PTMC in experienced centers are uniformly high (>98%).[4,5,7] Technical failure usually occurs in the operator's early experience, due either to failure in transseptal catheterization or to unsuccessful balloon crossing of the mitral valve.[4,15] In our large series of elective PTMC, an overall technical success rate of 99.5% was achieved despite the presence of a significant number of technically demanding scenarios and high-risk co-morbid conditions.[4] This is attributable to operator experience and the continuously evolving Inoue PTMC technique.[4,17,19,20,23]

With successful balloon valve dilatation, there is generally a two-fold increase in the mitral valve area (Table 28.3) and an associated dramatic fall in the transmitral valve gradient and left atrial pressure. These hemodynamic benefits are mirrored in clinical improvements in patient's symptoms and exercise tolerance after PTMC.[23]

Complications

A number of complications may occur with PTMC, including death, cardiac tamponade, emergency surgery, severe mitral regurgitation, systemic embolization and significant atrial septal defect. Procedure-related deaths may result from cardiac perforation, severe mitral regurgitation, cerebral embolism, and emergency surgery. The risk of death, however, as a direct consequence of the procedure is extremely low (0–1%) when PTMC is performed in experienced centers (Table 28.4).

Cardiac tamponade

The reported incidence of cardiac tamponade ranges from 0 to 4%[4,8,24–27] (Table 28.4). Cardiac tamponade commonly occurs as a consequence of erroneous transseptal puncture[28,29] and much less frequently as a result of guidewire or balloon catheter induced left ventricular perforation. The latter phenomenon appears to be unique to the

Table 28.3 Acute results of PTMC using the Inoue and double-balloon (DB) technique.

Authors	*Pt No.*	*Technique*	*MVA (cm^2)* *Pre*	*Post*
Inoue and Hung[2]	527	Inoue	1.1	2.0
Hung et al[4]	799	Inoue	1.0	1.8
Arora et al[5]	600	Inoue / DB	0.8	2.2
Ruiz et al[6]	407	Inoue / DB	0.9	2.0
Iung et al[7]	1514	Inoue / DB	1.0	1.9
NHLBI[8*]	591	DB	1.0	2.0

*Multicenter study; MVA = mitral valve area; Pre = before PTMC; Post = after PTMC.

Table 28.4 Complication rates (%).

Authors *Technique* *Pt No.*	*Hung et al[4]* *IN* *(799)*	*Arora et al[5]* *IN / DB* *(600)*	*Iung et al[7]* *IN / DB* *(1514)*	*NHLBI[8*]* *SB / DB* *(738)*
Failure	0.5	1.9	1.4	9
Mortality	0	0.7	0.4	1
Cardiac tamponade	0.1	1.3	0.3	4
MR (≥ +3)	4.4	—	3.4	3
Emergency surgery	0.1	3.3	—	4
Thromboembolism	1.4	0.5	0.3	2

*Multicenter study; DB = double-balloon technique; IN = Inoue-balloon technique; MR = mitral regurgitation; SB = single-balloon technique.

fixed balloon catheter technique[15] and has not been reported with the Inoue PTMC procedure. To avert cardiac perforation during transseptal catheterization, some interventionists have resorted to intra-procedural transesophageal echocardiography to facilitate optimal transseptal needle placement. However, even with echocardiographic guidance, cardiac perforation may still occur.[30] Therefore, the acquisition of skills for performing transseptal needle puncture is essential.

Mitral regurgitation

Mild angiographic mitral regurgitation (1+ to 2+) resulting from PTMC is common, occurring in 20 to 40% of cases.[4,15] However, this minor complication is usually the result of commissural over-splitting and bears no clinical relevance.[31]

Severe (≥ 3+) mitral regurgitation, reported in up to 17% of patients after PTMC,[4,31–34] is frequently due to leaflet tear, or less commonly to chordal rupture, and may require urgent mitral valve surgery. This major complication is largely dependent on valve anatomy, operator skill, balloon sizing strategy and whether there is pre-existing mitral regurgitation[4,24–28] Cited incidence of severe mitral regurgitation as a result of PTMC in experienced hands averages 3.7%[4,7] (Table 28.4). The presence of severe subvalvular disease is by far the most important independent predictor for severe mitral regurgitation.[4,23] Therefore, strict adherence to the controlled stepwise dilation technique[17] is essential for minimizing the risk of severe mitral regurgitation.[4]

Emergency surgery

Emergency surgery in PTMC is occasionally required because of cardiac tamponade or severe mitral regurgitation.[4,5,29]

Systemic embolization

Although systemic embolization as a result of air embolization from balloon rupture, fragmentation and embolization of calcified mitral nodules, and in situ thrombus formation on the

guidewire or balloon catheter has been sporadically reported,[24,29] the principal cause of systemic embolization is presumed to be a consequence of left atrial thrombus dislodgement. With the use of preprocedural transesophageal echocardiography for exclusion of patients with left atrial thrombi and improved operator skills, this complication can be minimized and is no longer a major problem.[4,7,27] Our studies have demonstrated that Inoue PTMC, when executed with extra care, is safe in patients with thrombi confined to the left atrial appendage.[4,17]

Atrial septal defect

Significant atrial septal defect (pulmonary-to-systemic flow ratio ≥1.3) after Inoue PTMC has been reported to occur in about 10 to 20% of cases.[4] Although the vast majority of atrial septal defects are clinically insignificant and close spontaneously within several months after successful PTMC,[15] on rare occasions, some do become hemodynamically significant and require surgical repair.[4] The Inoue balloon can be "slenderized" prior to its insertion or withdrawal across the septum and may thus inflict less damage to the septum compared with the double-balloon system, which lacks this feature.[15]

Long-term outcome of PTMC

The long term results of PTMC are excellent, especially when the acute results are optimal and in the presence of good valve morphology.[23,26,27,35–42] In a large French study, 5-year actuarial rates for global survival, survival with no cardiac-related death and without the need for repeat intervention, and for the composite end-point of good functional status were 93%, 97%, 84% and 76%, respectively.[40] Meneveau and coworkers[42] found that although the 7.5 years event-free survival was excellent for patients with favorable valve anatomy undergoing PTMC, it was dismal for those with unfavorable valves (70% vs 16%, respectively). In the National Heart, Lung and Blood Institute Balloon Valvuloplasty Registry of a series of 736 patients, event-free survival (defined as freedom from death, mitral valve surgery or repeat PTMC) was 60% at 4 years.[41] As expected, smaller mitral valve areas immediately after the procedure were predictive of poor clinical outcome. In our recent report with a high late echocardiographic reassessment rate (97%) at an average of 44 months (up to 63 months) after PTMC, the anatomic restenosis (defined as loss of 50% of the initial gain in mitral valve area or a valve area <1.5 cm^2) rate was 15%.[39] In their follow-up study of 561 patients, Hernandez and associates[43] found that survival free of major events (cardiac death, mitral surgery, repeat PTMC, or functional impairment) was 69% at 7 years, ranging from 88% to 40% in different subgroups of patients. Mitral area loss, although mild (0.13 ± 0.21 cm^2), increased with time and was ≥ 0.3 cm^2 in 12%, 22%, and 27% of patients at 3, 5 and 7 years respectively.

PTMC versus surgical commissurotomy

At least six randomized trials[44–49] comparing the two treatment strategies in >470 patients with favorable valve morphology (non-calcified, pliable valve with minimal subvalvular disease) and no or mild mitral regurgitation, have confirmed that PTMC is as efficacious as, if not better than, surgical commissurotomy in acutely relieving the obstructed valve and in maintaining a favorable outcome (Table 28.5). Furthermore, complications in terms of mortality, stroke, and severe mitral regurgitation were identical in the treatment groups. These results are not unexpected when we consider the close similarity in the underlying mechanism of valve orifice enlargement by the two techniques, namely that of splitting of fused mitral commissures.[50,51]

Apart from its excellent results, PTMC has other attractive benefits compared with surgical commissurotomy. It is inherently much less traumatic, inflicting no unsightly thoracotomy scar, does not require general anesthesia or blood transfusions, and entails a shorter hospital stay. It is also superior to its surgical counterpart in clinical scenarios where the risk of surgery is increased or prohibitive, such as in patients with restenosis after previous surgical commissurotomy,[52–55] in pregnant patients and in patients with acute pulmonary edema refractory to intensive medical therapy.[16]

Clinical utility of PTMC

Selection of patients for the PTMC procedure is a complex decision involving a consideration of multiple variables, including clinical profile, valve morphology, and operator skill.

Given the direct correlation between the severity of symptoms and survival in patients with mitral stenosis, the efficacy of surgical commissurotomy in prolonging survival in significantly symptomatic patients with moderate to severe mitral stenosis,[56] and the similarity in mechanisms of valve enlargement afforded by surgical commissurotomy and PTMC, it is logical that the latter procedure is best applied to patients with symptomatic moderate-to-severe mitral stenosis (mitral valve area <1.5 cm^2). They are the patients who are likely to benefit most from PTMC. Furthermore, observational and randomized studies on PTMC and surgical commissurotomy have provided incontrovertible evidence that PTMC should

Table 28.5 Randomized trials of PTMC versus surgical commissurotomy.

Author	*Pt no/ Technique*	*Mitral valve area (cm^2) Pre*	*Post*	*FU Restenosis FU*	*(mo)*	*Acute complications (%) rate %*	*Death*	*Stroke*	*MR*
Turi et al[44]	20 / PTMC	0.8	1.6	1.6	8	Equal	0	0	5
	20 / CSC	0.9	1.6	1.8		at 3.5 year	0	0	5
Patel et al[45]	23 / PTMC	0.8	2.1	—	—	—	0	0	4
	22 / CSC	0.7	1.3*	—	—	—	0	0	5
Arora et al[46]	100 / PTMC	0.8	2.4	2.0	24	5	2	0	—
	100 / CSC	0.8	2.2	1.9		4	2	0	—
Bueno et al[47]	20 / PTMC	1.3	2.1	2.0	3	—	0	0	0
	20 / CSC	1.3	2.6	2.3		—	0	0	0
Reyes et al[48]	30 / PTMC	0.9	2.1	2.4	36	10	0	0	6.6
	30 / OSC	0.9	2.0	1.8*		13	0	0	3.3
Farhat et al[49]	30 / PTMC	0.9	2.2	1.8	48	7	0	0	3
	30 / CSC	0.9	1.6*	1.3*		37*	0	0	0
	30 / OSC	0.9	2.2	1.8		7	0	0	0

CSC = closed surgical commissurotomy; FU = follow-up period; OSC = open surgical commissurotomy; MR = significant mitral regurgitation;
*Statistically significant for comparison between groups.

be the treatment of choice for patients with favorable valve anatomy, i.e. precisely the type of patients who would have been operated upon in the past. In this subset of patients, PTMC predictably yields excellent results and a low risk of resultant severe mitral regurgitation.

In contrast, utility of PTMC in patients with adverse valve morphology (calcified mitral valves and/or with severe subvalvular disease) is unclear and controversial.[15] Most operators contend that these types of patients are better served with surgery which often means mitral valve replacement. PTMC in this setting is associated with an increased risk of complications and inferior long-term results.[23,41,57] In patients who pose a prohibitively high risk for valve surgery, PTMC may be a better option than surgery and may occasionally be the only therapeutic modality available for some of these patients. On the other hand, some experienced operators[58,59] advocate the more liberal use of the procedure because of a low risk of major complications, in particular, resultant severe mitral regurgitation, and the procedure continues to offer sustained functional benefits in a substantial number of patients. Nevertheless, it cannot be overemphasized that PTMC in these patients can be technically demanding, and does require a higher level of technical skill and extra caution in executing the procedure.

There exists two absolute contraindications in PTMC: the presence of left atrial cavity thrombus and severe (grade 3+) angiographic mitral regurgitation. One may elect to administer long term (3 to 12 months) warfarin therapy in patients with non-mobile thrombi in the left atrial cavity, if their clinical and hemodynamic status does not warrant immediate surgery and the mitral valves are deemed suitable for PTMC. When the thrombus is observed to have resolved with echocardiographic reassessments performed at 3-month intervals, PTMC can then be performed safely.[60,61] In our centers, the presence of thrombi confined to the left atrial appendage (without protruding into the left atrial cavity) is not a contraindication. PTMC can be performed safely in this setting when performed with extra care using the Inoue balloon technique.[17,18]

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29

Interventional cardiac catheterization in adults with congenital heart disease

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Introduction

Congenital heart disease is present in 0.7 to 0.8% of live births and the vast majority of these patients are diagnosed and treated in infancy or childhood. The development of multiple surgical techniques for palliation of complex anatomic cardiac abnormalities and improvements in technology and postoperative care have produced survival rates for all patients with congenital heart disease in excess of 85%. The more common and less complicated diagnoses including patent ductus arteriosus (PDA), atrial septal defect (ASD) and ventricular septal defect (VSD) have survival rates approaching 100%. The simple VSD, ASD and PDA patients can often be considered cured with elimination of their defect, and require no follow-up. The majority of the remaining patients require long term follow-up and many have residual or recurrent structural defects that require further intervention. This has created a relatively new classification of adult cardiac disease, the adult with congenital heart disease or grown-up congenital heart disease (GUCHD).

The adults with congenital heart disease form two distinct groups: those with lesions that have not been previously diagnosed or not received prior intervention, and those who have had palliative procedures. The first group is a rapidly diminishing group as most forms of congenital heart disease are routinely diagnosed and treated in infancy or childhood. The second group is rapidly expanding as the children with palliated congenital heart disease reach adolescence and adulthood. It is estimated that up to 1 million patients are included in this group in the United States at the beginning of the twenty-first century.[1]

Pediatric cardiologists have become increasingly experienced with transcatheter interventional therapy for congenital heart disease. The rapid development of successful interventional procedures in the 1980s and 1990s has led to interventional procedures becoming the primary treatment for many forms of congenital heart disease. Interventional procedures have also become essential in the optimal staging of the surgical management of patients with complex anatomy. These same techniques are currently being applied to adults with congenital heart disease with excellent results. This chapter outlines the various transcatheter therapeutic techniques used for treatment of congenital heart disease. The primarily pediatric indications are presented to demonstrate what occurs in patients prior to reaching adulthood. The most common interventions in adults receive emphasis. Well-established procedures as well as investigational therapies and future directions will be discussed for the different clinical problems.

History

William Rashkind pioneered the field of interventional pediatric catheterization when he reported his technique of transcatheter balloon atrioseptostomy for palliation of a newborn with transposition of the great arteries.[2] The following year, Porstmann et al introduced the first interventional device, the Porstmann plug for patent ductus arteriosus occlusion.[3] The modern era of pediatric interventional cardiology rapidly advanced in the 1980s with improvements in balloon technology allowing transcatheter therapy of pulmonary valvular stenosis[4] and coarctation.[5] Following these initial successes the lesions amenable to transcatheter therapy and the methods of achieving that therapy have increased exponentially. Many of these therapies have become the standard of care and new techniques and devices are constantly being evaluated with results compared to surgical repair in regards to success rates, morbidity, mortality, and cost.

Balloon atrioseptostomy

The management of patients that require intra-atrial mixing of fully oxygenated and venous blood has improved since the

introduction of balloon atrioseptostomy in 1966. This was the first interventional procedure in pediatric cardiology.[2] Balloon atrioseptostomy may be indicated in the management of patients with transposition of the great arteries, tricuspid atresia, pulmonary atresia, mitral atresia, and total anomalous pulmonary venous return. The transcatheter atrioseptostomy procedure has changed little since its inception. Through femoral or transumbilical venous access a balloon catheter is passed across the intra-atrial septum through a patent foramen ovale (PFO). The balloon is inflated in the left atrium and rapidly 'jerked' back into the right atrium tearing the septum primum. The enlarged atrial septal defect (ASD) allows improved mixing and an improved cardiac output or systemic oxygenation. Many institutions perform atrioseptostomies at the bedside in the neonatal nursery with echocardiographic guidance.[6] The reported mortality is 0.7% and the success rate is 99%.[7] In general, balloon atrioseptostomy is limited to the first month of life as the intra-atrial septum later becomes thickened and the balloon fails to tear the septum.

Blade atrioseptostomy

Patients over one month of age can be effectively palliated with blade atrial septostomy as described by Park et al in 1975.[8] This procedure entails passing a retractable cutting blade across the atrial septum through a PFO or through a transseptal puncture site, opening the blade and pulling the blade across the septum. This procedure is performed several times in different planes and then the resulting defect is enlarged with balloon dilation or standard balloon atrioseptostomy.

In addition to the indications listed for balloon septostomy, blade septostomy can be useful in the management of adults with severe pulmonary hypertension. The resulting ASD allows right to left shunting with variable cyanosis. Cardiac output improves, which may improve the patient's symptoms and may be used as a bridge to lung transplantation.[9] Patients on extracorporeal membrane oxygenation due to left ventricular dysfunction have been shown to benefit from ASD creation and decompression of the LV. This is used as a palliative procedure until the return of normal LV function or as a bridge to heart transplantation.[10]

Pulmonary valvuloplasty

Kan and associates reported the first transcatheter balloon valvuloplasty in 1982.[11] The technique involves passing a balloon dilation catheter antegrade over a wire across the pulmonary valve. The balloon is then inflated to its maximum size, which is selected at 100 to 120% of the size of the pulmonary valve annulus. The procedure is repeated two to four times for less than 10–15 seconds per inflation. Balloon pulmonary valvuloplasty has uniformly excellent results in infants, children and adults. It has a low recurrence risk and can be easily repeated if necessary. This has become the procedure of choice for the treatment of pulmonary valve stenosis in any institution with the proper facilities.[12–14] The double balloon technique, which uses two smaller balloons from each femoral vein, has also been applied to pulmonary valve stenosis with equally excellent results.[15]

The same techniques have been applied to infants with critical pulmonary stenosis who require emergency intervention or a prostaglandin infusion to maintain ductal patency and allow increased blood flow through the patent ductus arteriosus (PDA) to the lungs. The success rate is significantly less in this patient group, with 6–23% of procedures being unsuccessful.[16–18] A comparison of surgical and transcatheter techniques demonstrated that the transcatheter treatment group had a lower mortality than surgical valvuloplasty. This has led many to use transcatheter balloon angioplasty as the first line therapy for critical pulmonary stenosis.

Patients with pulmonary atresia and intact ventricular septum have commonly required a staged procedure with initial palliation involving a modified Blalock–Taussig shunt (BTS) (a small 3–5 mm Gore-Tex tube is placed from the right subclavian artery to the right pulmonary artery) and an RV outflow tract patch. They would then require surgical closure of the BTS several months later. Many of these patients are now initially palliated in the interventional cardiac catheterization lab. Several techniques for perforation of an atretic pulmonary valve have been used successfully to allow balloon pulmonary valvotomy. The stiff end of a guidewire may be used to create a small hole in the atretic valve, which is then crossed with the floppy end of the wire.[19] Radiofrequency ablation catheters or laser perforation have also been used to perforate the atretic pulmonary valve. This is done as a retrograde technique from the aorta and through the patent ductus arteriosus or as an antegrade technique. The perforation hole allows passage of a guidewire and then a balloon catheter for balloon valvuloplasty.[20–24] The early worldwide results with these techniques demonstrate a combined success rate of 79.7% and a mortality of 4.3%.[25] A number of these patients may require prolonged prostaglandin infusions to maintain ductal patency and provide a second source of pulmonary blood flow. Some patients will still require a BTS due to continued severe cyanosis.

There is an incidence of repeat stenosis of the right ventricular outflow tract in both balloon valvuloplasty and surgical valvuloplasty despite improvement in the right ventricular size. Transcatheter balloon valvuloplasty is then the indicated procedure with good results.[26,27] When the right ventricular output becomes adequate a BTS becomes unnecessary and can be closed in the catheterization lab, as is discussed later in the occlusion devices section.

Aortic valvuloplasty

Aortic balloon valvuloplasty in children was initially reported in 1984 and due to the safety and efficacy of this transcatheter technique it has become the primary intervention in most centers.[28,29] Balloon aortic valvotomy is limited to patients with mild or absent aortic insufficiency and has had poor results in patients with unicommisural valves. The double balloon technique as mentioned for pulmonary valvuloplasty is also used for aortic valvuloplasty.[15] The recent use of a carotid artery cutdown to create a direct course to the aortic valve has demonstrated improved success rates and allowed shorter procedure times in neonates with critical aortic stenosis.[30,31] Transventricular balloon dilation of critical aortic stenosis facilitates balloon dilation of the stenotic valve in the operating room without requiring cardiopulmonary bypass. It can be converted to an open aortic valvuloplasty if necessary.[32,33]

Balloon aortic valvuloplasty may be repeated at any age in the approximately 30% of patients who have restenosis, as long as the aortic insufficiency is no worse than mild. A smaller number, 17–27% of patients, eventually require surgical valvuloplasty, valve replacement or a Ross procedure.[34,35] The Ross procedure includes replacing the aortic valve with a pulmonary autograft and replacement of the pulmonary valve with a cadaveric valve.

Balloon aortic valvuloplasty may be indicated for adults with bicuspid valves that have become significantly stenotic. The development of symptoms of angina, syncope, near-syncope or heart failure is an ominous sign as survival varies from 2 to 5 years.[36]

Mitral and tricuspid valvuloplasty

The incidence of congenital mitral or tricuspid valve stenosis is very low and these lesions are frequently associated with other congenital heart disease. There has been significant experience with balloon dilation of the rheumatic mitral valve, as described elsewhere.

Angioplasty and stents

Branch pulmonary artery stenosis presents in different locations and may be congenital or occur after surgical intervention. Tetralogy of Fallot repair, BTS placement, arterial switch, or RV to pulmonary artery (PA) conduit placement for truncus arteriosus repair or pulmonary atresia may all lead to branch PA stenosis at suture lines. Many of these sites become technically very difficult to repair surgically and can be effectively treated in the catheterization lab with balloon angioplasty or, more recently, stent placement. All patients with a history of these types of palliative repairs should be fully evaluated for branch pulmonary stenosis, as this is a common reason for RV deterioration in previously well palliated patients. Patients with any evidence of stenosis or increased RV pressure should receive a pulmonary perfusion scan to quantify the degree of branch PA stenosis.

Balloon angioplasty of branch PA stenosis has a variable success rate. Approximately 60% of procedures are technically successful but mid-term follow-up suggests that up to two thirds have significant residual stenosis.[37,38] This has led interventionalists to treat branch PA stenosis with primary stent placement.[39] The implantable stent is crimped onto a balloon catheter the size of the pulmonary artery segments adjacent to the stenosis. A long sheath is passed over a wire distal to the site of stenosis and the balloon catheter is advanced over the wire to the stenotic area. The sheath is withdrawn and the balloon is inflated to dilate the stenosis. This expands the stent to the size of the balloon and the radial strength of the stent prevents elastic recoil or refolding of the stenotic site. Multiple stents can be placed sequentially in long segment stenosis. Bilateral stents can be placed at the same time using the 'kissing technique', which involves simultaneous stent implantation in the site of both proximal right and left pulmonary artery stenosis. This prevents either stent from being partially collapsed or distorted by the inflation of a balloon in the contralateral pulmonary artery.

Patients who require a surgical procedure and have distal pulmonary stenosis can also be treated with pulmonary artery stenting in the operating room. The sites of the stenosis need to be well established prior to the surgical repair. The surgical field allows relatively easy access to the central pulmonary arteries. A stent can then be advanced into the more distal pulmonary artery and expanded under direct vision and palpation. This technique is useful for patients who have failed attempts at stent placement in the catheterization lab or for patients without suitable venous access. A staged procedure with the stent placed before or after surgical repair is the more common therapy and is the preferred course.

Stents are available in a variety of sizes that can be expanded to accommodate growth in children. The results of stent placement have been impressive, with up to a 97% success rate with a 2% complication rate.[40–42] The need for a larger introducing sheath and the difficulty in placing a stent in a small child that can be dilated to the normal adult size of the vessel have been concerns regarding stent placement. New stent technology will undoubtedly improve the results and allow smaller catheters and sheaths to be used. Future directions include self-expanding nitinol stents that can enlarge with the patient's growth and absorbable stent material. Absorbable stents may remove the need for large stent placement in small children and the potential difficulties a stainless steel stent could present at the time of subsequent surgical procedures.

Balloon angioplasty or stent placement has also been used to relieve stenosis within RV to pulmonary conduits. This can increase the interval between conduit replacement and possibly decrease the total number of sternotomies a patient requires. This is an important consideration for the best staged approach to complicated RV outflow tract abnormalities that will require several procedures during childhood and may suffer RV dysfunction in adulthood.

Coarctation angioplasty

Balloon angioplasty of the aorta was first reported in 1982 with successful relief of a recoarctation in a patient who had been surgically repaired as a critically ill neonate.[43] The following year an infant with cardiac failure secondary to a native coarctation was successfully treated with balloon angioplasty.[44] There is significant controversy concerning the use of balloon angioplasty for native coarctation. The procedure has a success rate of approximately 80%, with success defined as a post procedural gradient <20 mm Hg.[45] There have been reports of up to a 20% incidence of aneurysm formation[46] and some incidence of restenosis has been noted in every series of patients.

Balloon angioplasty has been used successfully for premature infants with weights as low as 460 grams using the umbilical artery. Abdominal coarctation has also been successfully treated.[47,48] The restenosis rate is high in neonates, but much less in older children where it is reported to be 7.3 to 8%.[49,50] Long-term follow-up of adolescents and adults demonstrated normalization of blood pressure in 74% of patients treated with balloon angioplasty.[51] The reasonable success rate and low complication rate has led many groups to use balloon angioplasty as the primary therapy of choice for coarctation in adults, adolescents and children outside of infancy.

Recoarctation

The use of balloon angioplasty for recoarctation following surgical repair is less controversial, with early success rates of 88 to 91% and a restenosis rate of 16 to 28%.[52–54] A balloon catheter is advanced from the femoral artery and the stenotic segment is dilated to two to three times its diameter, but no more than 2 mm larger than the descending aorta. Most cardiology-cardiothoracic surgery groups now use balloon dilation as the first line therapy for postoperative recoarctation at any age.

Coarctation stent

The need to dilate the coarctation segment to a size larger than the final anticipated diameter requires a large balloon and is thought to contribute to the low risk of aneurysm formation and the rare cases of fatal vessel rupture. Some groups have begun intervening at gradients of 10 to 15 mm Hg to reduce the long-term potential of hypertension and limit the known transient increase in gradient and hypertension that occurs with exercise. The use of intravascular stents for coarctation (Fig. 29.1) achieves these goals and limits the risk of angioplasty. The stent is enlarged to the measured size of the adjacent aorta with a balloon no larger in diameter than the transverse or descending aorta. This commonly results in a measured gradient of 0–10 mm Hg during the procedure and a predictable vessel diameter.[55,56] The stents can be further dilated in patients who still have growth potential. It is obviously important to place a stent that can be dilated to the size of an adult aorta to prevent future physiologic narrowing of the stented site. This limits this technique to older children and adults. This technique has also been used for coarctations that were not effectively treated with balloon angioplasty alone including long segment coarctation.

Future technological developments with improved catheter and stent design and the potential for absorbable stents may increase the effectiveness of balloon angioplasty. This is an area of active research. The development of 'covered stents', which are stents that have a non-permeable membrane fixed circumferentially around the stent, are being investigated for the treatment of aneurysms and the dilation of venous obstruction.[57]

Balloon angioplasty and the use of stents should be considered as a potential part of the treatment plan in any patient with coarctation.

Systemic veins and venous channels

The success of the Senning and Mustard type venous switches for the treatment of the transposition of the great arteries has led to the long-term survival of many of these patients. These intra-atrial surgical baffles allow the systemic venous return to flow through the atria and cross the MV to fill the LV. The LV then pumps the blood to the pulmonary arteries. The fully oxygenated blood returns to the left atrium and flows over the other side of the baffle to the RV and out the aorta. A number of these patients have been noted to have progressive obstruction of these venous baffles. The surgical results of repair were not favorable and transcatheter therapy with balloon dilation and stenting of the narrowed baffles was investigated.[58,59] Complete obstructions can be perforated and residual gradients of zero have been achieved with single or multiple stents. Redilation for neointimal hyperplasia induced stenosis following stent placement is also successful.[60]

The growing number of patients who have palliated single ventricle physiology is a group with significant adult onset

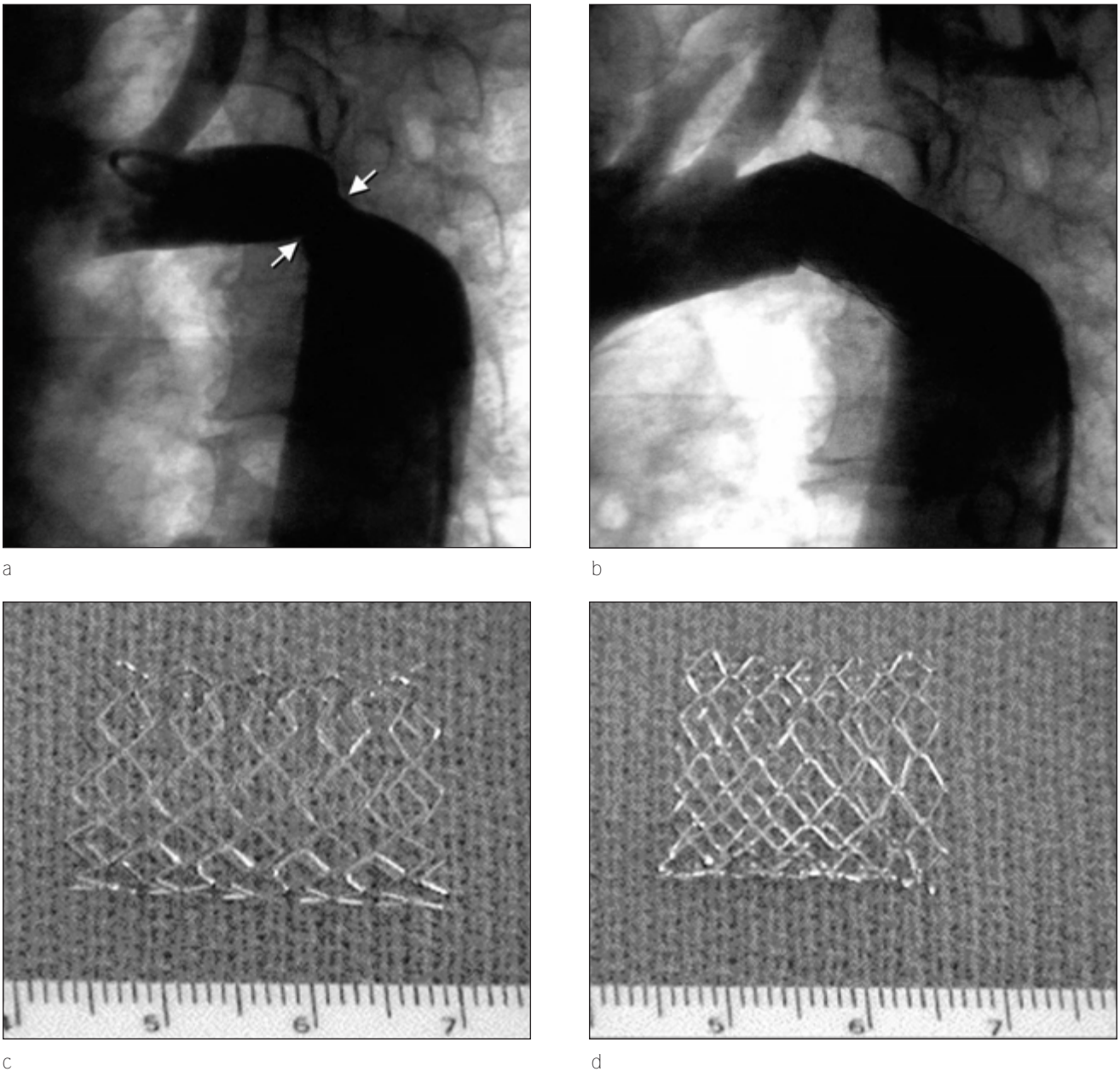


Figure 29.1
(a) An angiogram of the descending aorta in the LAO projection in a 54-year-old male with native coarctation of the aorta (arrows) and a gradient of 40 mm Hg. The narrowest area was about 8 mm in diameter. (b) Repeat angiogram after placement of a P5014 Johnson and Johnson stent inflated to 18 mm in diameter with complete elimination of the gradient and reconstruction of the aorta.
(c) and (d) Typical stents that are currently available. (c) Intratherapeutic stent. (d) J & J stent.

complications. These patients typically have undergone a variation of the Fontan procedure to shunt all the systemic venous blood directly into the pulmonary arteries. Dysrhythmia is the most frequently noted problem as these patients have significant suture lines in their atria. The dysrhythmia can be treated with RF ablation techniques, but often anatomic obstruction complicates their care. The low, non-pulsatile flow in the systemic venous circulation and multiple suture lines can lead to significant stenosis within the Fontan circulation. The same techniques of balloon angioplasty and stent placement have produced good results in this complicated patient population.

Transcatheter stenting should be the intervention of choice for obstruction in venous vessels or channels. Any patient

with palliated complex GUCHD and dysrhythmia should receive a complete hemodynamic catheterization and appropriate interventional treatment of any obstruction prior to attempted RF ablation.

Occlusion devices

Transcatheter techniques to occlude unwanted vessels have been performed since 1967 when Porstmann introduced the first interventional device, the Porstmann plug for patent ductus arteriosus occlusion.[3] This is the most rapidly advancing aspect of interventional catheterization in patients with congenital heart disease as multiple devices for occlusion of ASD, PFO, VSD, PDA and other vascular structures are currently available or under investigational trials.

Atrial septal defect

The atrial septal defect (ASD) is the most common form of congenital heart disease to escape detection in childhood. This is due to the relatively subtle physical findings and lack of symptoms until well into the adult years. The first non-surgical closure of an ASD in the catheterization laboratory was performed in 1974 with a double umbrella design.[61] Since this initial procedure multiple devices have been introduced and tested.

The first clamshell device has been modified since its early use and now has two versions, the CardioSEAL device and the self-centering version, the STARFlex occluder (Nitinol Medical Technologies, Boston, Massachusetts). The CardioSEAL device (Fig. 29.2) is expected to achieve at least the same results as its predecessor, the clamshell occluder, with 57% having complete closure and 97% having complete closure or insignificant residual shunts at a mean follow-up of 41 months.[62] The STARFlex occluder (Fig. 29.3) has not had a large series published. The button device (Custom Medical Devices, Athens, Greece) (Fig. 29.4a–b) has gone through four generations since its introduction in 1989. The Phase I FDA trial results demonstrated a complete closure rate of 74% and 98% of 46 patients with at most a small residual shunt.[63] These excellent results have not been reproduced in international reports.[64,65] The Das Angel wings device (Microvena Inc, Minneapolis, Minnesota, USA) (Fig. 29.5) had a reported 96% closure rate in 72 patients with 1–17 months of follow-up. The 4% serious complication rate and a device placement rate of only 71% tempered this excellent closure rate.[66]

The most promising technique is ASD closure with the Amplatzer septal occluder (ASO) (AGA, Medical Corporation, Golden Valley, Minnesota, USA) (Fig. 29.6). The ASO device has a user-friendly delivery system, high complete closure rate, a small delivery system to allow use in children, and the ability to retrieve or reposition the device prior to release from the delivery system.

The ASO device is a self-expanding, double-disc device made from nitinol wires with Dacron polyester patches sewn into each disc and the connecting waist, to increase the thrombogenicity of the device. The mechanism of closure involves stenting of the ASD by the waist of the device and subsequent thrombus formation within the device with eventual complete neoendothelialization. To ensure successful stenting, a variety of device sizes up to 38 mm are necessary (Fig. 29.7).

The initial closure of surgically created ASDs in 15 minipigs achieved a 100% closure rate at 3 months' follow-up. There was complete neoendothelialization and fibrous incorporation of the device within 1 to 3 months.[67] The initial human use was reported in 1997 with correct placement in all 30 patients studied with a 100% complete closure rate in 25 patients completing the 3-month follow-up.[68] Since that initial report, there have been multiple reports of initial experiences from investigators throughout the world.[69–73]

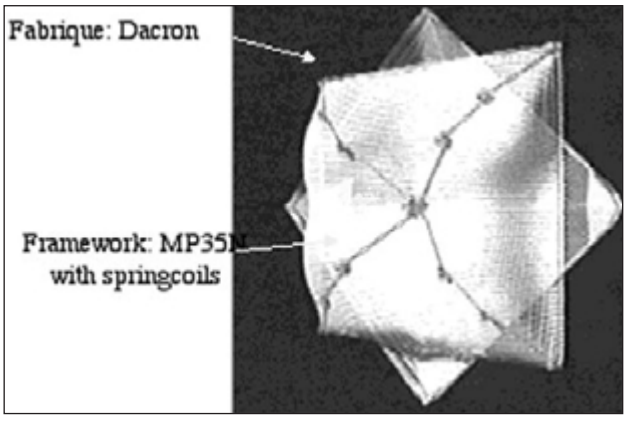


Figure 29.2
CardioSEAL device.

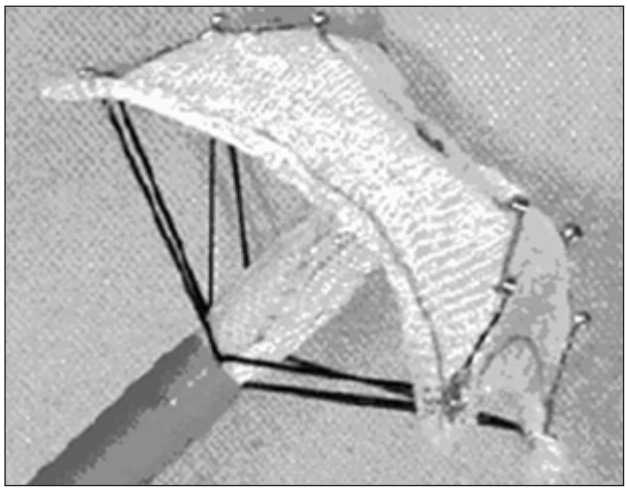
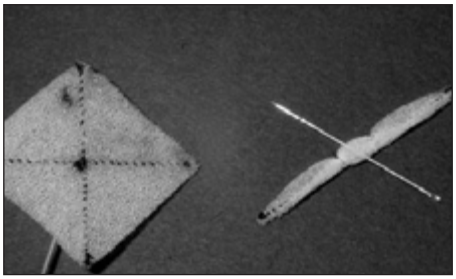
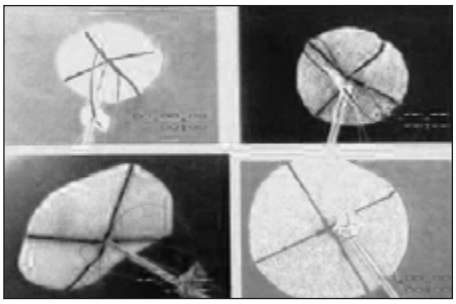


Figure 29.3
STARFlex device.



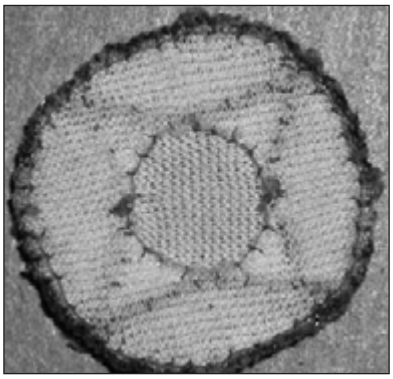
a



b

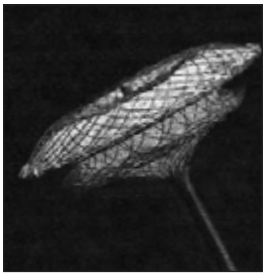
Figure 29.4
(a) Old button device.
(b) New button device. Centering on Demand (COD).

a



b

Figure 29.5
(a) Angel wings device.
(b) Guardian angel device.



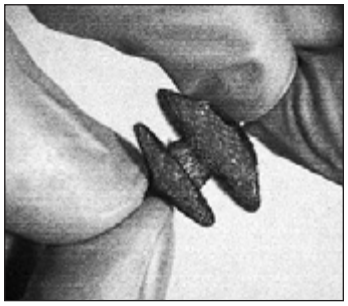


Figure 29.6
Amplatzer septal occluder.

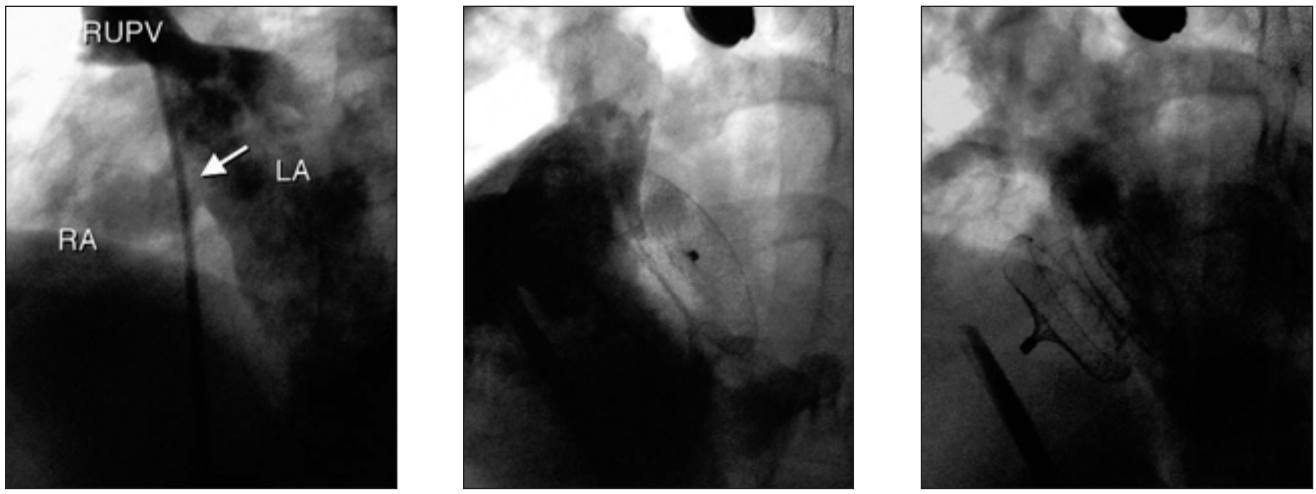
The excellent initial experience with the ASO has led to its use in more complex cases and for other non-ASD closure indications.[74–77] The ASO has finished phase I and II clinical trials in the USA with very good results.[78] The device is available outside of the US for general use and is considered the first line therapy for ASD closure in many institutions.[79]

Direct comparison of the ASO device with the buttoned device, the Angel wings device and with surgery has led to selection of ASO placement as the preferred therapeutic procedure for some groups.[80–82] The authors cite the easier use, shorter procedure time, the very simple and effective design of the ASO device, and the higher implantation rate as reasons to prefer the ASO over other devices. The shorter hospital stay and reduced morbidity were cited as reasons for ASO placement over surgical closure as the closure rates and complication rates were identical. The ASO device has demonstrated excellent clinical success in the closure of secundum ASDs. The closure rate is greater than 98% and the implantation rate is exceptional at 95.6%. The ASO is safe and its user-friendly characteristics allow excellent clinical outcomes with initial usage without an extensive learning curve. The ASO device is poised to be the procedure of choice for secundum ASD closure by both patients and cardiologists.

These ASD occlusion devices should be considered as primary therapy for secundum ASD in adults with evidence of a significant shunt and for patients with co-morbidity that would place them at increased surgical risk.

Patent foramen ovale

The same devices that have been used for ASD closure have been used for patent foramen ovale (PFO) closure. Patients with a history of paradoxical embolism have been treated with either anticoagulation or surgical closure of their PFO. The introduction of transcatheter PFO closure has created a



a b c

Figure 29.7
(a) Angiogram of the right upper pulmonary vein in the hepatoclavicular projection in a 27-year old female, 59 kg with a 23-mm atrial septal defect and left-to-right shunt (arrow). The balloon stretched diameter was 30 mm. (b) Right atrial angiogram after implantation of a 30-mm Amplatzer septal occluder demonstrating good device position and patency of the superior vena cava. (c) Pulmonary levophase demonstrating no residual shunt. RUPV: right upper pulmonary vein; LA: left atrium; RA: right atrium.

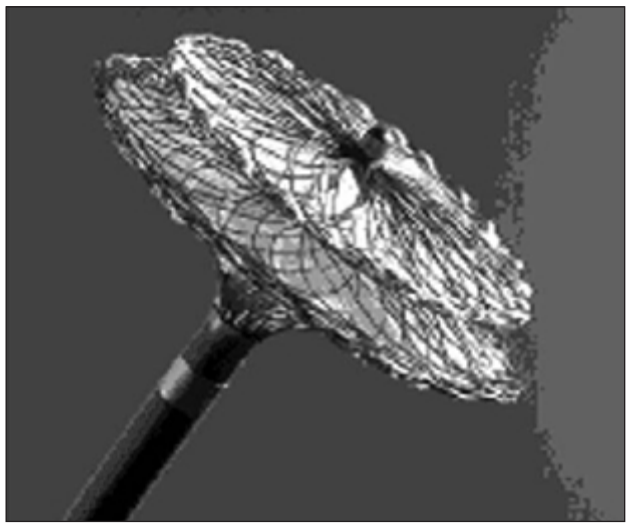


Figure 29.8
Amplatzer PFO occluder.

third option that prevents the risk of paradoxical embolism without the trauma of surgery or the risk of bleeding present with anticoagulation. The need for complete occlusion is much higher for this group of patients as any residual shunt may allow further embolism.[83] The same rationale exists for avid scuba divers with a history of neurological decompression illness.[84]

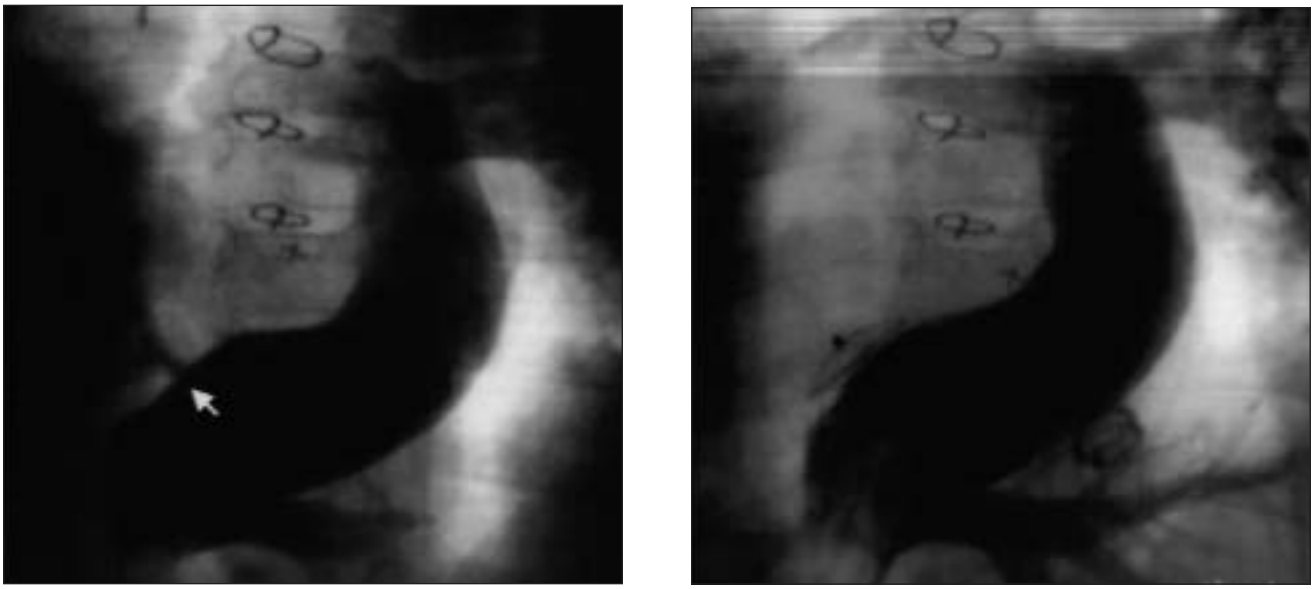
Transcatheter techniques are also possible for PFO closure in patients with the rare syndrome of orthodeoxia-platypnea, which consists of desaturation due to a right-to-left shunt across a PFO that increases with upright posture. This debilitating condition is usually seen in patients with significant co-morbidity that makes them high-risk surgical candidates. Transcatheter closure of the PFO and elimination of the right-to-left shunt produces immediate clinical improvement and should be considered the treatment of choice.

The Amplatzer PFO occluder (Fig. 29.8) has been designed exclusively for transcatheter occlusion of PFO and is beginning clinical trials. The device is similar in construction to the Amplatzer septal occluder. The right atrial disc is larger than the left atrial disc and measures 25 or 35 mm. There is a short 3 mm waist segment. The initial results have been very encouraging with 100% successful placement and 100% complete occlusion. Long term results and clinical follow-up will need to be obtained before recommending transcatheter occlusion for all right-to-left atrial level shunts.

Fontan fenestration

The fenestrated Fontan procedure was developed for patients thought to have a higher risk of morbidity and mortality following a Fontan completion. A surgical fenestration is created in the Fontan baffle to allow right-to-left atrial shunting in the immediate postoperative period. When the patient is stable with good antegrade flow into the pulmonary arteries transcatheter closure of the fenestration is indicated. The increasing experience with transcatheter occlusion techniques has allowed multiple devices to be used for fenestration occlusion.

The original work with the Rashkind and clamshell occluders[85,86] has continued with the Starflex and Cardioseal devices. The buttoned device was modified into an inverted



(a) (b)

Figure 29.9
(a) Angiogram of the lateral tunnel in a 7-year-old child status post fenestrated Fontan for single ventricle/dextrocardia with oxygen saturation of 87% demonstrating a right-to-left shunt (arrow). (b) Repeat angiogram after placement of a 7-mm Amplatzer™ septal occluder demonstrating complete closure. Oxygen saturation improved to 95%.

buttoned device for use in fenestration occlusion.[87] The Amplatzer septal occluder (Fig. 29.9) has also been successfully used for fenestration occlusion.[88] Gianturco coils and detachable coils can also be effective for fenestration occlusion.[89,90] The technical consideration of coil occlusion has even prompted some surgeons to adapt their surgical procedure to create a fenestration that is more amenable to coil occlusion.[91] This staged palliation of the management of single ventricle physiology requires the talents of both congenital heart surgeons and interventionalists.

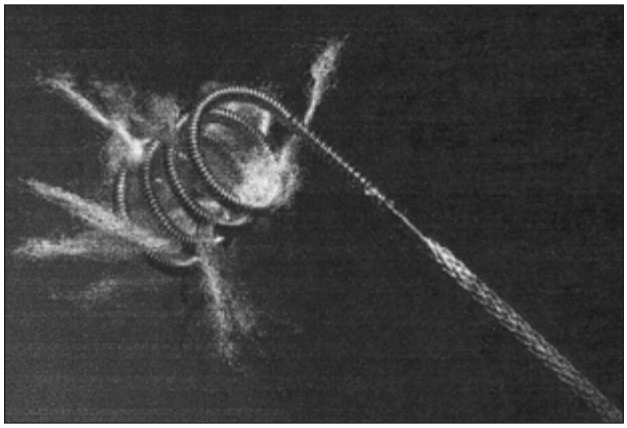


Figure 29.10
Detachable Gianturco coil.

Ventricular septal defect

Many of the occlusion devices used for other shunts have also been used for ventricular septal defect (VSD) closure. Gianturco coils (Fig. 29.10) have been used to close small VSDs.[92,93] The Grifka bag (Fig. 29.11) has been used to close both muscular and perimembranous defects. The Rashkind type devices have the longest record of VSD occlusion with the ASD and PDA device both being used for VSD closure. Perimembranous, muscular and post infarction VSDs have all been effectively treated.[94–99]

The button device has also been used for VSD closure with 18 of 25 patients having devices placed in a multi-institutional study. Patients with membranous and muscular defects were selected for occlusion. Two devices needed to be surgically removed and 13 of the remaining 16 patients had complete occlusion achieved.[100]

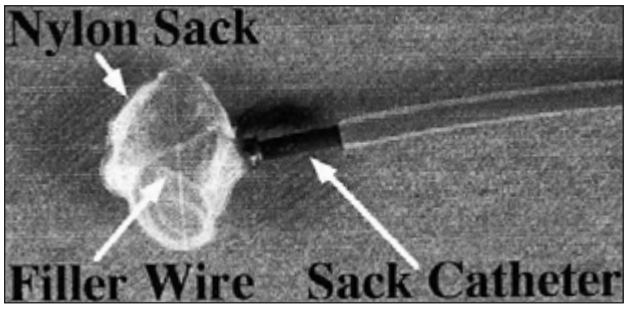


Figure 29.11
Gianturco Grifka vascular occlusive device.

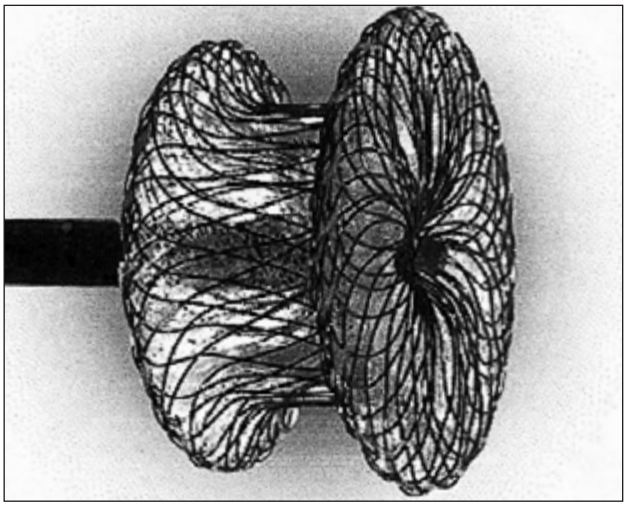


Figure 29.12
Amplatzer muscular VSD occluder.

The Amplatzer VSD occluder device (Fig. 29.12) was designed exclusively for VSD closure and has been undergoing clinical trials since 1998. This device is designed for muscular VSD closure and can be effectively repositioned or retrieved until it is released in an optimal position. The device has been used for mid-muscular, apical, post infarction and multiple 'Swiss cheese' type VSDs with good results.[101–105]

The preferred technique for all devices is transcatheter placement through percutaneous access, which avoids a surgical procedure and allows angiographic localization of the defect to be closed. The devices are often placed from a jugular approach, which allows a straight catheter course into the right ventricle, and across the VSD (Fig. 29.13). This is a relatively technically complex procedure that requires general anesthesia and is assisted by transesophageal echocardiographic guidance. Device closure of a VSD during an open surgical procedure has also been performed with effective

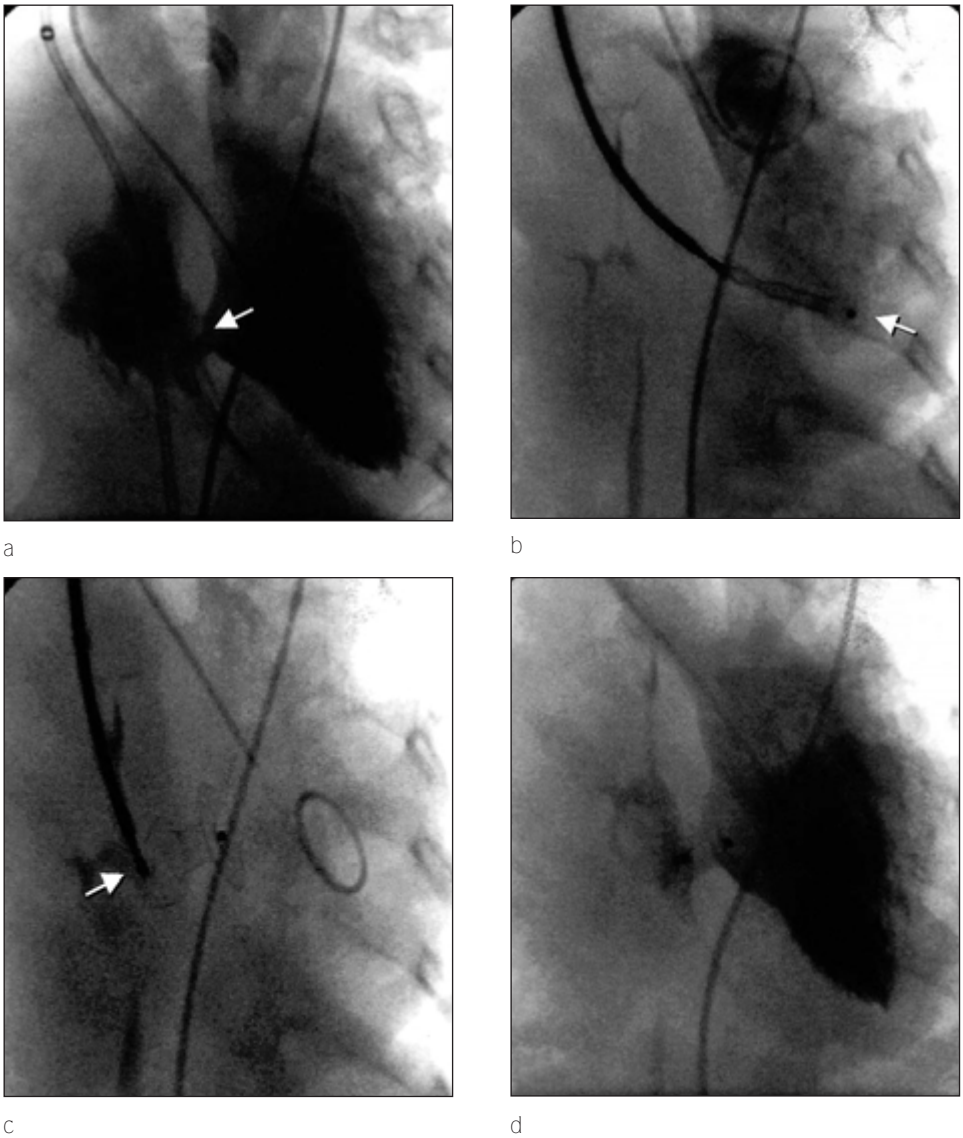


Figure 29.13
(a) LV angiogram in 4-chamber view demonstrating a 7-mm mid-muscular VSD (arrow) in a 2-year-old child. (b) The LV disk is deployed in the LV (arrow). (c) The right ventricular disk has been deployed and the device is still attached to the delivery cable (arrow). (d) Repeat LV angiogram after device release demonstrating good device position and minimal 'foaming' through the device.

VSD occlusion.[106–108] This approach may improve device placement as the surgeon can position the device under direct vision, which could improve the successful implantation rate. We have experience with a single case of a large VSD device that was pushed partially into the left ventricle by the moderator band after release. The device was easily pulled back into proper position and secured with a single suture through a small right ventriculotomy. It may be possible to avoid bypass and a large ventriculotomy by performing transcatheter device placement through a right ventricular puncture, as performed in animal studies with the Amplatzer VSD occluder.[109]

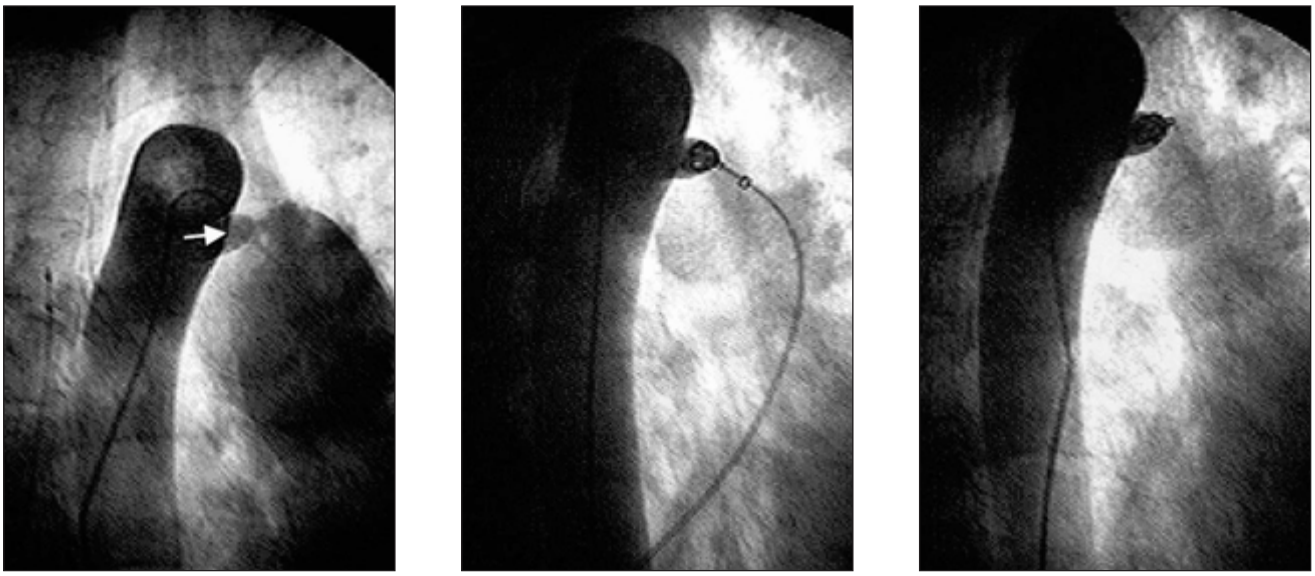
The development of devices suitable for VSD closure has created an alternative to and an adjunct treatment that can be used in conjunction with surgical VSD repair. Patients with complex congenital heart disease who require a staged approach to repair and patients with contraindications to surgical closure of their VSD have formed the early patient population undergoing transcatheter VSD occlusion. If the results of larger series of transcatheter VSD occlusion are comparable to the surgical results this technique may become more widespread.

Patent ductus arteriosus

Efforts to perfect a transcatheter method for PDA occlusion have been ongoing since Porstmann and associates placed the first Ivalon foam plug prosthesis in 1967.[110,111] Coil occlusion is currently the most commonly used technique. Gianturco coils (Cook Inc, Bloomington, Indiana) are small coiled spring wires with fabric strands woven into the springs (see Fig. 29.10). They are packaged straightened and are then pushed through a small diameter catheter to the PDA. When extruded from the catheter they assume a coiled shape and induce thrombosis, which is promoted by the fabric strands. They are available as standard 0.035, 0.038 and 0.052 inch Gianturco coils. The accurate placement of coils in a PDA can be technically difficult and multiple alternative delivery techniques have been devised to improve the success rate. These include the use of a nitinol snare,[112,113] a snare and bioptome combination,[114] forceps delivery,[115] and the use of a modified delivery catheter.[116] Detachable coils have also been developed which allow the coil to be placed and assessed for correct position prior to release.[117]

Devices have also been developed and evaluated to allow closure of larger PDAs and improved control of delivery. The Gianturco–Grifka vascular occlusion device (Cook Inc, Bloomington, Indiana) (see Fig. 29.11) is a fabric sack into which a long coil is extruded which conforms to the size and shape of the vascular structure and can be used for larger PDAs (Fig. 29.14) with improved delivery control.[118] The Rashkind occluder and the buttoned device can be used for a variety of PDA sizes and types, but a significant incidence of initial residual shunt, shunts present at 1 year follow-up, and risks of LPA stenosis have prevented their widespread acceptance.[119,120]

The Amplatzer duct occluder (ADO) (AGA, Medical Corporation, Golden Valley, Minnesota) (Fig. 29.15) was designed exclusively for PDA occlusion and in the initial report



a b c

Figure 29.14
(a) Angiogram of the descending aorta in a 47.5-year-old male with a 5.3 mm patent ductus arteriosus (arrow). (b) Angiogram during placement of a 9-mm Gianturco-Grifka vascular occlusive device prior to release from the delivery catheter. (c) Repeat angiogram the descending aorta demonstrating good device position and no residual shunt.

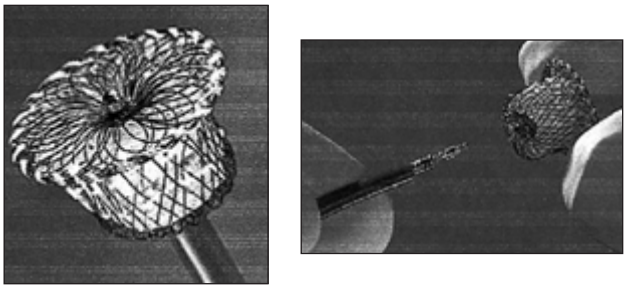


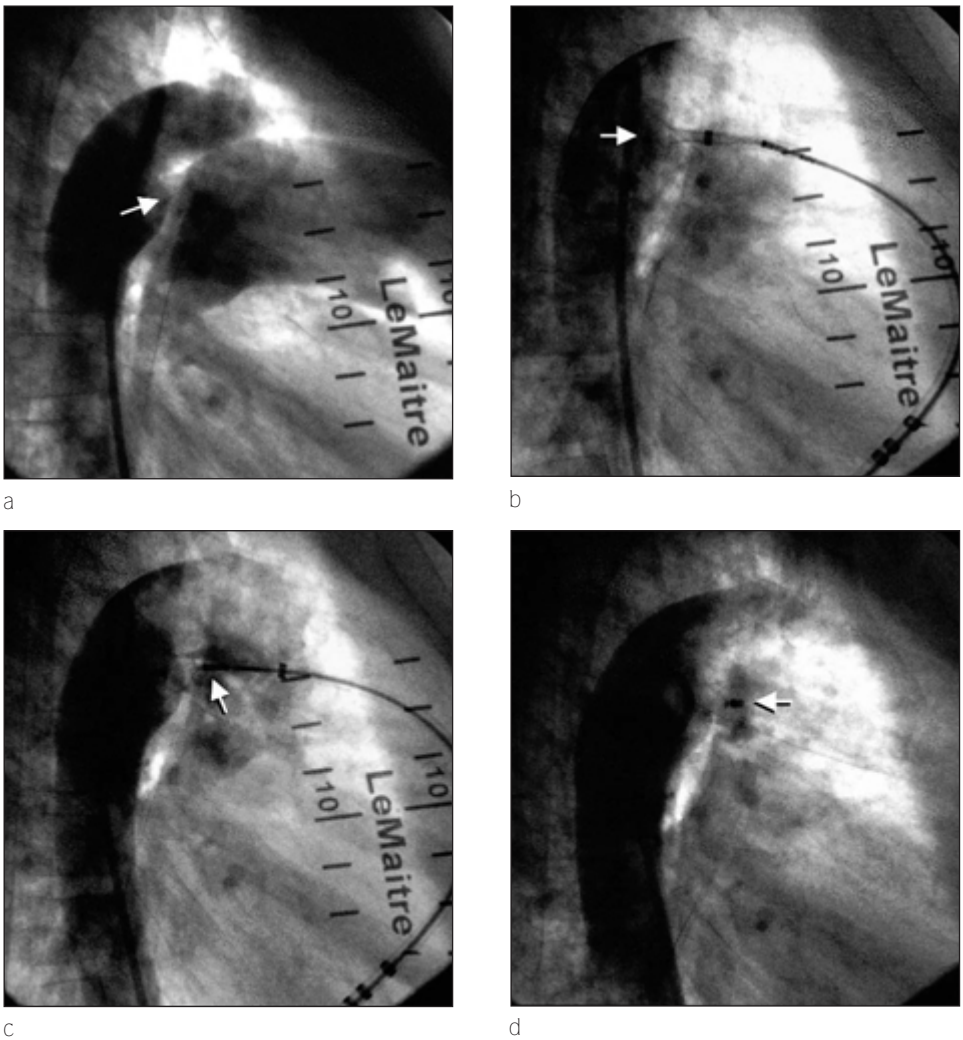
Figure 29.15
Amplatzer duct occluder.

has proven to have excellent success with a complete closure rate of 100% at 1 month follow-up and no complications.[121] The ADO device has several advantages over the other methods available for PDA closure. It has a complete closure rate that is as high as, or is achieved sooner than, other methods and has not been noted to have recurrence of shunting. The variety of device sizes allows it to be used effectively in cases of large PDAs up to 11 mm and it can be used in all PDA types. The ADO may be more desirable in adults where calcification of the PDA may be present which can complicate surgical closure. The transvenous delivery route and the small 5–7 French sheath required for delivery limits the risk of vascular compromise. The ability to retrieve and reposition the ADO device is an important feature not available with many other transcatheter occlusion methods (Fig. 29.16).

These transcatheter techniques for PDA occlusion should be explored for patients with a simple PDA and can certainly be useful for patients with a contraindication to surgical closure of any PDA.

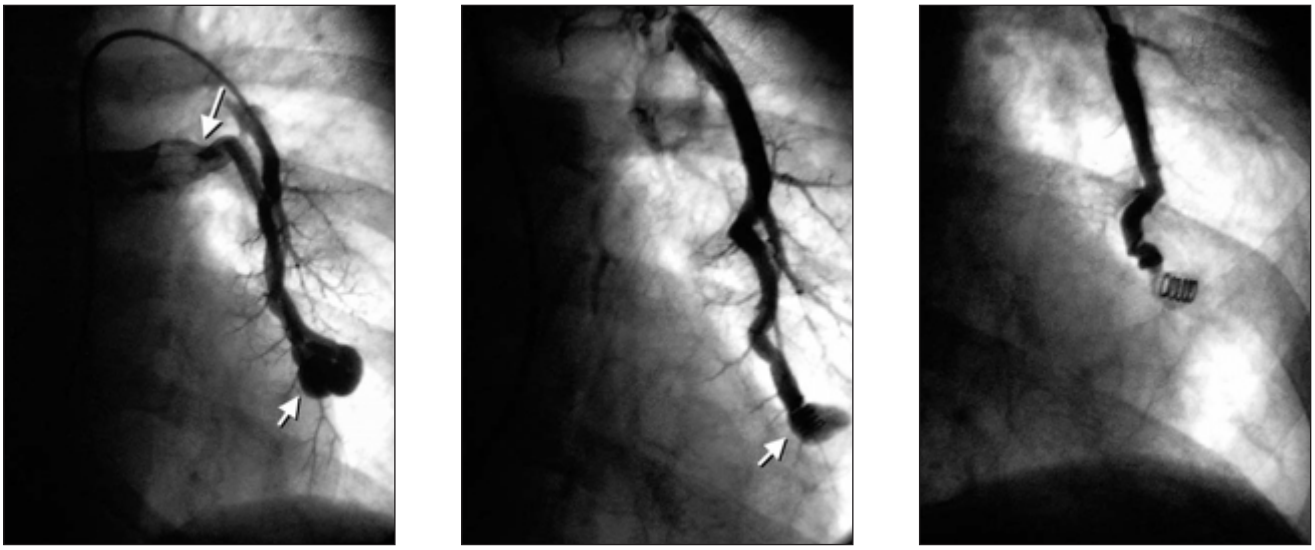
Pulmonary arteriovenous malformation

Transcatheter embolization is the preferred therapy for elimination of a pulmonary arteriovenous malformation (PAVM).[122] The preservation of normal lung parenchyma and the ability to repeat the transcatheter embolization if recurrence is noted are important factors in its selection as primary



a b c d

Figure 29.16
(a) Descending aorta angiogram in an 8-year-old child with large patent ductus arteriosus measuring 7 mm (arrow). Note, there are 10 mm markers on the child's chest.
(b) Angiogram after deployment of the retention disk of a 12–10 mm Amplatzer duct occluder (arrow) in the ampulla.
(c) Angiogram of the descending aorta after deployment of the tubular part of the device, prior to release (arrow), demonstrating good device position and residual flow.
(d) Final angiogram 10 minutes after device release demonstrating minimal 'foaming' through the device and good device position (arrow).



a b c

Figure 29.17
(a) Angiogram of the distal left pulmonary artery in a 60-year-old female who sustained a transient ischemic attack due to right-to-left shunt via the pulmonary arteriovenous malformation. The angiogram demonstrates the fistula (short arrow) and the pulmonary vein (long arrow). (b) Repeat angiogram after placement of one (5 mm x 5 cm) Gianturco coil demonstrating minimal residual shunt (arrow). (c) Final angiogram after placement of a second coil (5 mm x 5 cm) demonstrating complete closure.

therapy. This is very significant as 20% of patients in one series required treatment in the contralateral lung after initial therapy.[123] The embolization procedure can be complicated by the presence of multiple feeding vessels requiring extensive embolization. There are several methods of embolization. Coil embolization is the most commonly reported therapy. Coils are readily available and can be delivered through 4 French catheters (Fig. 29.17). There is a significant rate of recanalization of embolized PAVMs of 5 to 57%.[122,124] Detachable balloons have been used with good results, but a low incidence of spontaneous deflation has been observed. Coils require a site of narrowing in the vessel to be occluded to prevent migration of the coil and are limited to structures less than 7–8 mm in diameter. This limitation led to the development of the Gianturco-Grifka vascular occlusion device which has been suggested as an alternative therapy for PAVM occlusion. This has the advantages of increased control of delivery, limited risk of embolization, and the ability to embolize large afferent or efferent vessels. Its use in a neonate is limited by the requirement of an 8 French sheath. Its higher cost may limit its use in the presence of multiple feeding vessels.

The ADO device is designed for PDA occlusion, but its polyester-filled, mushroom-shaped, nitinol wire frame produces excellent embolization of many different vessels including PAVMs. The ADO produces almost immediate complete closure and recanalization has not been reported. Afferent or efferent vessels can both be occluded without a significant risk of embolization as the self-expanding ADO device fixes itself within the vessel. Multiple devices can be delivered through a single sheath and the device can be repositioned or retrieved until the operator is sure of proper positioning.

Transcatheter occlusion of PAVM should be used as the primary therapeutic option for PAVM diagnosed at any age. The use of coils and other occlusion devices has been well established, offers significantly reduced morbidity compared with surgical resection, and can be repeated as needed. Long term follow-up is required and should include pulse oximetry, contrast echocardiograms, and chest radiography.

Vascular occlusion

Multiple substances have been used for occlusion of unwanted vascular structures since Porstmann's initial PDA occlusion. Coils are useful for the occlusion of most abnormal collateral vessels. These are often found in patients with an abnormal pulmonary arterial supply and in patients who have been palliated with Glenn shunts (SVC to right PA) or who have completed Fontan circulation for single ventricle physiology. The use of coil occlusion reduces pulmonary overcirculation and simplifies subsequent surgical procedures on these patients as it prevents the need for extensive surgical dissection to locate and ligate these vessels. There is also evidence that if collaterals are left without occlusion, pleural drainage following a Fontan completion may be prolonged.[125] The staged repair for these patients almost always requires a cardiac catheterization prior to surgical

intervention. Efforts to occlude any unnecessary collateral should be attempted as part of the routine care of these complex patients.[126–128]

Coils have been used for occlusion of other vascular structures including coronary-cameral artery fistulae and unneeded BTS. Other devices have been used for occlusion of these same structures including the ADO device and the Rashkind occluder.[129]

Summary

Pediatric cardiologists have seen vast improvements and advances in the treatment of congenital heart disease that have led to excellent long term survival of the vast majority of our patients. These patients are reaching adulthood and form a large and complicated group of patients. A smaller group of adults are now benefiting from improved echocardiographic techniques allowing diagnosis of previously unrecognized congenital heart disease. These patients require specialized care by physicians familiar with congenital heart disease, adult medicine, dysrhythmias, and interventional procedures.

Advances in interventional cardiac catheterization have changed the therapeutic strategy for many patients with congenital heart disease. Transcatheter interventions are now the procedure of choice for valvular stenosis, recoarctation, collateral vessel occlusion, and branch pulmonary artery stenosis. Interventional techniques now exist for transcatheter closure of ASD, VSD, and PDA which are effective and safe. These advances have led to investigational procedures including covered stent repair for aortic aneurysm, puncture of the patch closed SVC and placement of a covered stent to complete the Fontan circulation in patients after a modified Glenn shunt, multiple stent designs for all vascular stenosis, partial pulmonary artery lined stent inflation to create an internal pulmonary artery band, and transcatheter valve insertion into the right ventricular outflow tract. The adult with congenital heart disease may benefit from the growing experience in pediatric interventional cardiology and should be considered for transcatheter directed therapy whenever possible.

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30

Ablation of arrhythmias

Stephen S Furniss and John P Bourke

Introduction

Arrhythmia management has had a chequered history. Only relatively recently have the shortcomings of antiarrhythmic drug therapy been recognized. Antiarrhythmic surgery and the implantable cardioverter defibrillator were born out of the disillusionment with drug options. Surgery was developed for the management of the arrhythmias of Wolff–Parkinson–White (WPW) syndrome and has also been applied extensively to the management of sustained post infarction ventricular tachycardia. A successful surgical attack on an arrhythmia demands detailed knowledge of the arrhythmia anatomy. Intraoperative mapping has revealed that many arrhythmias arise from an apparent point source. A focal arrhythmia may be due to different mechanisms such as re-entry or abnormal automaticity, but irrespective of the mechanism the essence of interventional antiarrhythmic strategies is finding the small well-defined zones of cardiac tissue crucial to the maintenance of the arrhythmia. While WPW surgical techniques involved, by present criteria, extravagant dissection of around 50% of the mitral or tricuspid annulus and while directional current (DC) ablation traumatized tissue many centimetres away from the electrode tip, radio frequency (RF) ablation achieves the same results with lesions of between 5 and 10 mm in diameter. Thus RF ablation has forced a major re-evaluation of arrhythmia management and cardiac mapping. RF ablation is indicated for the management of accessory pathway arrhythmias, atrioventricular junctional re-entry tachycardias, true atrial tachycardias, atrial flutter and some forms of ventricular tachycardia. It also has a role in the management of atrial fibrillation.

Principles of RF production

Tissue heating by RF energy delivery occurs at sites of high current density where there is high tissue impedance.[1] Heat is generated in the thin rim of tissue in direct contact with the catheter electrode and is then conducted passively to deeper tissues. The temperature rises rapidly at the tip but much slower in deeper tissues. Irreversible tissue injury occurs at temperatures $>52°C$.

The size of the lesion produced depends upon several factors, including the power delivered, the tip–tissue contact, the duration of energy delivery, the number of catheters through which RF energy is delivered and the size and shape of the catheter tip.[2] The position of the indifferent electrode does not influence lesion size. Thermometry and tip irrigation also produce greater lesion volumes.[3]

General principles

Most ablation procedures are combined with diagnostic electrophysiological tests. It is helpful to explain to the patient that the procedure consists of three stages; the first stage is insertion of wires, usually from the right groin and occasionally from the neck; the second stage is clarifying the diagnosis and determining the site of origin of the arrhythmia; and the final stage is detailed mapping and ablation of the arrhythmia.

Anticoagulation (5000 units heparin iv) is only necessary for procedures that involve left heart instrumentation or if the procedure is very prolonged (>4 h).

Post procedural electrophysiological testing is unnecessary, as is echocardiography unless there has been difficulty during the procedure.

Figure 30.1
Equipment for electrophysiology study, including a stimulator, computerized recording system, and amplifiers interfacing with the catheters coming from the various sites within the heart. An ablation system delivering RF energy is seen on the right.

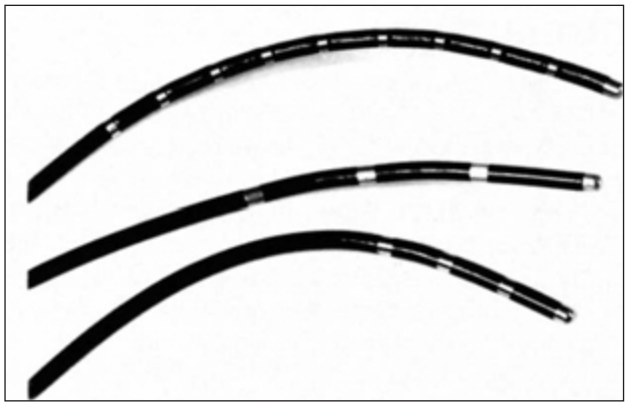

Figure 30.2
A range of catheters with different inter-electrode spacing and number of poles for recording during diagnostic electrophysiology procedures.

Facilities and equipment

RF ablation requires some specialized equipment and at present is best focused on tertiary centres. High-quality fluroscopy is essential with good radiation protection, as procedures may be prolonged. Although biplane screening is advantageous, particularly for some types of arrhythmia ablation, it is not essential. The advent of computerized electrophysiology equipment (Fig. 30.1) has made an enormous difference to the practice of ablation, and the use of this should be considered as an essential prerequisite for ablation. Computer-based electrophysiology systems are available from a number of companies. The other pieces of equipment that are essential in addition to the standard electrophysiology catheters (Fig. 30.2) are steerable ablation catheters (Fig. 30.3) and a source of RF energy (Fig. 30.4). The first RF generators were modified diathermy machines or neurosurgical devices but now a number of dedicated cardiovascular devices are available. First-generation devices merely produced a definable power output and gave an indication of impedance. Newer machines and catheters employ thermometry in which power is delivered sufficient to maintain the tip temperature at a predetermined temperature. These systems may have largely replaced standard power generators for ablation.

Staffing an ablation service requires a nurse to supervise the patient throughout the procedure and perhaps control the conscious sedation, a radiographer, a trained technician and an electrophysiologist. It is helpful for complex procedures to have two electrophysiologists available so that one can manipulate the catheters and the second can interpret the signals at the computer.

Conscious sedation during electrophysiological studies

Conscious sedation plays an important role in the management of patients during ablation procedures. Anxiety is common and the more complex the procedure, the more important is sedation. The benzodiazepines (diazepam and midazolam) remain the main agents to achieve sedation, hypnosis, co-operation and anxiolysis. The usual loading dose of diazepam is 5–10 mg with a maintenance of 2–5 mg/10 min to a maximum of 30 mg. Midazolam is more potent than diazepam and has an earlier onset and shorter half-life. The usual loading dose is 1–2.5 mg over 2 minutes with a maintenance of 25% of the load every 2 minutes to a maximum of 20 mg.

For safe care of the sedated patient it is essential to have intravenous access, resuscitation facilities, pulse oximetry and ECG monitoring and to have flumazenil (benzodiazepine antagonist) available.

Accessory pathways arrhythmias

Accessory pathways are conducting bridges that break the insulation plate of the atrioventricular ring and provide an electrical link between atria and ventricles. They may occur at any point around the mitral and tricuspid annuli. The mitral annulus is well developed and accessory pathways on the left are sometimes epicardial. The tricuspid annulus is less well developed and pathways there are more endocardial in their

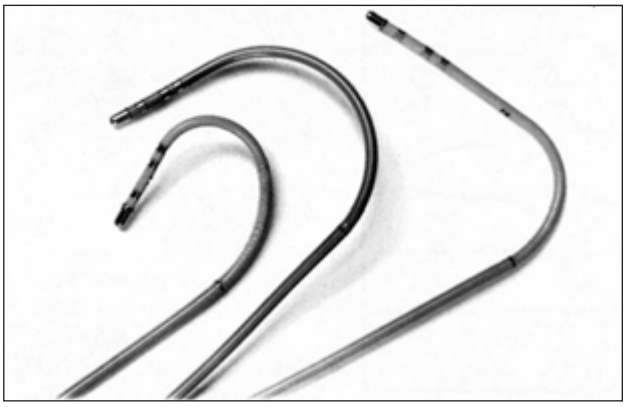

Figure 30.3
A range of ablation catheters from the same manufacturer. Each has a 4 mm distal electrode length but differs in the configuration of the distal curve length. This gives each a different 'reach' when deployed in the heart.

Figure 30.4
For ablation procedures an energy source is required. Impedance, temperature and energy output dials are seen in this example. The junction box connects the ablating catheter to the energy delivery system, allowing signals to be recorded by the recording computer or ablation energy to be delivered to the patient. During ablation, energy is delivered between the distal pole of the ablation catheter in the heart and a backplate on the patient's

location. Accessory pathways may also course above or around the coronary veins and have been associated with saccules and diverticula near the coronary sinus orifice.[4] Accessory pathways are not visible to the naked eye. Their presence is most readily exposed electrocardiographically, either by the surface ECG features of ventricular pre-excitation during sinus rhythm or by their participation in arrhythmias. Accessory pathway ablation requires firstly the precise localization of the pathway and then its destruction by the delivery of a controlled RF lesion.

Principles of accessory pathway localization

When surgical management of accessory pathways was in vogue, epicardial activation mapping during sinus rhythm was frequently employed to show an unusually early area of ventricular activation around either the mitral or tricuspid annulus and distinct from the atrioventricular (AV) node. In sinus rhythm, there is almost always a degree of fusion of activation over the accessory pathway and that occurring over the AV node. Maximizing pre-excitation by pacing the expected ipsilateral atrium markedly improves pathway localization. A similar process can be employed for the catheter localization of an accessory pathway. A number of different algorithms have been proposed to determine the site of an accessory pathway in WPW syndrome.[5–8]

When there is evidence of significant pre-excitation, the pathway can be mapped in sinus rhythm. Pre-excitation can be increased by pacing close to the pathway or slowing conduction over the AV node either by introducing premature extrastimuli or by using agents which slow AV nodal conduction such as verapamil. Electrograms on the ventricular side of the AV ring at successful ablation sites typically show short AV times or fusion of the atrial and ventricular electrograms, a local ventricular electrogram preceding the delta wave on the surface ECG and a ventricular electrogram at least twice as large as the atrial electrogram[9] (Fig. 30.5).

If the pathway is concealed (conducts retrogradely only) the pathway can only be mapped during either ventricular pacing (Fig. 30.6) or, preferably, during orthodromic reciprocating tachycardia (Fig. 30.7). In normal individuals with ventricular pacing, a central spread of excitation from the AV node is seen. In patients with accessory pathways, early activation is on the tricuspid or mitral annulus, usually at locations away from the AV node. As pathways get closer to the AV node it becomes more and more difficult to separate AV nodal activation from that of an accessory pathway. The advantage of mapping retrograde activation during tachycardia is that activation is then exclusively via the accessory pathway and the problem of retrograde fusion is removed.

Although during intraoperative mapping of accessory pathways there were sporadic reports of accessory pathway potentials being recorded, such potentials were not used to refine pathway localization to reduce the extent of the dissection. In contrast, accessory pathway potentials can be found in a relatively high proportion of patients during endocardial mapping of accessory pathways and may be present with either anterograde or retrograde activation.[10,11] Accessory pathway potentials are usually recorded from only a very small area and are a good indicator of accessory pathway location. When accessory pathway potentials are recorded at various sites separated by more than a centimetre of the AV ring, obliquity of the accessory pathway or multiple pathways

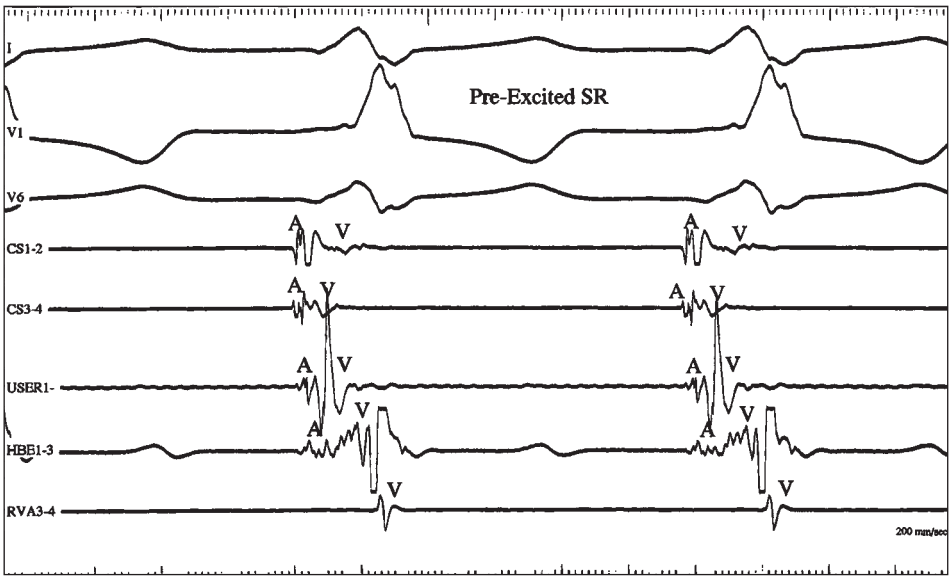

Figure 30.5
Local electrograms at successful ablation site in WPW. Electrophysiology trace showing (top to bottom) three pre-excited surface ECGs in sinus rhythm (SR), distal (CS 1–2) and proximal (CS 3–4) coronary sinus recordings, distal ablation catheter recording (User 1–2), His catheter recording (His 1–3) and right ventricular apical electrogram (RVA 3–4). Note the short AV internal and AV signal ratio in the ablation catheter recording just prior to successful pathway ablation.

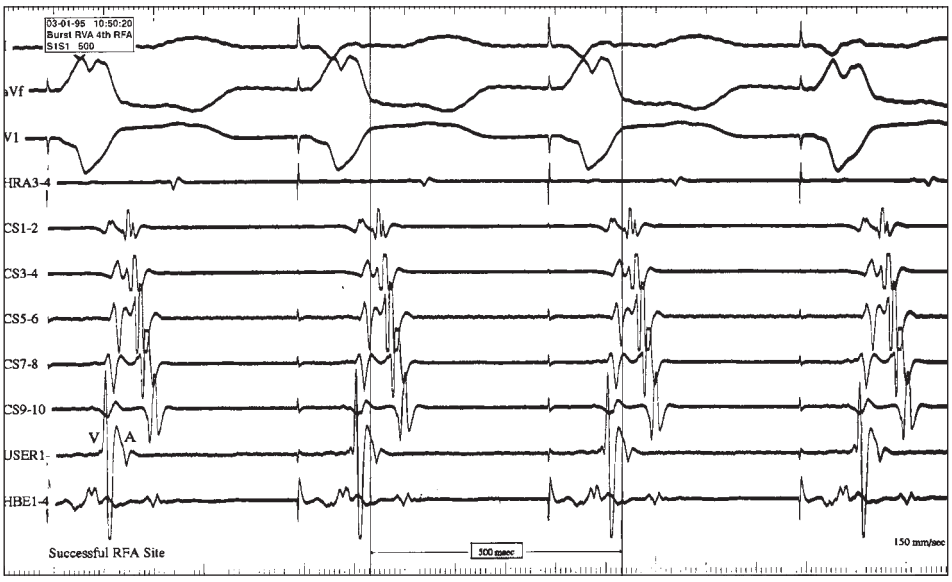

Figure 30.6
Retrograde atrial activation sequence during ventricular pacing. Electrophysiology trace showing three surface ECGs in ventricular paced rhythm. Pacing is from the right ventricular apex and atrial activation occurs eccentrically with the distal coronary sinus sites (CS 1–2) recording an earlier atrial electrogram and shorter VA time than more proximal sites (CS 3–4; 5–6; 7–8; 9–10). The His (HBE 1–4) and high right atrial recording sites show even longer VA times and later atrial activation. The distal poles of the ablation catheter (User 1–2) show a fused VA signal and earliest atrial activation at the site of subsequently successful ablation.

should be suspected. Identification of an obliquely running pathway is important as it infers that its atrial and ventricular attachments may be a considerable distance from each other.

Approach to left-sided accessory pathways

Despite the usual epicardial location of the left-sided accessory pathways, the majority can be approached by a catheter placed retrogradely under the mitral valve.[12] A steerable ablation catheter is passed via the femoral artery across the aortic valve into the left ventricle (Fig. 30.8). The catheter is deflected to pass behind the mitral valve onto the annulus until both atrial and ventricular electrograms are recorded. Sometimes, particularly with some left-sided pathways, catheter placement must be on the atrial side, either by passing the catheter retrogradely across the mitral valve or by the trans-septal approach.[13] Even using both approaches there are some pathways, typically in the posteroseptal region, which may not be accessible and which demand exploration of the coronary sinus and its draining veins.[14]

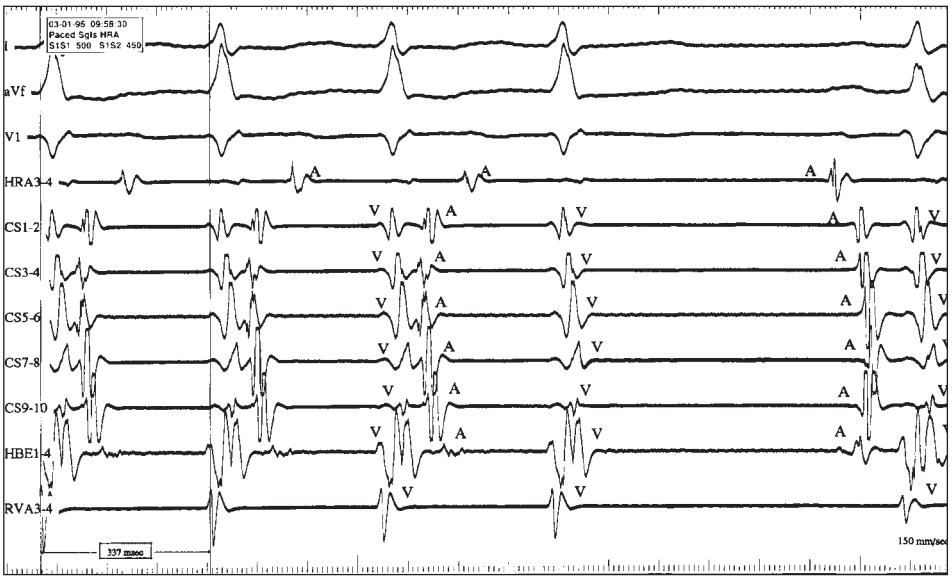

Figure 30.7
Electrophysiology trace showing AV re-entrant tachycardia for the first four complexes. Antegrade conduction occurs over the AV node and retrograde conduction over a left free wall pathway (CS 5–6). Tachycardia terminates spontaneously with block in the retrograde limb, and sinus rhythm returns for the last beat of the panel.

Approach to right-sided accessory pathways

The right-sided AV ring is less well developed than the left. Maintaining catheter stability in the tricuspid annulus may pose difficulties and call for special configurations of catheter or shapes of ablating electrode.[15]

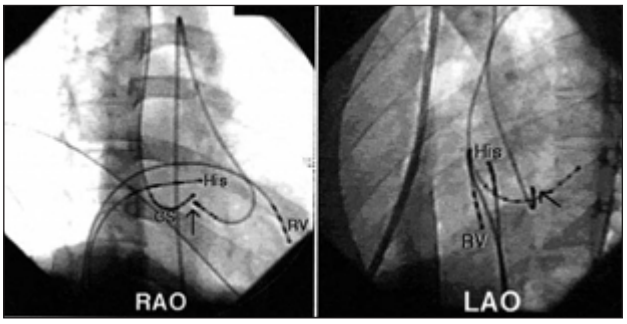

Figure 30.8
Catheter positions for retrograde approach to pathway ablation. Biplane angiogram showing 30° right anterior oblique (RAO) and 60° left anterior oblique (LAO) frames. Right ventricular apical (RV), His and coronary sinus (CS) catheters are indicated. The ablation catheter (arrowed) has been sited retrogradely from the right femoral artery to the mitral annulus in the left ventricle. The distal poles are at the site of successful pathway ablation (see signals 'Users 1–2' in Fig. 30.3).

Procedure

The accessory pathway should be localized, preferably by defining both the atrial and ventricular insertions and by finally reaching a catheter position in which equal atrial and ventricular electrograms are found and there is an accessory pathway potential. In such ideal circumstances, successful ablation with the first RF delivery is to be expected. Often, less than ideal circumstances pertain. The more propitious the electrogram features, the more likely is the success of RF energy delivery. In a typical procedure, RF energy is delivered either for a predetermined time, e.g. 40 s at a predetermined energy, e.g. 35 W, or, alternatively, at a rate to maintain a predetermined tip temperature.

About 50% of patients complain of discomfort during RF ablation and in some the energy levels must be turned down. The ECG, and more particularly evidence of accessory pathway function should be monitored constantly during RF delivery (Fig. 30.9). The earlier that accessory pathway function disappears during RF delivery, the more likely was it that the catheter was very close to the pathway and that a long-term successful result will be obtained (Fig. 30.10). The original practice of adding 'consolidation' burns around the site of successful ablation cannot be recommended. Ideally screening should also be continued during the period of RF delivery, lest the catheter move and energy be delivered to a vulnerable and inappropriate site.

It is customary to wait an arbitrary period of time after apparently successful RF ablation to determine whether the accessory pathway function returns. Typically 20–30 minutes may be allocated, and during this time detailed tests should be conducted to establish that accessory pathway function has indeed been lost.

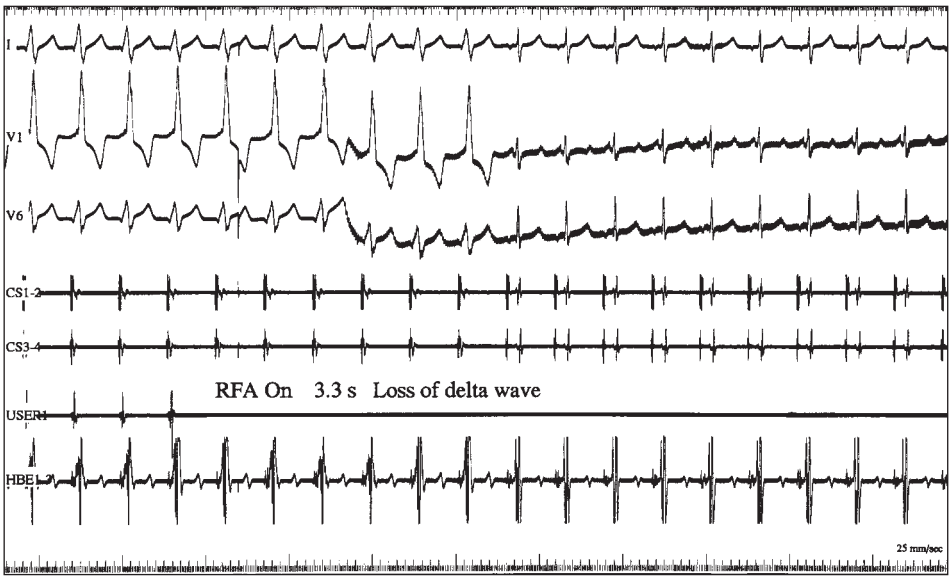

Figure 30.9
Pathway ablation during pre-excited sinus rhythm. Electrophysiology trace showing three surface ECGs with coronary sinus recordings (distal and proximal), distal ablation catheter recording and His channel underneath. After the fourth complex from the left, ablation is started (loss of recording is 'Users' channel). Five pre-excited complexes later the delta wave is abolished (3.3 s) by the RF lesion. Note the increased AV time on the His and CS recordings with loss of pre-excitation.

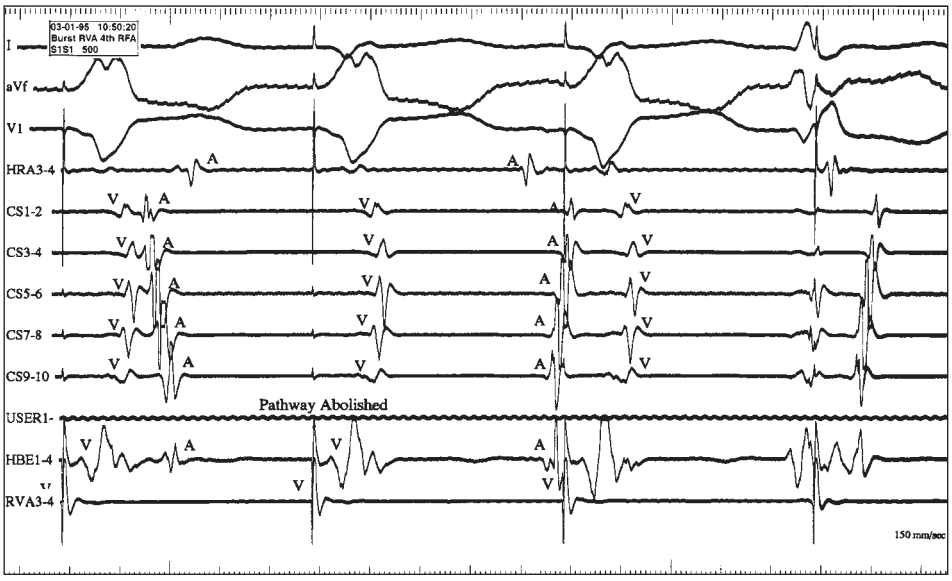

Figure 30.10
Pathway ablation during ventricular paced rhythm. Electrophysiology trace showing three surface ECGs in ventricular paced rhythm as in Fig. 30.2. For the first paced beat, atrial activation occurs eccentrically with the distal coronary sinus sites (CS 1–2) recording an earlier atrial electrogram and shorter VA time than more proximal coronary sinus (CS 3–4; 5–6; 7–8; 9–10), His or high right atrial sites. Thereafter there is a VA block and the atrial components of each signal are dissociated from the ventricular paced complexes, indicating loss of retrograde conduction over the left free wall pathway.

Special precautions

Some accessory pathways lie very close to the AV node and His bundle. Extreme care is necessary for ablating such pathways, as AV nodal damage may occur.[16] Delivery of RF energy may be necessary in the coronary sinus but this should never be undertaken lightly.[17] Perforation of this thin wall structure is relatively easy. The risk is probably higher when ablation is undertaken in a tributary vein. Damage to the coronary arteries and to the AV valves may also occur.[18] Sudden rises in impedance which may be associated with bubble formation and barotrauma should be avoided by the use of automatic impedance cut-off facilities.

Prolonged instrumentation in the left heart may be necessary and anticoagulation is essential for all left heart procedures.

Results of RF ablation of accessory pathways

Many large series have now been reported.[19–21] Success rates of between 95% and 100% are usual. There is a learning curve but this pertains more to the time taken to perform the procedure than to the overall success itself. RF ablation techniques for accessory pathways usually involve positioning several catheters, both to determine the electrical characteristics of the target arrhythmia and to provide visual markers for movement of the ablation catheter. Ablation procedures can also be performed with fewer catheters. Typical accessory pathway ablations may employ only two catheters: a single standard electrode catheter for arrhythmia initiation and termination and an ablation catheter. Single-

catheter procedures are also possible.[22] RF ablation of accessory pathways is not entirely safe, however.[23,24] In the Multicentre European RF Survey (MERFS), cardiac tamponade was reported and there are occasional instances of AV block. Nonetheless, the morbidity and mortality for RF ablation is considerably less than that for surgery. In many centres RF ablation is offered as first-line therapy even in asymptomatic patients on the basis of patient preferences. Currently, it is first-line therapy for those with a life-threatening arrhythmia due to the accessory pathway (a fast conduction capability during atrial fibrillation, RR intervals in AF typically less than 220 ms). The technique is also appropriate for those who have failed drug therapy. There is a growing body of opinion that RF ablation may be first-line management for the majority of patients with arrhythmias due to accessory pathways, but this would require excellent results in terms of success and safety in a reliable and well-equipped centre.

Atrioventricular junctional re-entry tachycardia (AVJRT)

AV junctional re-entry tachycardia is the second most common regular supraventricular tachycardia in adults.[25] Our understanding of the pathophysiology has undergone major changes since the advance of curative ablative therapy.[26,27] The AV node lies at the apex of the triangle of Koch, which is bordered in the right atrium by the coronary sinus posteriorly, the tendon of Todaro superiorly and the septal leaflet of the tricuspid valve inferiorly.[28] The classical feature of AVJRT is duality or multiplicity of AV nodal physiology; the AV node conduction is functionally dissociated into two or more functionally discrete 'pathways' as a result of different refractory periods and conduction properties. However, dual AV node physiology is only demonstrable in 50–90% of cases with AVJRT.[29] This may be because of the limitations of the extrastimulus technique, the effect of changes in autonomic tone or particular conduction properties of the pathways. Demonstration of echo beats is much less common and is probably a better marker of the substrate for AVJRT, as they reflect antegrade and retrograde conduction over both limbs of the circuit. A number of elegant studies have demonstrated that this functional duality of the AV node is related to the different input sites from the atrium to the AV node.[30,31] The 'fast' pathway is usually situated superiorly, close to the AV node, and the slow pathway (which is the antegrade limb of the circuit in the common tachycardia) is situated more inferiorly in the region of the CS os. The CS anatomy is different in AVJRT from that in patients with other forms of narrow complex tachycardia; a characteristic windsock appearance to the ostium is found.[32] Whether this is causally related to the functional multiplicity of the AV node in these patients is speculative at present.

Technique of ablation for AVJRT

Several different techniques have been proposed for dealing with the arrhythmia:

- Superior approach targeting the fast pathway.[33]
- An inferior anatomical approach targeting the slow pathway.[34]
- An electrogram-guided approach to the slow pathway guided by the local electrograms in sinus rhythm showing (a) high-frequency spike potentials[35] and (b) low-frequency slow potential.[36]
- Retrograde mapping of the slow pathway.[37]

Superior or anterior approach[33]

This technique developed from the fortuitous experiences of curative modification of the AV node following attempted complete DC ablation.[38] Following identification of the His bundle position, the ablation catheter is withdrawn and rotated clockwise to produce a large atrial potential and a very small His potential. Because of the risk of heart block, a useful modification of this technique has been advocated whereby RF energy is gradually increased until junctional tachycardia appears (Fig. 30.6).[39] However, even with this modification the risk of complete heart block is higher than with more posterior approaches and this technique should not be a first-line approach.

Inferior or posterior approach[34]

Several techniques have been proposed for slow pathway ablation that do not rely on the electrogram characteristics at the ablation site. Most use a technique starting at the coronary sinus os or just below it and more anteriorly, closer and closer to the AV node until slow pathway ablation is successful[40] (Fig. 30.11). Moulton et al[41] have used a technique that produces a linear burn from the tricuspid valve to the inferior vena cava. The catheter is gradually withdrawn during energy application until junctional tachycardia is seen.

Electrogram-guided spike potential

Jackman et al[35] have advocated selective slow pathway ablation by delivery of RF energy at sites with low-amplitude, high-frequency spikes that follow the local atrial electrogram. They probably reflect the atrial end of the slow pathway and such targeting is certainly effective. Hunting for spike potentials, however, is time-consuming and such potentials are not always seen in patients with AVJRT. Paradoxically they may be found in patients without AVJRT.

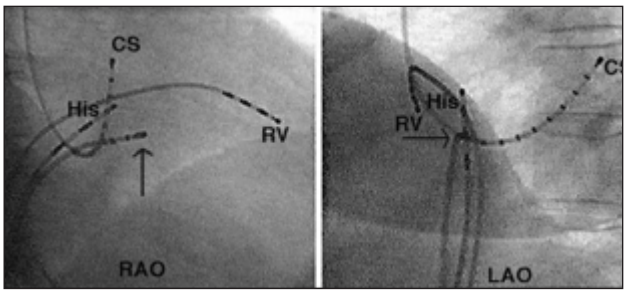

Figure 30.11
Catheter positions for slow-AV nodal pathway ablation. Right and left anterior oblique projections of right ventricular apical, His and coronary sinus catheter relationships to the ablation catheter (arrowed) during ablation of the 'slow AV nodal pathway' (posterior inputs to the AV node).

Electrogram-guided slow potential

This technique described by Haissaguerre et al[36] requires identification of low-amplitude low-frequency potentials that follow the atrial electrogram (Fig. 30.12) but can be separated from it by pacing techniques. Such potentials are usually identified above the CS os and may reflect slow pathway activation. Most centres now incorporate slow potential mapping into their ablation procedure.

Retrograde slow pathway activation[37]

In approximately 5% of patients retrograde slow pathway activation is seen during ventricular pacing. Identification of the earliest atrial activation can then be used successfully to guide ablation.

Ablation technique

The risk of inadvertent complete heart block during energy delivery to ablate AVJRT dictates a careful technique. Gradual energy titration may reduce the risk, as will careful examination for junctional rhythm (Fig. 30.13), AH prolongation, AV block and catheter movement. There is no evidence to justify 'bonus' or 'security' burns.[42]

Results of ablation

Reported success rates >95% are common, but even in experienced centres incidents of complete heart block occur.[23,24] The risk of complete heart block and the subsequent need for permanent pacemaker implantation must be explained to the patient prior to the procedure. Discussing this risk is also useful for reassessing the risk benefit of the procedure and reaffirming whether ablation is warranted. Some patients will decide that any risk of a pacemaker is too high and they will continue with drug therapy.

Atrial flutter

A number of recent studies have clearly shown that atrial flutter is a macro re-entrant arrhythmia that arises in the right atrium.[43,44] An isthmus of slow conduction is located between the inferior vena cava and the tricuspid valve annulus.[45] This common form of atrial flutter (type I flutter) which has negative flutter waves in the inferior leads is characterized by anticlockwise rotation of the circuit (high to low in the lateral wall and low to high in the septum) (Figure 30.14).

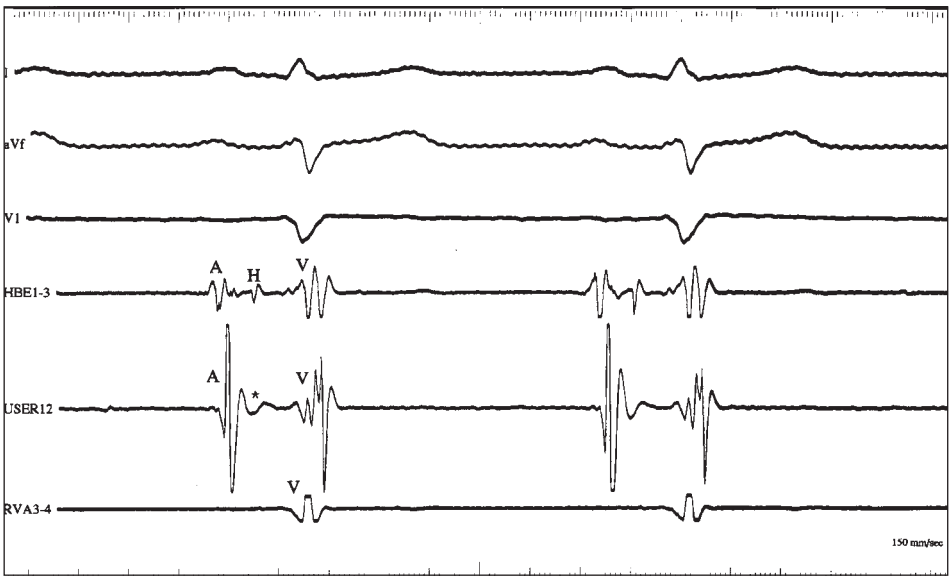

Figure 30.12
Haissaguerre type slow AV nodal pathway potential. Low-amplitude low-frequency potential (*) following the sharp atrial deflection. Note its relationship to His recording in the His channel.

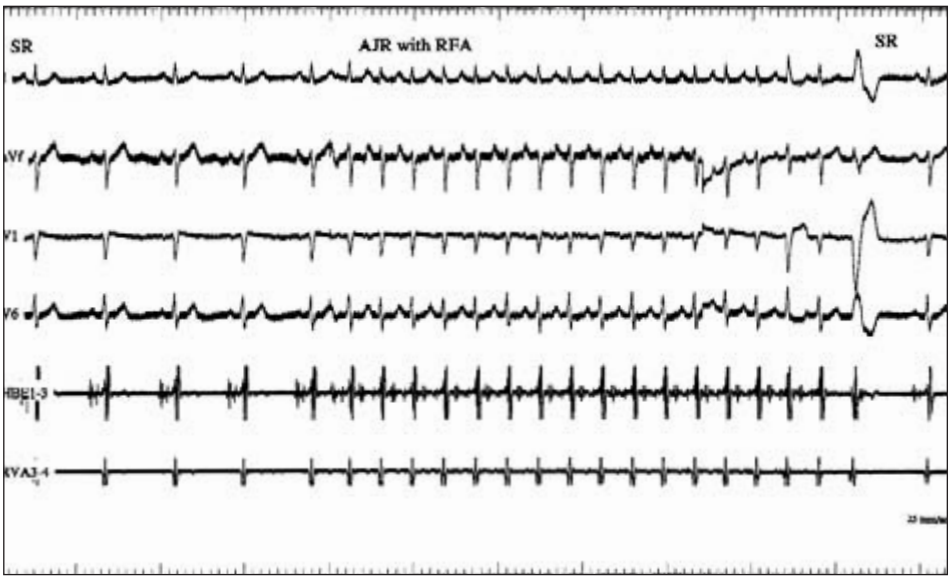

Figure 30.13
Accelerated junctional rhythm during slow-AV nodal pathway ablation. Electrophysiology trace showing, left to right, sinus rhythm followed by RF energy-induced accelerated junctional rhythm and then return of sinus rhythm with normal PR and AH intervals.

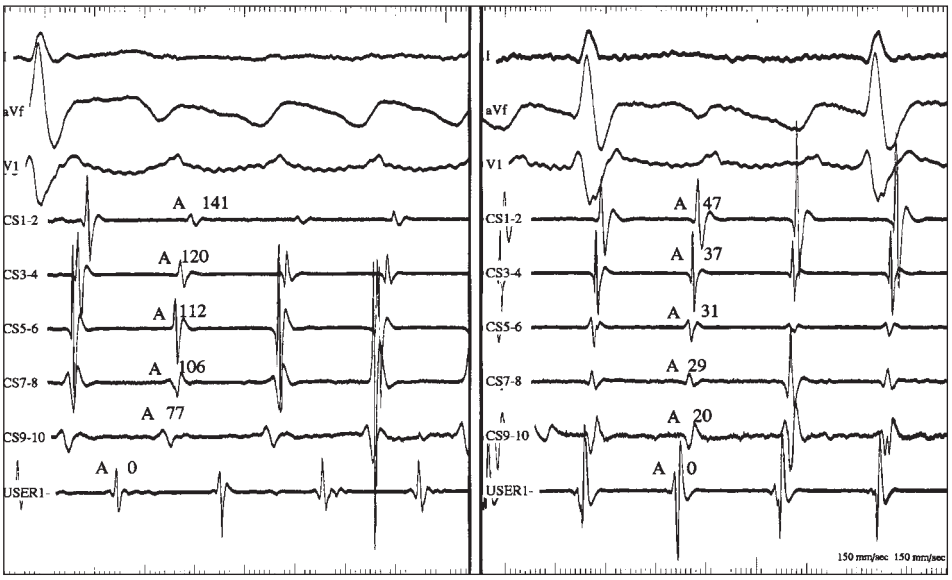

Figure 30.14
Right atrial activation sequence in common type atrial flutter. Recordings obtained from two bipole recordings in the right atrium during atrial flutter. 'Users' is duplicated on both panels and represents the earliest atrial activation (time '0') and occurs before the onset of the flutter wave on the surface ECG. Activation spreads sequentially from the bottom right-hand panel to the top left-hand panel (timing 20 ms to +141 ms). This activation wavefront moves down the lateral wall of the right atrium, across the floor of the right atrium in the region of the coronary sinus ostium and tricuspid annulus and up the interatrial septum. The 'User' catheter is sited in the low right atrium.

Mapping technique

There are two different approaches employed for mapping of atrial flutter. The first seeks a zone of slow conduction characterized by particular electrogram patterns and entrainment mapping[46] and the second is a purely anatomical approach based upon the seeming consistency of the site of the zone of slow conduction.[47] Most centres are now using a predominantly anatomical approach with the aim of producing linear lesions in the region of the low right atrium to interrupt conduction in this slow conduction zone. The first is aligned from the tricuspid valve to the inferior vena cava and 80% of flutters will be terminated when this line of block is completed (Fig. 30.15).[48] Long-term success correlates with a small left atrium and no prior atrial fibrillation.[49] The endpoint of ablation is production of bi-directional block within the isthmus rather than flutter termination or non-inducibility.

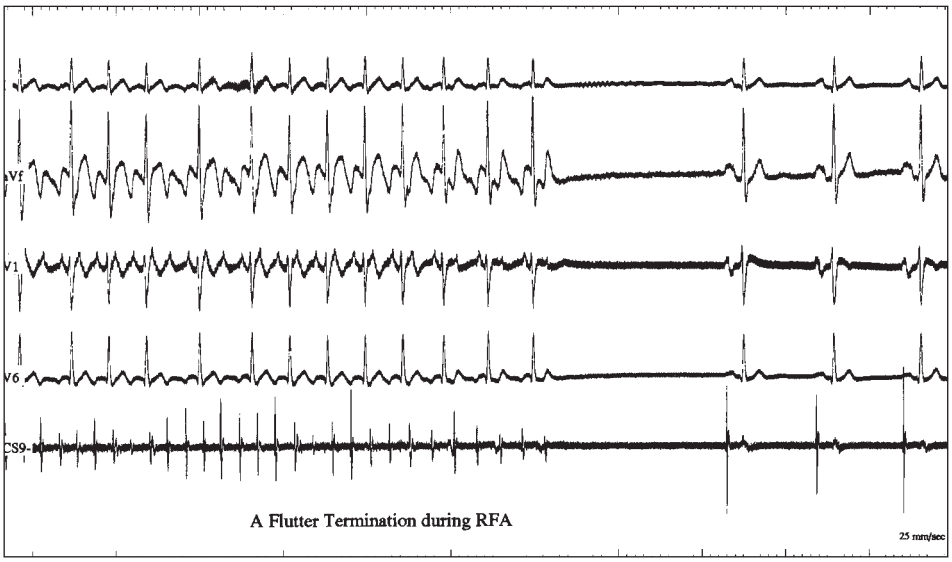

Figure 30.15
Termination of common type atrial flutter during RF energy delivery. Electrophysiology trace showing termination of atrial flutter during the last in a series of RF energy deliveries designed to create a line of conduction block in the low right atrium.

Atrial fibrillation

Atrial fibrillation is the commonest arrhythmia in adults. There are three RF approaches for managing the arrhythmia: complete AV node ablation with pacing, RF ablation of a focal trigger of AF and linear RF delivery in the right atrium.

Complete AV node ablation with pacing

Although control of the ventricular response is achieved in many patients with AV nodal blocking drugs, some patients remain very symptomatic. Complete AV junctional ablation followed by rate responsive ventricular pacemaker implantation is a very effective but aggressive strategy that can be achieved safely by RF ablation from either the right or left side of the septum in nearly all patients (Figs. 30.16–30.18).[50] It has superseded DC ablation and with the development of safe ablation and small rate-responsive pacemakers has made this a very attractive option for an increasing number of patients. This technique may also be of great value in patients with paroxysmal AF in whom a mode-switching pacemaker is implanted following ablation. This type of pacemaker allows normal AV synchrony while in sinus rhythm but switches to VVIR pacing when AF is detected.

The initial enthusiasm for AV node modification in patients with AF[51] has dwindled and has largely been replaced by complete AV junction ablation.

Focal AF ablation

Haissaguerre at al[52] have reported successful cure of AF by elimination of focal atrial tachycardia that initiates and may sustain AF. Such focal AF sources are most commonly located just inside the pulmonary veins and are characterized by spike electrograms preceding the local left atrial electrogram. In only a third of patients is a single focus identified. The long-term results of this strategy are unclear and at present the most suitable patients appear to be those with no or minimal structural heart disease and frequent asymptomatic unifocal atrial ectopics.

Linear AF ablation

Of several surgical approaches to abolish atrial fibrillation, the Maze procedure is the best established. Multiple wavelet re-entry is prevented by a series of incisions in the atria. Recently, successful 'catheter Maze' procedures have been reported and with the development of specialized catheters this approach is becoming feasible. Linear ablation is best considered in patients who show disorganized activity in the septum but not the lateral wall of the right atrium.

Atrial tachycardia

Experience of RF ablation for atrial tachycardia (Fig. 30.19) is much more limited than for atrial flutter or AV re-entry tachycardia. Atrial tachycardia may arise in either the right or left atrium and tends to occur particularly in relation to the crista terminalis in the right atrium.[53] Tachycardia is generally mapped using a fixed right atrial catheter and a roving ablation catheter which is moved to the region with earliest atrial

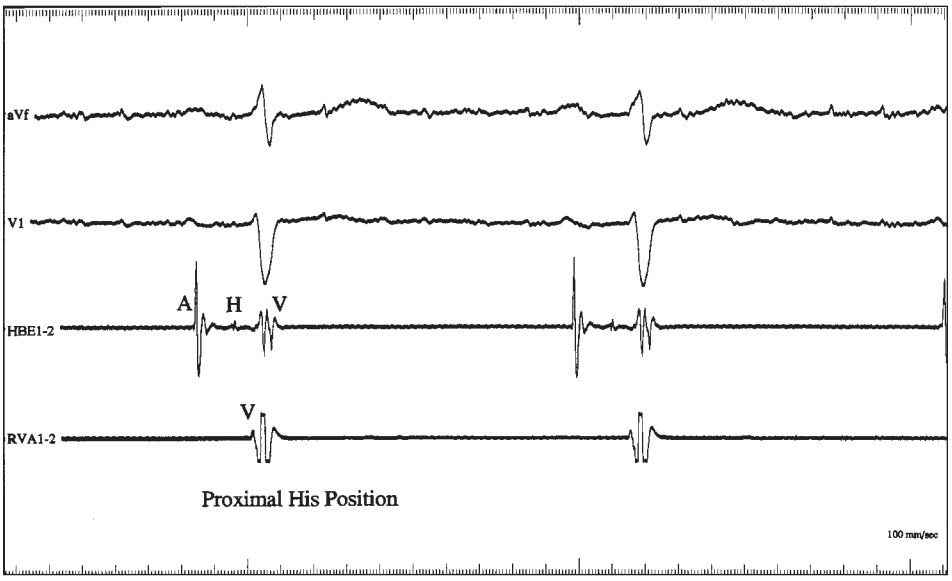

Figure 30.16
Proximal His recording for complete AV node ablation. Electrophysiology trace showing position of the His catheter prior to RF ablation to completely abolish AV nodal conduction. The His catheter has been sited in standard fashion and then withdrawn so that the His signal ('H') has almost disappeared and the atrial signal ('A') is large. The intention here is to leave the patient with an escape junctional pacemaker below the AV node after ablation by burning at a proximal site.

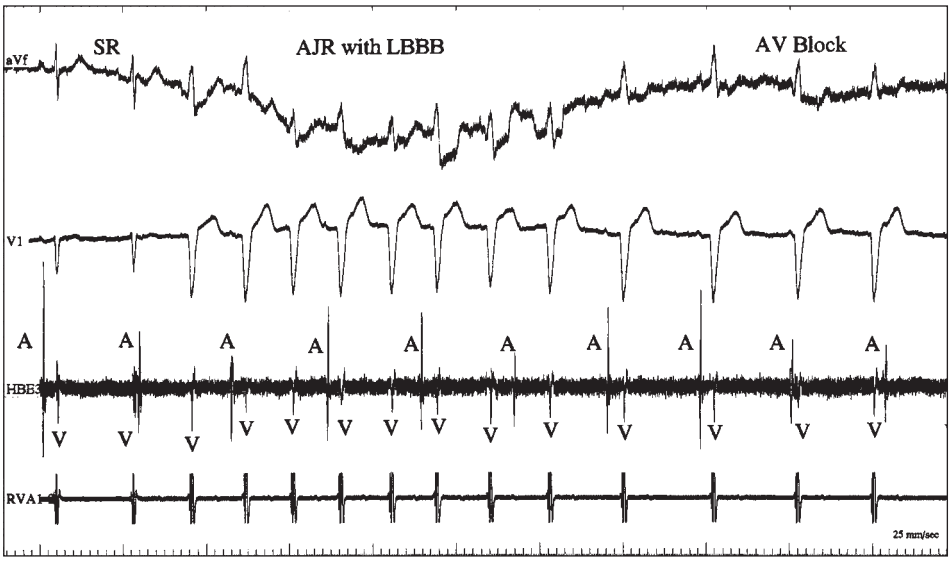

Figure 30.17
Complete AV node ablation by RF energy. Electrophysiology trace showing surface and intracardiac recordings during complete AV nodal ablation. Trace shows sinus rhythm (SR) on the left, followed by accelerated junctional rhythm with left bundle branch block in the middle and complete AV dissociation on the right. The patient is left with a native escape pacemaker with left bundle branch morphology. The electrical 'noise' (channels 'aVR' and 'HBE') is due to the RF energy delivery.

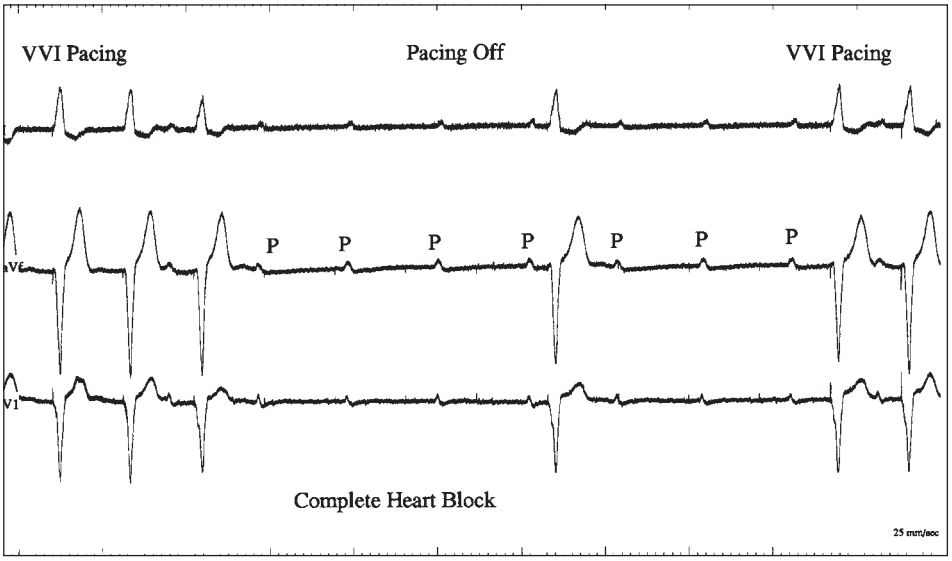

Figure 30.18
Result of complete AV node ablation by RF energy. Following complete AV node ablation, ventricular demand pacing (VVI) is instituted, which overrides the slow native escape pacemaker rhythm (see Fig. 30.13). When pacing is temporarily discontinued, complete AV dissociation is confirmed by the presence of a series of seven non-conducted P-waves. Pacing is restarted on the right of the panel.

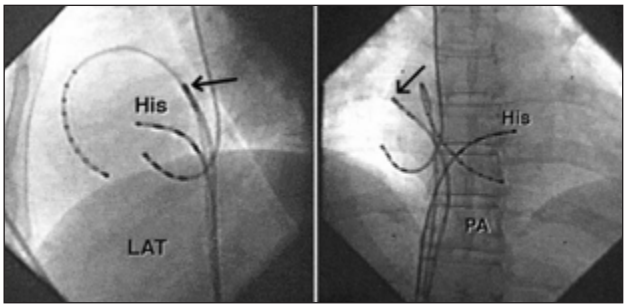

Figure 30.19
Mapping of right atrial tachycardia. X-ray pictures of catheter positions in the left lateral (LAT) and posteroanterior (PA) projections are shown. Decapolar catheters (5 mm spacing) have been sited in the anterior right atrium and at the mouth of the coronary sinus. A His catheter maps the region of the AV node. The ablation catheter has been used to map the remaining sectors of the atrium serially, locating the high posterior region as the site of earliest activation during tachycardia (arrow).

depolarization in relation to the surface P-wave and the fixed atrial electrogram. Occasionally fragmented or split electrograms are present at sites of successful ablations (Figs. 30.20 and 30.21).

Ventricular tachycardia

RF ablation has rapidly become a first-line treatment for many with supraventricular arrhythmias but its success has highlighted the deficiencies of current treatments for ventricular tachycardia (VT). The problems of antiarrhythmic drug therapy have been brought into focus by the CAST trial. Implantable cardioverter defibrillator therapy provides acute arrhythmia control. However, there is no arrhythmia cure and the cost is substantial. Map-guided arrhythmia surgery provides arrhythmia cure at an acceptable risk but is neither sufficiently safe nor widely enough available to be applicable to the majority of patients. All of these facets have led to a growing interest in RF ablation in VT.

VT mechanisms

VT may have a variety of mechanisms. Although the majority of patients have scar-related tachycardia, a few patients have focal abnormalities as a result of either triggered automatic activity or micro re-entrant circuits. These arrhythmias, particularly in those patients with structurally normal hearts, are theoretically a much more attractive group for RF ablation.[54] Current classification systems for VT are inconsistent. For RF ablation it is useful to consider the arrhythmia not only by its mechanism (eg abnormal depolarization favouring re-entry or disordered repolarization predisposing to increased automaticity) but also on whether the underlying disease is focal (and hence ablatable) or diffuse. Diffuse arrhythmias such as right ventricular dysplasia and post-infarction VT may also be usefully treated by ablation if a focal critical component can be identified or a very large area can be destroyed. Currently, catheter ablation for VT is well established for cyclic AMP-dependent outflow tract tachycardia, idiopathic left ventricular tachycardia and bundle branch re-entry.

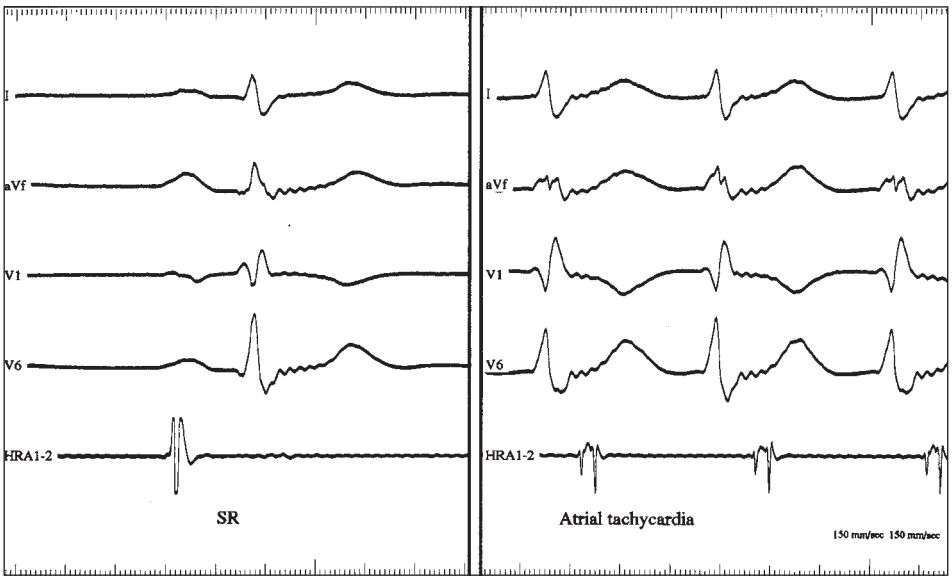

Figure 30.20
Local electrogram morphology at atrial tachycardia ablation site. In both panels the bottom channel is located at the site of successful ablation of the atrial tachycardia (see also Fig. 30.15). The left-hand panel shows that in sinus rhythm (SR) the local electrogram is normal. The right-hand panel shows that during atrial tachycardia the local electrogram is biphasic.

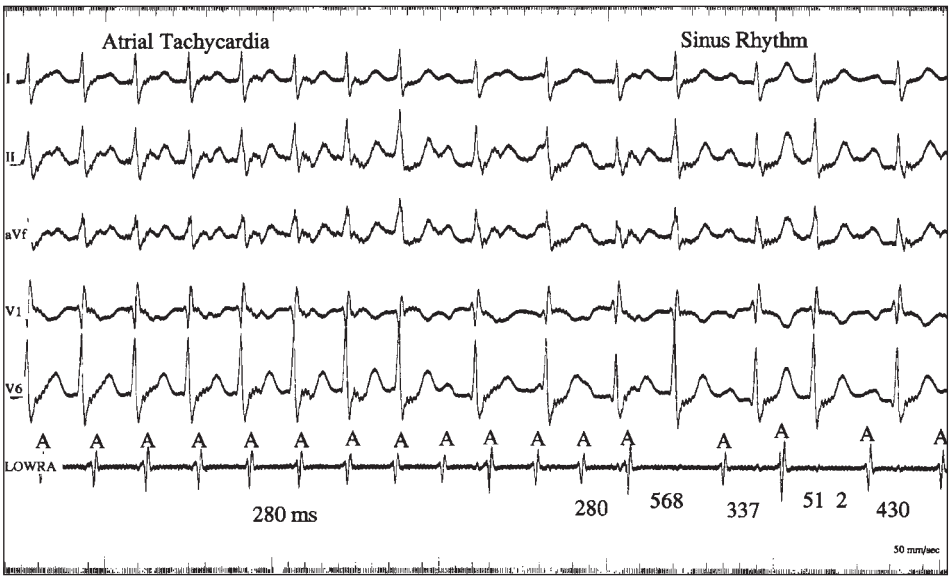

Figure 30.21
Right atrial tachycardia ablation by RF energy. Trace shows, on the left of the panel, sustained atrial tachycardia of cycle length 280 ms (214 beats/min) with 1 : 1 AV conduction. Tachycardia terminates abruptly shortly after the start of the RF energy application and sinus rhythm returns.

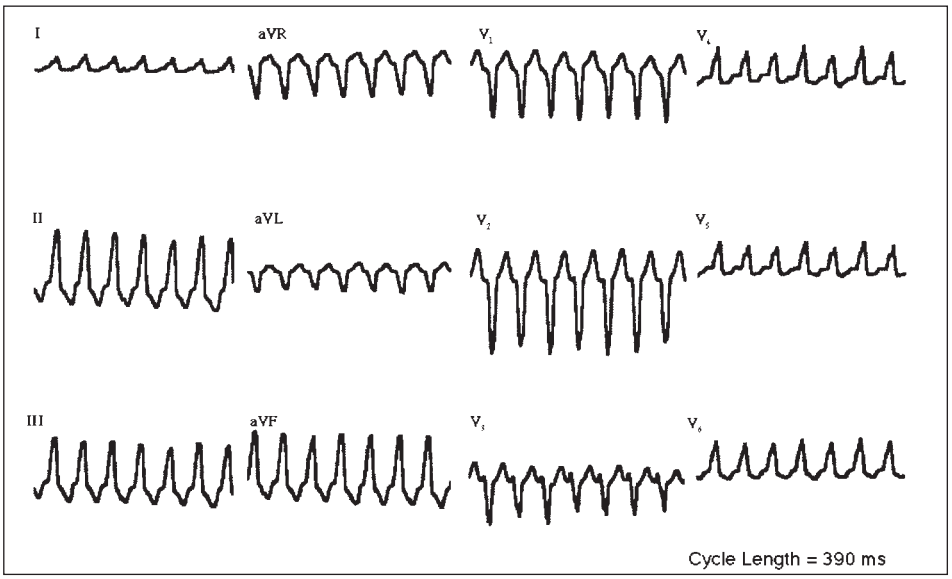

Figure 30.22
Idiopathic right ventricular outflow tract tachycardia. Twelve-lead ECG of a non-re-entrant form of ventricular tachycardia arising from the outflow tract of the right ventricle in the context of an otherwise normal heart. Note the inferior axis and left bundle branch block pattern.

Cyclic AMP-dependent outflow tract tachycardia

This arrhythmia typically occurs in young adults with structurally normal hearts. Usually it is non-sustained and exercise related. The ECG has a characteristic appearance with a left bundle morphology and an inferior axis (Fig. 30.22). The arrhythmia usually arises from the septal surface of the right ventricular outflow tract (Fig. 30.23) and is characteristically adenosine sensitive.[55]

Mapping technique

This arrhythmia is strongly influenced by autonomic tone and is usually best localized by pace-mapping in the outflow tract. A characteristic 12-lead morphology can be used to guide ablative therapy, provided an identical 12-lead match is sought.[56] RF ablation is 100% successful in most series and is now the first line therapy for this condition (Fig. 30.24).

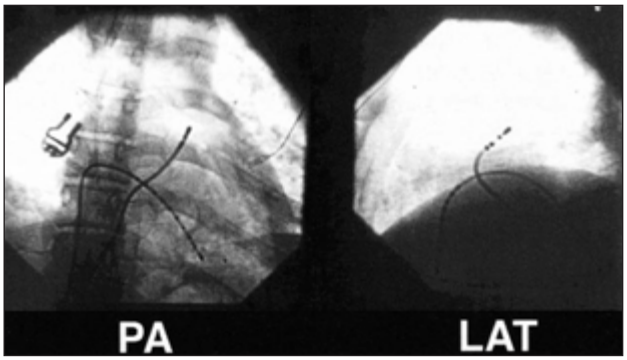

Figure 30.23
Catheter position during RF ablation of idiopathic right ventricular outflow tract tachycardia. Biplane posteroanterior (PA) and left lateral (LAT) projections of catheter position during a typical RVOT tachycardia ablation procedure are shown. In addition to the ablation catheter (more superior one), a reference catheter is sited in the right ventricular apex to facilitate timing of the mapping/ablation catheter positions.

Other forms of 'normal heart VT'

Catheter ablation is also ideal therapy for other rare forms of VT that have a focal target. These include idiopathic left ventricular tachycardia (verapamil sensitive, fascicular tachycardia). This arises in the basal left ventricular septum and is associated with the presence of Purkinje potentials that may be used to guide ablation.[57] Bundle branch re-entry is a macro re-entrant VT that involves the specialized conducting tissue. The usual arrhythmia passes antegradely down the right bundle and retrogradely back up the left bundle. Although it is a macro re-entrant arrhythmia, it can be successfully abolished by selective ablation of the right bundle because the right bundle is critical to maintenance of the tachycardia.[58]

Catheter ablation of VT secondary to ischaemic heart disease

The standard working model of the VT circuit in a patient with ischaemic heart disease is of a figure of eight.[59] This has

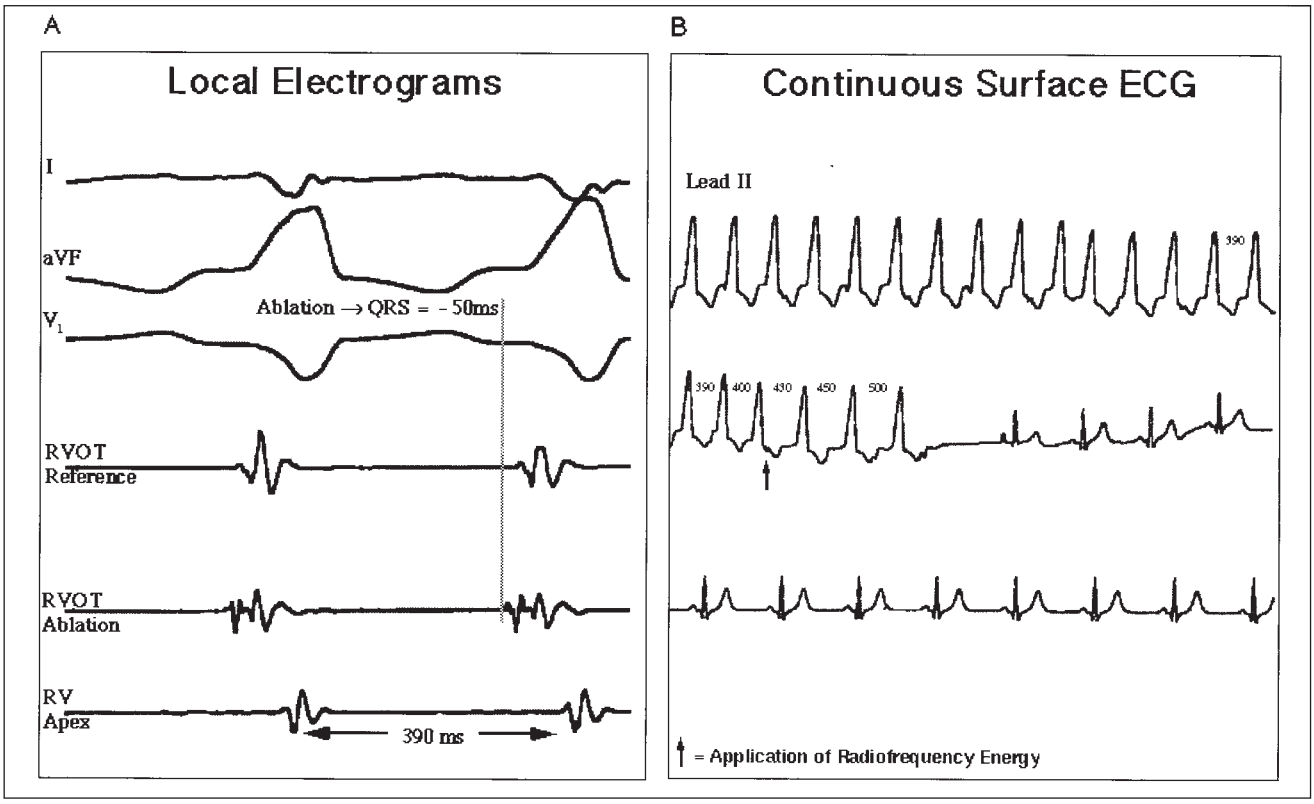

Figure 30.24
RF ablation of right ventricular outflow tract tachycardia. The left-hand panel shows local electrogram timing during sustained tachycardia (cycle length 390 ms: 154 beats/min) from catheters positioned at the right ventricular apex (RV apex), a reference site in the right ventricular outflow tract (RVOT Reference) and the site of successful ablation (RVOT Ablation). The 'RVOT Ablation' site is activated 50 ms ahead of the surface QRS. The right-hand panel shows a continuous ECG from top left to bottom right during continuous RF energy delivery at the 'RVOT Ablation' site. Tachycardia terminated after initial slowing shortly after initiation of RF energy delivery and sinus rhythm is restored.

a central zone of slow conduction with activation spreading to the exit from where the rest of the myocardium is activated. The activation wavefront then spreads around, re-entering the entrance of the slow conduction zone and thus completing the circuit. A number of detailed multipoint mapping studies have shown that arrhythmia circuits in such patients are much more complicated and may be associated with dead ends, multiple exits and multiple potential circuits. Initial experience with catheter ablation of this type of VT proved disappointing,[60] and the technique is applicable to only 10% of the total pool of patients with VT. Failure of ablation may be explained by three possible reasons:

- The arrhythmia cannot be mapped or a critical component of the circuit cannot be identified.
- The critical component cannot be destroyed (eg: too large or deep or insulated by scar).
- There is more than one circuit.

In any patient a combination of these reasons may underlie the failure of the technique and there are major difficulties that have yet to be overcome before RF ablation will be widely applicable to this population. The major limitation to VT ablation is the requirement for prolonged periods of VT so that the arrhythmia can be mapped in detail. In the series by Morady et al[61] a 73% success was reported, but this was only 10% of the total number of patients with VT who were deemed suitable for catheter mapping. Other problems include uncertainty about whether non-clinical tachycardias need to be mapped and ablated as well as the difficulty in producing a lesion of sufficient size to destroy the critical area. Of importance is the fact that there is lack of agreement about the criteria for successful ablation.

New developments in catheter ablation of VT are appearing through a combination of advances in mapping and also in catheter technology to produce greater lesion volume. New energy sources such as microwave and ultrasound are being investigated and may prove more appropriate for the management of patients with post-infarction VT.[1] At present, ablation in patients with post-MI VT is indicated in those who have incessant tachycardia or as palliation to reduce frequent ICD shock.

Conclusions

RF ablation has transformed the management of many arrhythmias. It is cost-effective and has rapidly become first-line therapy for most supraventricular arrhythmias. New technologies are becoming available that are widening the scope of catheter ablation and may make this interventional approach relevant to most arrhythmias.

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31

Percutaneous removal of retained intracardiac foreign bodies

Ever D Grech and David R Ramsdale

Introduction

Over the last 30 years, the complexity of percutaneous diagnostic and therapeutic techniques involving the heart and circulation has increased worldwide. These procedures are carried out not only by the cardiologist, but also by radiologists, anaesthetists, surgeons and physicians, with varied levels of experience. Procedures commonly involve insertion of temporary or permanent pacing electrodes and central venous lines or catheters. These are carried out in general on cardiac surgical intensive-care units and coronary care units, for drug administration and haemodynamic monitoring. Moreover, subcutaneously implanted long-term intravenous cannulae, such as Hickman lines, have proved useful for treating various conditions. Catheter-based coronary diagnostic and interventional procedures have also become widely practised and more recently intracoronary stenting has been introduced to help deal with the acute complications of percutaneous transluminal coronary angioplasty (PTCA) and to reduce restenosis rates.

Unfortunately, hand-in-hand with this rise in vascular intervention has come an increase in the incidence of lost or embolized foreign bodies in the venous[1–4] and arterial circulations,[5–8] including cannulae, pacemaker electrodes, catheter and balloon fragments, intracoronary guidewires and stents. It is therefore necessary for practising interventional cardiologists to become familiar with retrieval equipment and the techniques of percutaneous removal of foreign bodies. This not only circumvents the need for major thoracic or open heart surgery, but may also avoid potentially life-threatening complications.[9] For the adult cardiologist, the commonest sites for retrieval of lost components are the great veins and the right heart including the pulmonary arteries, and the coronary arterial tree. This chapter reviews the various types of retained components and the different methods for their successful retrieval.

Devices

A variety of transcatheter devices for retrieval of components are available. These include the following.

Loop-snare retrieval systems

The loop-snare device is often the first choice in view of its safety and ease of use.[1,10] Three examples of loop-snare systems are shown in Figs. 31.1–31.4. Figure 31.1 shows the Welter retrieval loop catheter (Cook (UK) Ltd, Letchworth, Hertfordshire) which consists of a wire snare and is operated from a proximal handle. Its design permits orientation of the loop at right angles to its shaft, enabling access to free floating foreign bodies. Radio-opaque markers at the catheter tip and at the origin of the loop area facilitate visualization of the device during retrieval (Fig. 31.3). Figure 31.2 shows the Retriever snare (Target Therapeutics, Fremont CA, USA) which consists of an adjustable platinum loop. This can be visualized under fluoroscopy and allows retrieval of different-sized objects. Its low profile design allows use with a 6 F guiding catheter and permits access to distal, tortuous vasculature. The soft conformable materials are relatively non-traumatic to vessel walls. The size of the snare loop can be adjusted by pushing or pulling back on the wire. Figure 31.4 shows the Amplatz goose-neck snare (Microvena Corp, White Bear Lake MN, USA) which has a Nitinol 90° snare-loop to shaft orientation and remains coaxial to the vessel lumen.

Retrieval baskets

Examples of retrieval baskets include the Dotter retrieval catheter,[11–13] the minibasket[14] and the Dormia stone

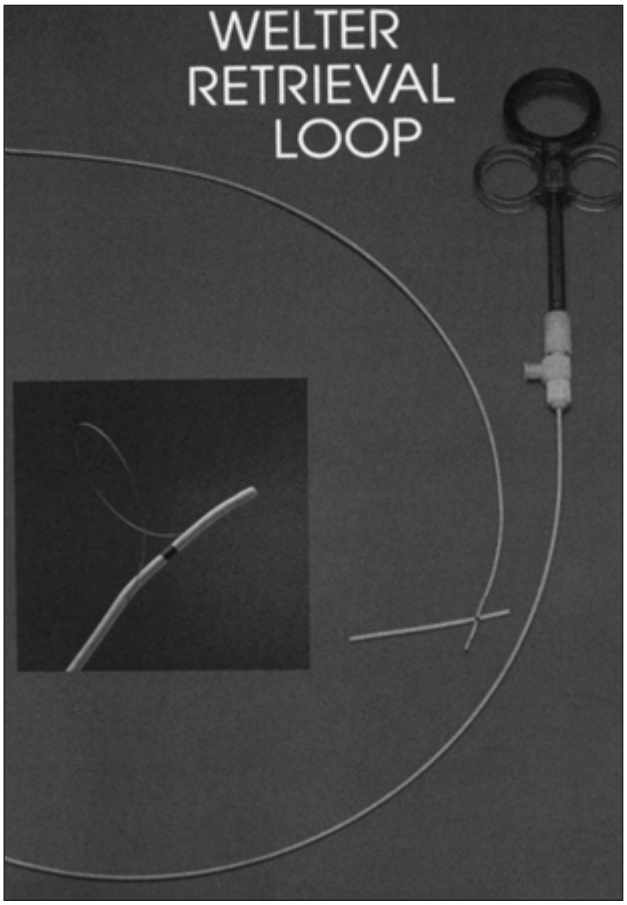


Figure 31.1
The Welter retrieval loop.

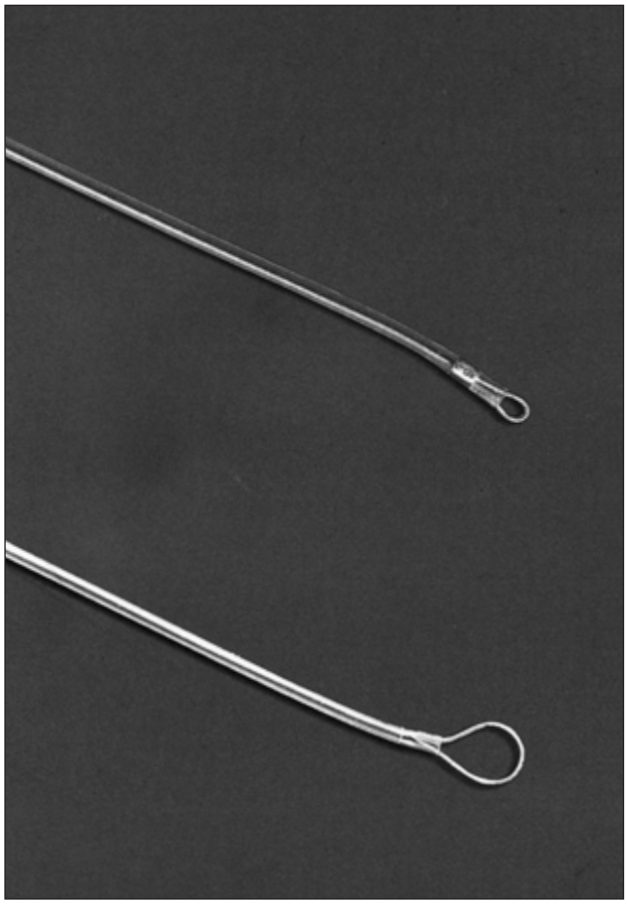


Figure 31.2
The Retriever snare with the loop open (below) and closed (above).

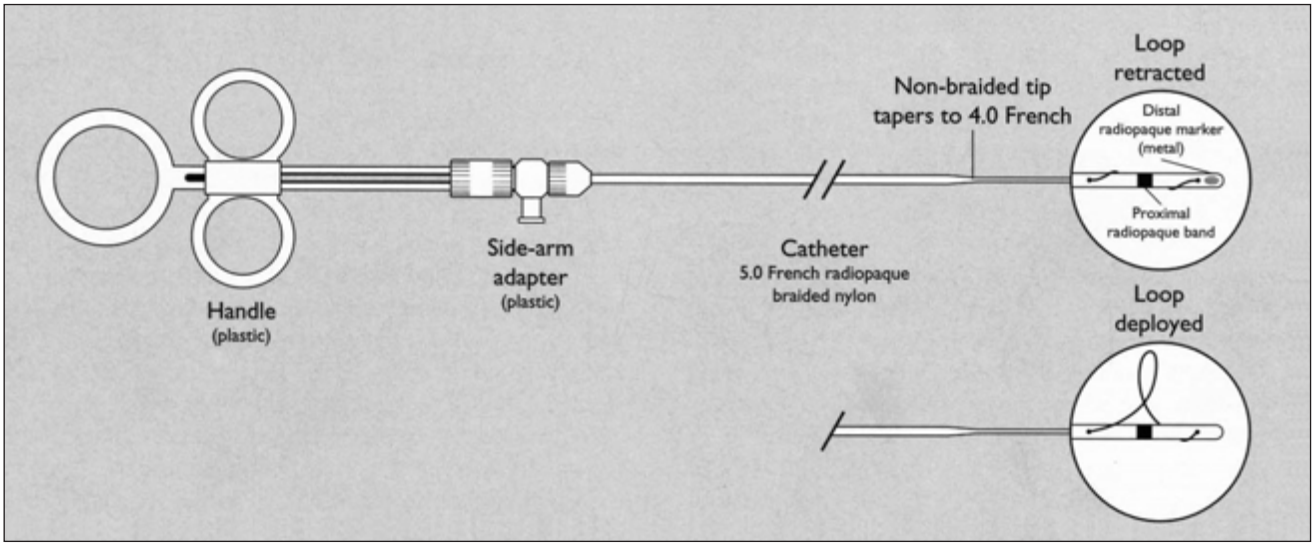


Figure 31.3
Diagrammatic representation of the Welter retrieval loop showing retracted and deployed loop. The radio-opaque markers at the catheter tip and at the origin of the loop area are also shown.

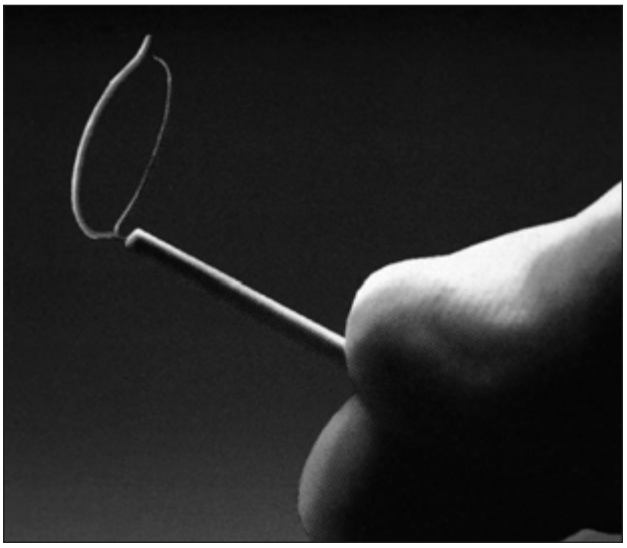


Figure 31.4
The Amplatz goose neck snare.

catcher.[15] These consist of an outer sheath enclosing movable parallel metal wires, which can be opened or closed by sliding a cone in and out of the coronary catheter. A diagram of a Dotter basket device and introducer set is shown in Fig. 31.5. As this instrument has a rigid tip, vessel or cardiac chamber perforation may occur if it is not handled with care. To deploy the device, the basket is placed beyond the fragment and then opened. It is then withdrawn, allowing entrapment of the foreign body, at which time the basket is pulled shut and removed as a single unit. Retrieval basket devices are particularly useful in retrieving objects in the great veins or intracardiac chambers. In the arterial circulation, they are only useful if the object extends into the aorta. Figures 31.6a, b and c shows X-ray images demonstrating retrieval of a Hickman catheter from the superior vena cava by a Dotter basket (Cook (UK) Ltd). Figure 31.7 shows a close-up of a broken pacemaker electrode tip trapped in a Dotter basket.

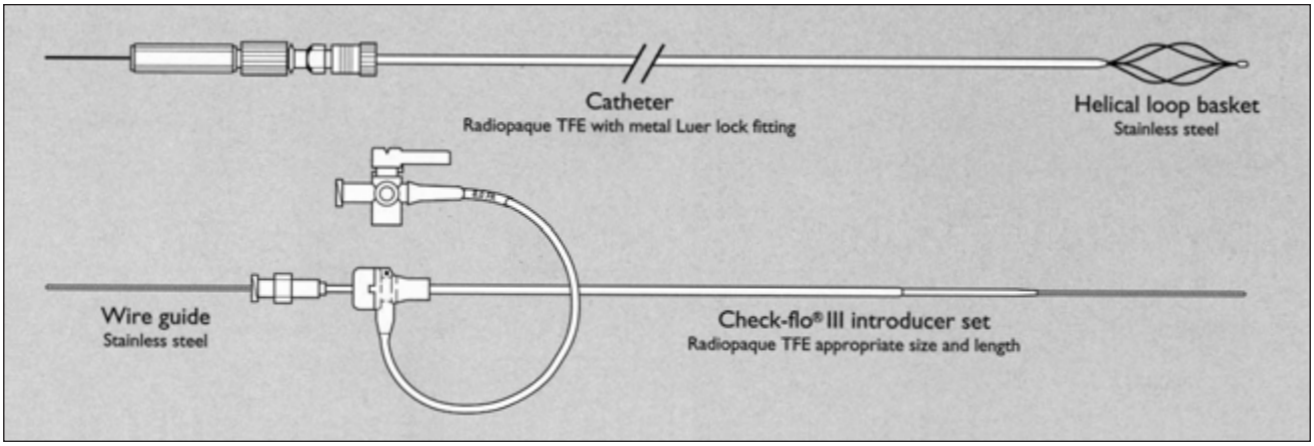
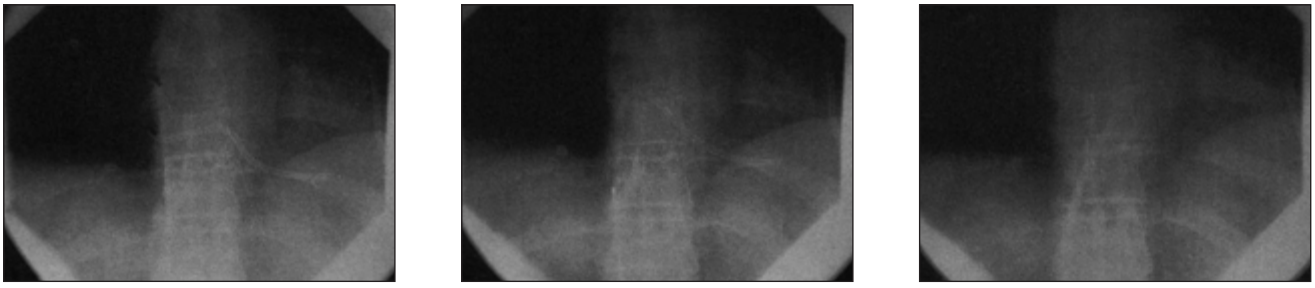


Figure 31.5
Diagrammatic representation of the Dotter retrieval basket and introducer set.



a b c

Figure 31.6
(a) Sequential X-ray images showing retrieval of a Hickman catheter from the inferior vena cava by a Dotter basket. The catheter tip lying in the right atrium is successfully ensnared within the Dotter basket passed from the femoral vein. (b) Gentle traction of the Dotter basket allows the catheter to be removed into the inferior vena cava. (c) Most of the catheter is now in the inferior vena cava and only the distal portion of the Hickman catheter is visible.

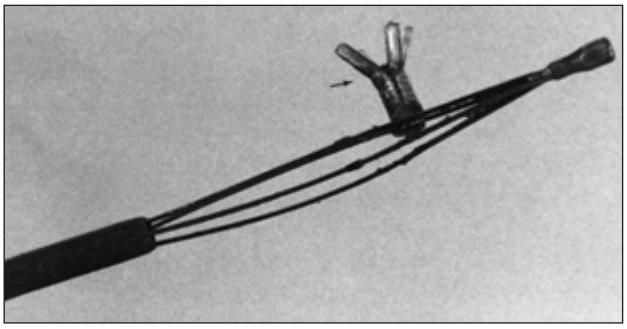


Figure 31.7
Tined pacemaker electrode tip (indicated by arrow) ensnared within a closed Dotter basket.

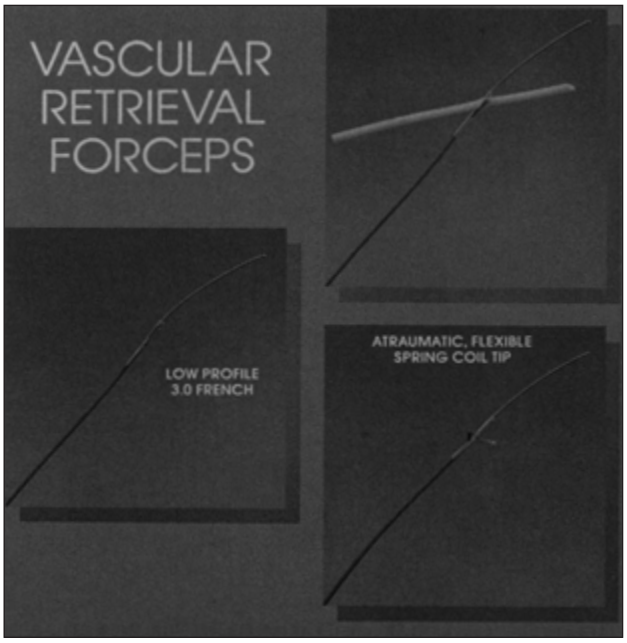


Figure 31.8
The Cook grasping forceps.

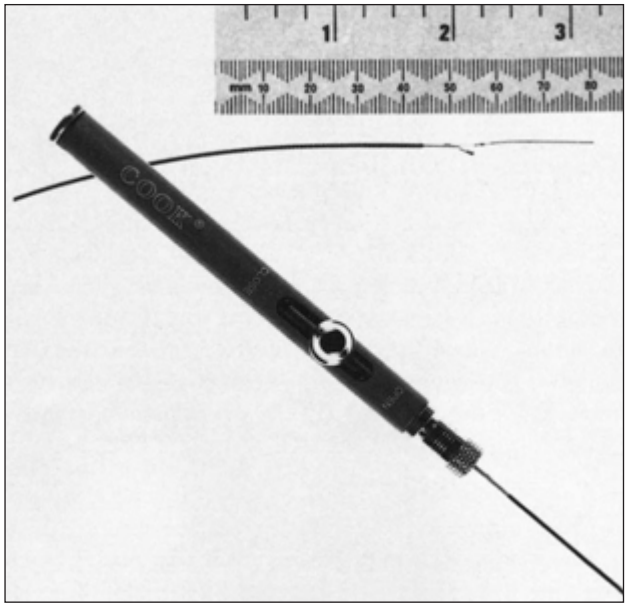


Figure 31.9
The Cook grasping forceps showing the proximal operating handle and distal forceps.

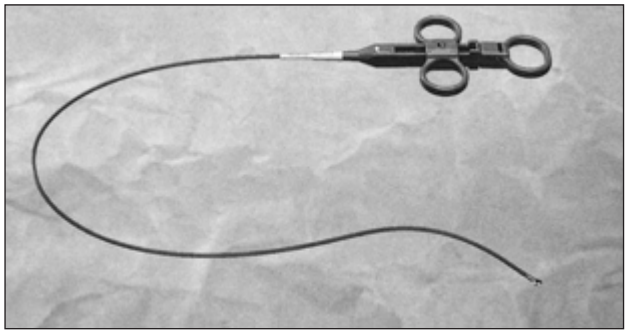


Figure 31.10
The Cordis biopsy forceps.

Bioptome/grasping forceps

Different types of jaw forceps are available including those used for myocardial biopsy.[7,16,17] Two examples of bioptome/grasping forceps are shown in Figs. 31.8–31.10. Figure 31.11 shows a close-up of the open jaws of Cordis biopsy forceps. The Cook retrieval forceps (Cook (UK) Ltd) is a 3 F low profile device which includes a distal spring coil to prevent inadvertent vascular wall trauma during manipulation. The forceps' grasping jaws are operated from a proximal handle. The Cordis biopsy forceps (Cordis Corp, Miami FL, USA) are also operated from a proximal handle. This catheter is larger and stiffer and care is needed when it is used to retrieve foreign bodies in less resilient vascular areas. Figure 31.12 shows a broken temporary pacemaker electrode successfully retrieved using grasping forceps.

Miscellaneous techniques

A simple, handmade snare may be fashioned using single[18–20] or twin guidewires.[21,22] The snare is created by doubling over an exchange-length wire at its mid-section and inserting it down a 4 Fr probing catheter. Alternatively, a snare may be created by looping the distal 5 cm of a standard-length wire, or tying together the flexible ends of two 0.014-inch wires. The probing catheter is then passed through the guide catheter and positioned just proximal to the retained fragment. The loop is front-loaded through the probing catheter and gently passed over the object. Ideally, the loop should have a moderate bend to help encompass the fragment. Once the object is trapped, the wire ends are pulled firmly to secure the object against the catheter tip. The whole assembly is then withdrawn until it passes through the femoral sheath.

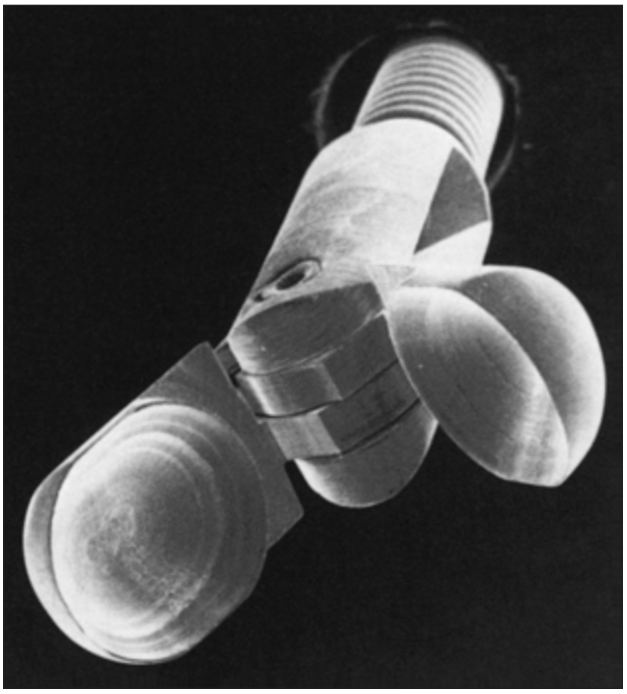


Figure 31.11
Magnified view of the Cordis biopsy forceps jaws in the open position.

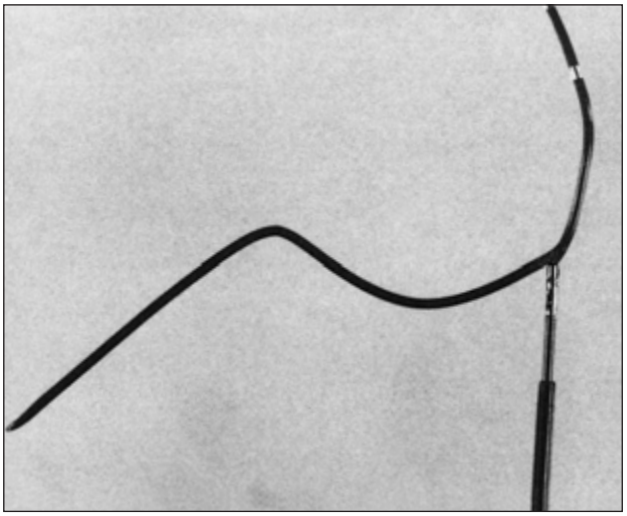


Figure 31.12
Example of a broken temporary pacemaker electrode successfully retrieved using a jaw forceps device.

If the snare device cannot be steered into a tortuous or acutely angled coronary artery, twin 0.014-inch guidewires may be used. The wires are advanced separately into the coronary artery and positioned beside the fragment. The proximal wire ends are inserted into a torquer and clamped firmly together. The torquer is then rotated in a clockwise direction to form a helix of the two wires. With the Y-connector partially open, the double helix is propagated distally into the coronary artery, ensnaring the object which can then be withdrawn into the guiding catheter and removed.[21,22]

Inflated[5,23] or deflated balloon catheters[24,25] may be used to drag fragments physically from the vessel into the guide catheter. The inflated-balloon technique has the potential for significant mechanical vascular injury and must be used cautiously.

A pigtail ventriculography catheter has been used to snare a catheter fragment in the venous system[26] and a broken guidewire in a coronary artery.[23] Again the potential for causing vessel wall damage demands caution when this procedure is attempted.

Sites of retained components

Retained components can only be removed percutaneously if they are radio-opaque. High-resolution fluoroscopy is required, preferably digital with magnification options to enable accurate definition of the object. Full haemodynamic monitoring is essential. Systemic heparin (10 000–15 000 units) should be administered if not already given beforehand, to avoid thrombus formation on the retrieval device or the retained fragment.

Right heart

Within the venous system, Swan–Ganz balloon catheters,[13] introducer sheaths,[10] fractured pacemaker electrodes,[27–30] redundant ventriculo-atrial shunts for hydrocephalus[12,20] and other right heart catheters[19,31] have been removed percutaneously.

For retrieval of central venous or right heart objects, the preferred technique is to use the right femoral vein for access. Under local anaesthetic an 8 F haemostatic sheath is inserted into the right femoral vein using a Seldinger technique. A long sheath is then advanced over a 0.035 mm diameter long guidewire into the appropriate part of the great veins or right heart chamber. On removal of the guidewire, the retrieval device is inserted to grip or ensnare the free end of the foreign body. The retrieval device can be manipulated to both subclavian veins, superior vena cava, right heart chambers and pulmonary arteries. Once captured, the device is withdrawn into the long sheath and the long sheath, retrieval device and foreign body are removed intact from the vein. A second venous sheath may sometimes be useful for insertion of another catheter such as a pigtail, Judkins or Cournand which can be used to help unfold loops of catheters in order to present a free end for the retrieval device (Figs. 31.13 and 31.14). Alternatively, a grasping forceps (Fig. 31.15) or snare device can be used (Fig. 31.16). At the end of the procedure,

haemostasis can be achieved by simple direct pressure. When larger objects, knots or loops have been removed, protamine sulphate can be given to reverse heparin anticoagulation.

Pacemaker electrodes

The transvenous extraction and/or repositioning of chronically implanted permanent pacemaker electrodes presents special difficulties due to scar-tissue adhesion at the lead tip,[32] which may extend along the length of the lead (Fig. 31.17). If a lead has failed, the usual practice is to cap it at the connector terminal so that it is sealed, leaving it buried under the patient's skin. However, removal is essential if the lead becomes infected, the patient develops septicaemia or there is a free-floating lead in the vascular system.

In some instances, removal of an adherent electrode can be achieved by continuous traction on the lead, sometimes with the use of weights, until it comes away from the myocardium. However, this is generally unsatisfactory because of the risk of myocardial avulsion. Until recently, the alternative and more complex option has been thoracotomy. However, a purpose-made lead extraction system (Cook (UK) Ltd) has been described by Byrd et al,[33] which enables removal to be performed reasonably safely without the need for surgery. The system uses a countertraction technique and hence lessens the risk of myocardial avulsion (Fig. 31.18).

The procedure is carried out either in the cardiac pacing laboratory or in a theatre equipped with fluoroscopy. Electrocardiographic and blood pressure monitoring, and a defibrillator, are essential. A temporary pacing wire may be required if the patient is pacemaker-dependent. In addition, echocardiography and a pericardiocentesis set should be rapidly available in case pericardial effusion leading to tamponade develops. The patient should be cross-matched for at least 2 units of blood and a stand-by thoracic surgical team should be available. Lead extraction can be performed via the superior approach, when the lead is extracted through the implant vein (the subclavian, cephalic or jugular vein). Alternatively, the femoral approach is used if the lead is inaccessible or if the superior approach is difficult or unsuccessful.

Using the superior approach, routine surgical aseptic technique is used and the pacemaker pocket site and/or groin region is cleaned and draped. Surgical cutdown to the pacemaker generator is performed and it is removed. The terminal connector of the pacing lead is cut off cleanly using the clippers supplied. The two main tools used are the special locking stylet and the dilator sheath set. The locking stylet, which stiffens the lead, is passed down the lumen of the lead to its tip. It consists of a loop handle at the proximal end (Fig. 31.19) and an expandable wire coil at the distal end (Fig. 31.20). The size of the locking stylet is selected beforehand using gauge pins. By rotating the loop handle anticlockwise several times, the fine-wire filament unwinds inside the coil, wedging the stylet shaft tightly into the coil at the lead tip and locking it there. A system of two telescoping dilator sheaths is advanced over the protruding lead end and manipulated along its length via the subclavian vein and on into the heart, thus disrupting the scar tissue along the lead (Fig. 31.21). If the lead has not been freed by the time the

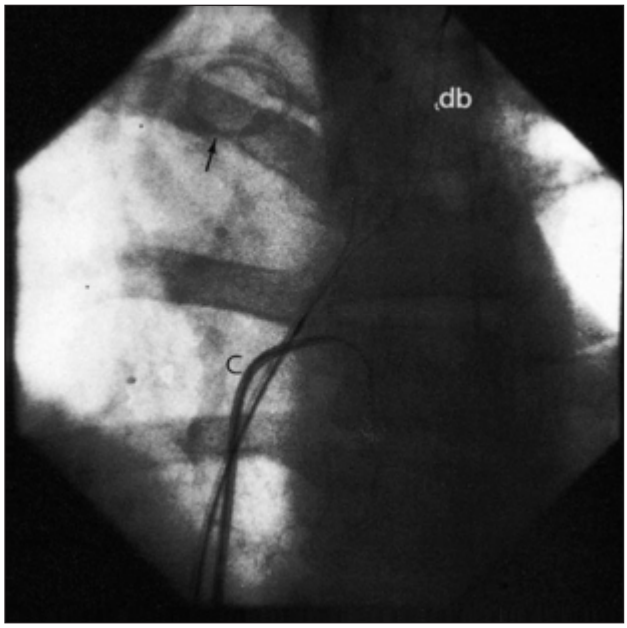


Figure 31.13
Use of a Cournand catheter (C) and guidewire to present free end of embolized catheter (arrowed) to open Dotter basket (db).

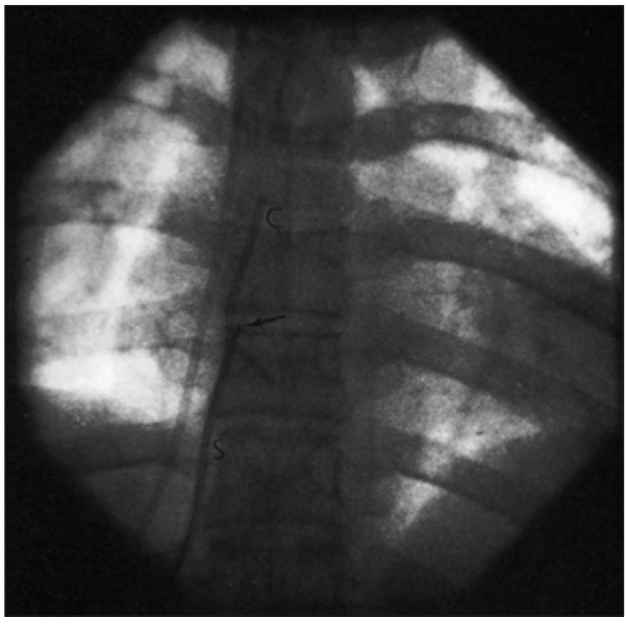


Figure 31.14
X-ray showing catheter (C) being withdrawn by the Dotter basket (S).

a b c

d e f

g h i

j

Figure 31.15
(a) Embolized 'cut off' permanent pacemaker electrode. Loops of electrode are present in the right atrium and both tips are firmly embedded at the apex of the right ventricle. (b) A Dotter basket was unable to ensnare a loop. (c) A grasping forceps successfully captures the electrode (arrow). (d) Electrode is straightened with inferior traction. (e) Further traction is applied. (f) The proximal end of the electrode is freed from the right ventricular apex. (g) The free end of the electrode is ensnared within the helical Dotter basket. (h) Both are pulled firmly down into the inferior vena cava and the distal electrode tip is freed from the right ventricular apex into the right atrium. (i) Electrode and Dotter basket are pulled into the common iliac vein. (j) The electrode ensnared in the Dotter basket is successfully removed from the patient.

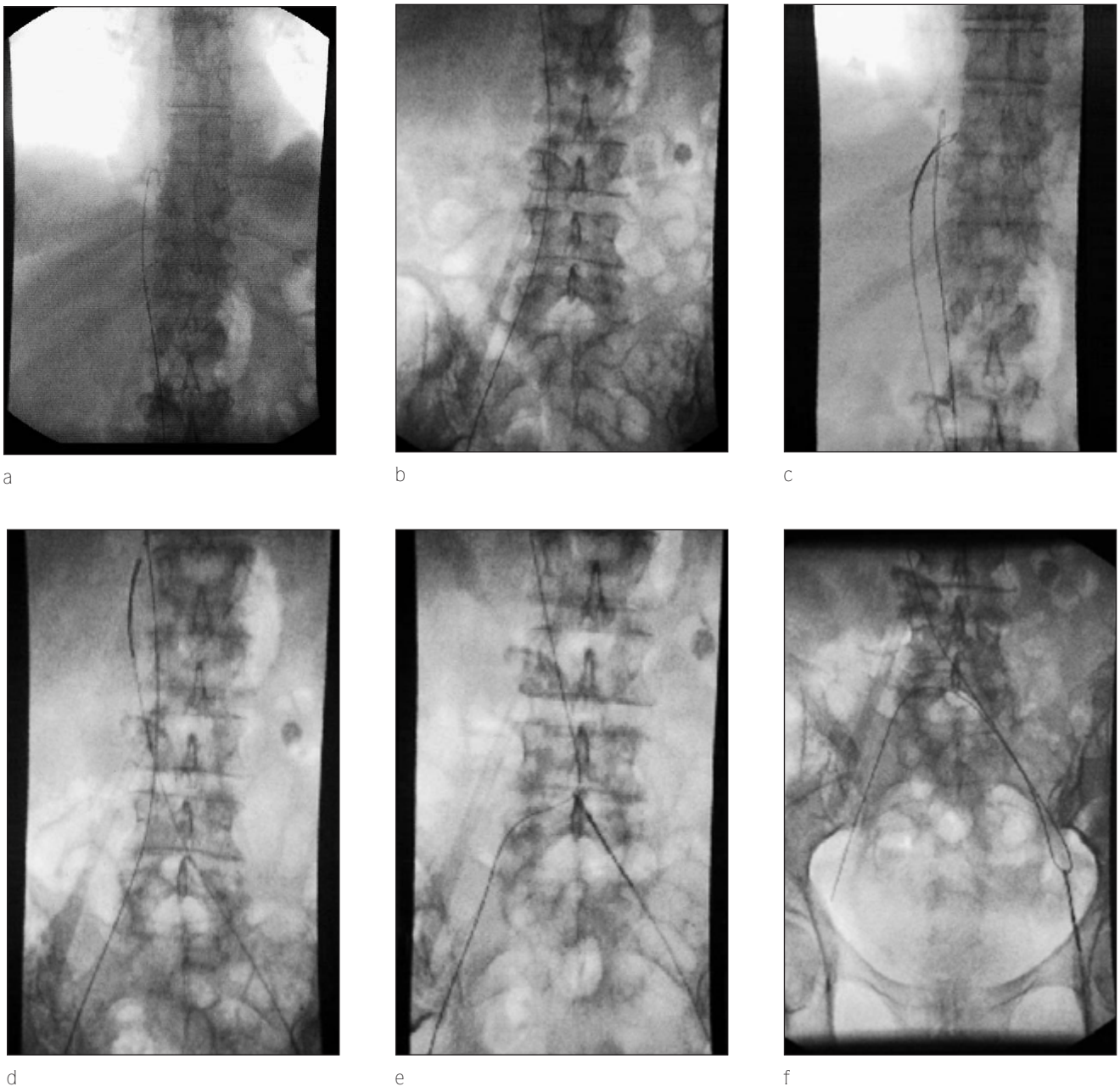


Figure 31.16
Sequential X-rays demonstrating the retrieval of a J-wire sited within the inferior vena cava and right iliac vein (a), (b), using a loop snare inserted from the left femoral vein (c). The open snare was looped over the top of the free end of the J-wire (d), and advanced downwards toward its mid-segment before being tightened and fixed (e). Gentle traction then allowed its successful removal via the left femoral vein (f). (Courtesy of Dr R Hartley, South Cleveland Hospital, Middlesbrough.)

sheath is near the myocardium, the outer sheath is advanced onto the myocardium (Fig. 31.22). With firm traction on the lead via the locking stylet and countertraction on the sheath supporting the myocardial wall, the lead can be freed and pulled through the sheath (Figs. 31.23 and 31.24). If required, a new lead can now be inserted through the outer sheath. Lead removal using this system may not be possible if there is excessive scar tissue along the length of the lead or if the locking stylet will not pass through a damaged lead. It may be necessary to use the femoral approach if the lead has retracted into the venous system and cannot be reached with the superior approach.

The femoral system comprises a long sheath with a tip-deflecting guidewire threaded through a Dotter retrieval

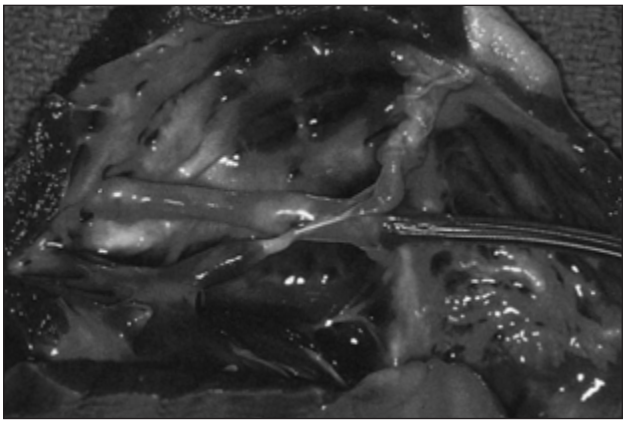


Figure 31.17
Pacemaker lead after 6 months in a dog heart. Note the fibrous sheath encapsulating the lead which extends well past the fixation mechanism at the lead tip. A lead implanted for a few years in a patient may have severe scar tissue attached at several sites.

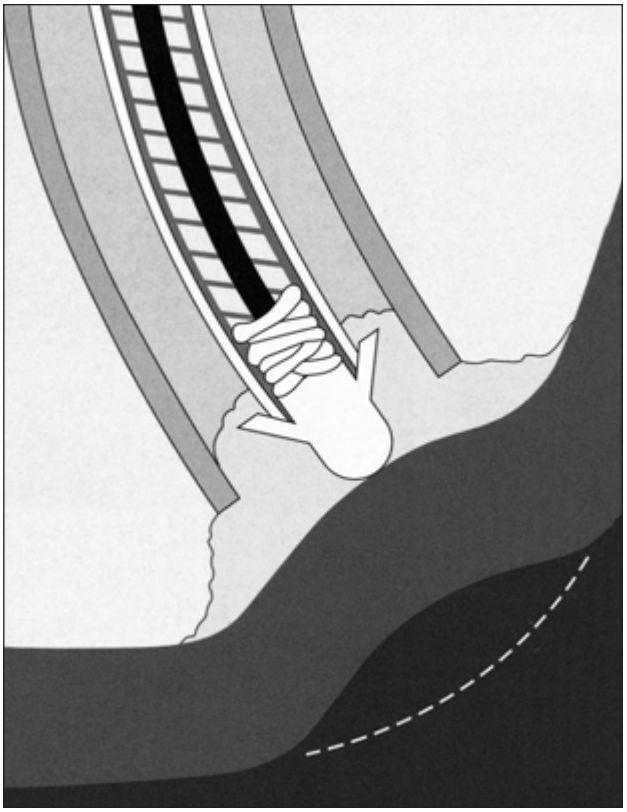


Figure 31.18
Pacing lead tension applied with countertraction within the sheath.

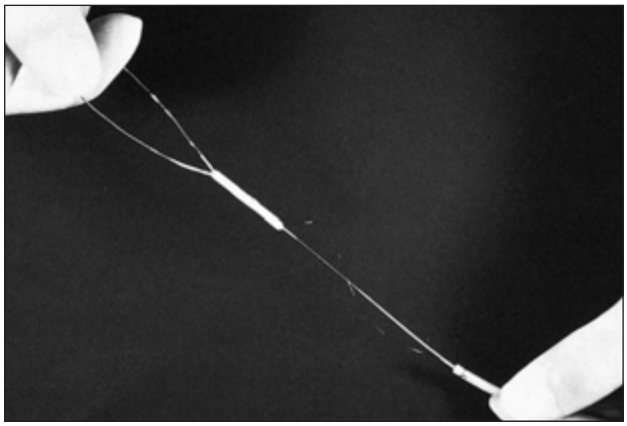


Figure 31.19
Turning loop handle of the stylet, which is rotated anticlockwise several times. This causes the wire at the tip to unwind and lock against the inner coil of the lead.

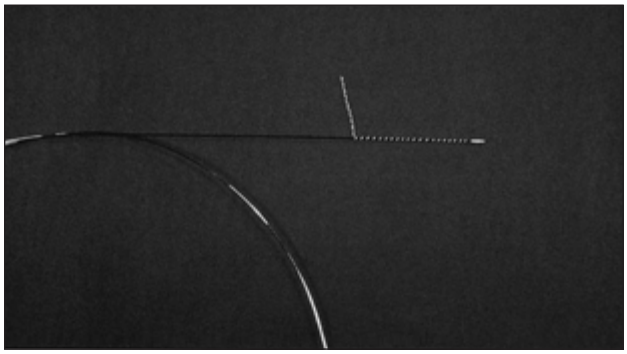


Figure 31.20
Close-up of the locking stylet tip showing the locking mechanism. The appropriately sized locking stylet is inserted in the coil lumen and advanced to the tip of the lead.

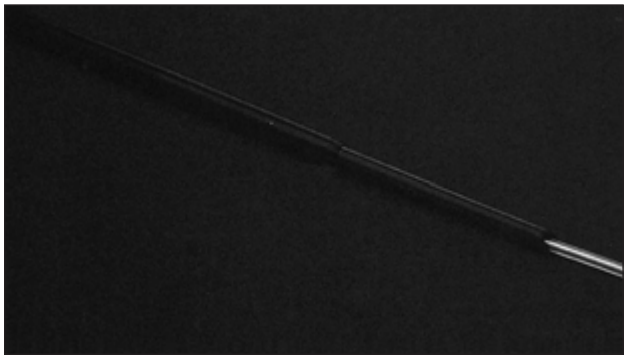


Figure 31.21
Polypropylene or Teflon polymer sheaths are used to disrupt scar tissue along the vein and into the heart.

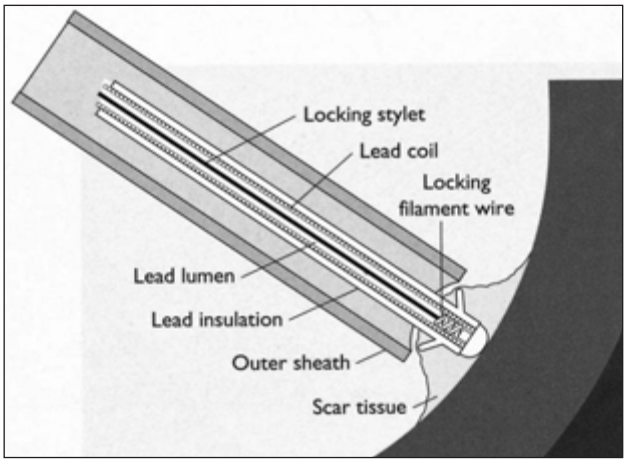


Figure 31.22
The stylet is locked inside the lead coil. If the lead has not been freed by the time the sheaths reach the heart, the outer sheath is advanced to the myocardium.

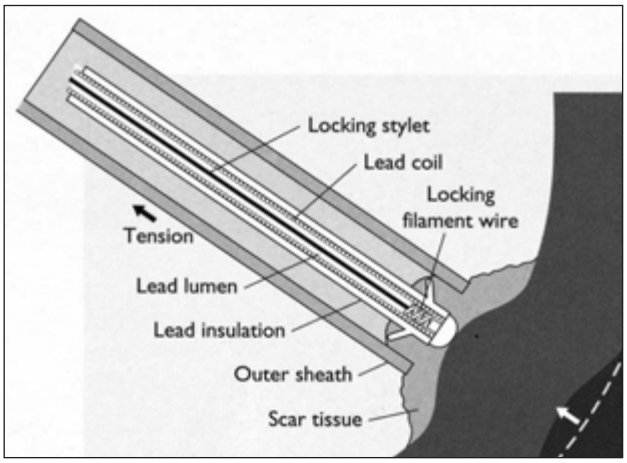


Figure 31.23
Firm traction is placed on the locking stylet, while the sheath provides countertraction, preventing invagination of the heart and confining the force within the circumference of the sheath.

basket (Fig. 31.25). A long sheath system is inserted via the femoral vein using the routine Seldinger technique and advanced up into the right atrium. A tip-deflecting wire is lassoed around the lead and is pulled down onto the Dotter basket. A longer sheath is then advanced over the lead and in a similar manner to the superior approach, thus removing the lead from the scar tissue and myocardium (Fig. 31.26). The femoral system with the lead attached is then removed from the body.

In the largest published series using the above technique, Byrd et al performed 3450 lead extractions in 2338 patients

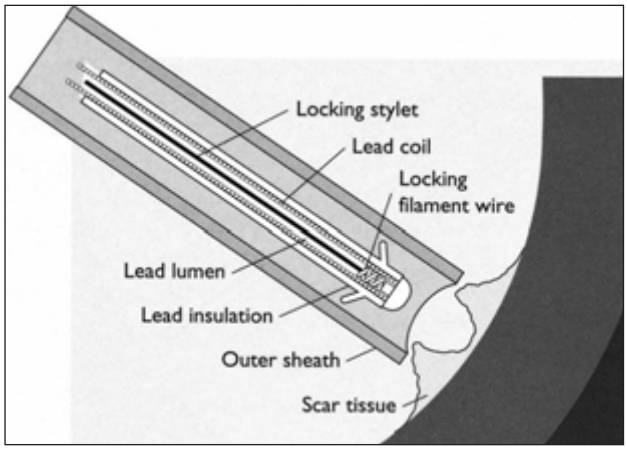


Figure 31.24
When the lead tip is freed from the scar tissue, it is removed through the sheath. The outer sheath can even be used as an introducer for a new lead.

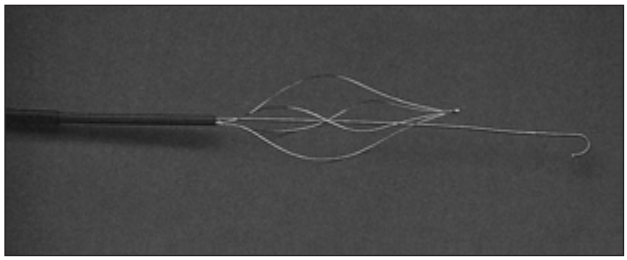


Figure 31.25
The tools most frequently used for the femoral approach are a tip-deflecting guidewire threaded through a Dotter basket, which are inserted through coaxial femoral sheaths.

Figure 31.26
The Dotter basket is closed over the lead and the sheaths advanced towards the myocardium to free the lead from scar tissue in a manner similar to the superior approach.

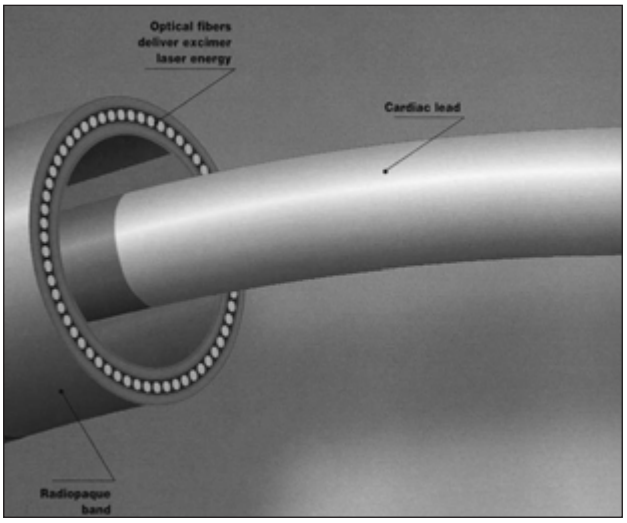
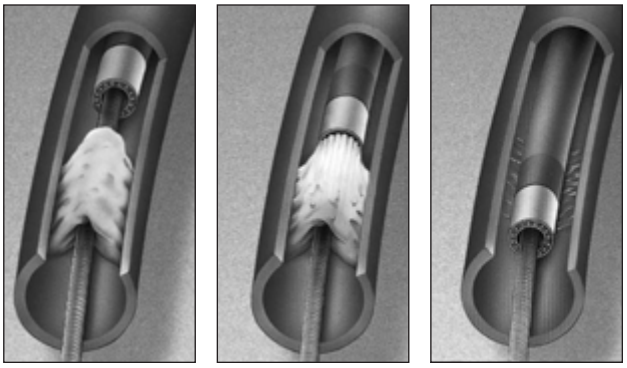


Figure 31.27
The Spectranetics laser sheath (SLS) with circumferential array of optical fibres around the pacemaker/ICD electrode.



a b c

Figure 31.28
(a) The laser sheath is advanced over the pacemaker/ICD electrode towards the binding site. (b) Controlled bursts of excimer laser energy photo-ablate fibrous tissue. (c) The laser sheath is advanced through the binding site to the next site until the lead is released.

at 226 centers, over a period of 28 months. The indications for extraction were infection (27%), non-functional or incompatible leads (25%), removal of Accufix or Encor atrial J-leads following their recall by Teletronics due to the risk of potential fracture and protrusion of their J retention wires (46%), or other causes (2%). A superior approach was used for 84.4% of leads, a femoral approach in 4.3% and a combined approach in 11.3%. Additional devices, such as retrieval baskets, loop snares, coronary guiding catheters and pigtail catheters were also used. Ninety-three per cent of leads were completely extracted (and 5% partially extracted) with a major complication rate of 1.4%, which was statistically significantly

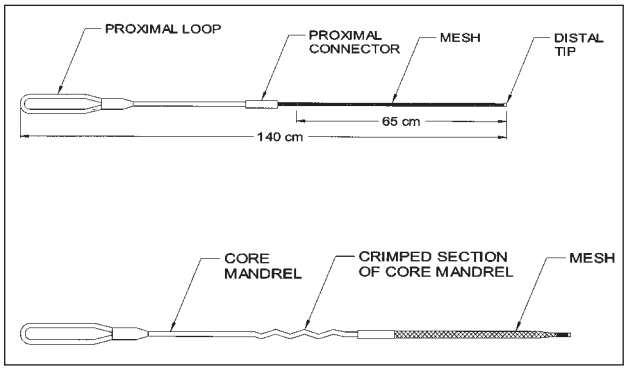


Figure 31.29
Diagrammatic representation of the Lead Locking Device (LLD) showing unexpanded and expanded locking mesh.

higher in women than in men (2.3% v 0.8%, $P < 0.01$). Only one death was reported (0.04%) and the minor complication rate was also low at 1.7%. The overall complication risk increased significantly with the number of leads removed and less operator experience. The authors concluded that the indication for extraction should be balanced against the risk of complication, and that experienced operators should be conscious of the need to be fully equipped and prepared for every eventuality before undertaking lead extraction.[34]

A new technique using excimer laser has recently been introduced by Spectranetics (Colorado Springs, Colorado, USA). Data from the randomized PLEXES (Pacemaker Lead Extraction with the Excimer laser Sheath) trial indicate that this system is more effective than standard non-laser methods.[35] The Spectranetics laser sheath (SLS) contains optical laser fibres, which allow 308 nm invisible, ultraviolet light pulses from a xenon–chloride laser to ablate tissue at the sheath tip, allowing it to cut through adherent scar tissue (Fig. 31.27). It is threaded over the pacemaker (or ICD) electrode and advanced towards further fibrous binding sites until the tip of the electrode is reached (Fig. 31.28). This system is used in conjunction with the lead locking device (LLD) which comprises a loop wire handle and a core mandrel that has a stainless steel mesh fixation mechanism (Fig. 31.29). This is inserted down the lumen of the electrode and the proximal end of the mesh is attached to a proximal connector which is used to deploy and lock the device in the electrode. Following advancement of the laser sheath over the locking device, traction to the lead using a proximal suture allows its successful removal (Fig. 31.30).

Left heart

There are only limited data concerning the incidence of retained components within the left heart. However, one series that reviewed 500 consecutive elective coronary

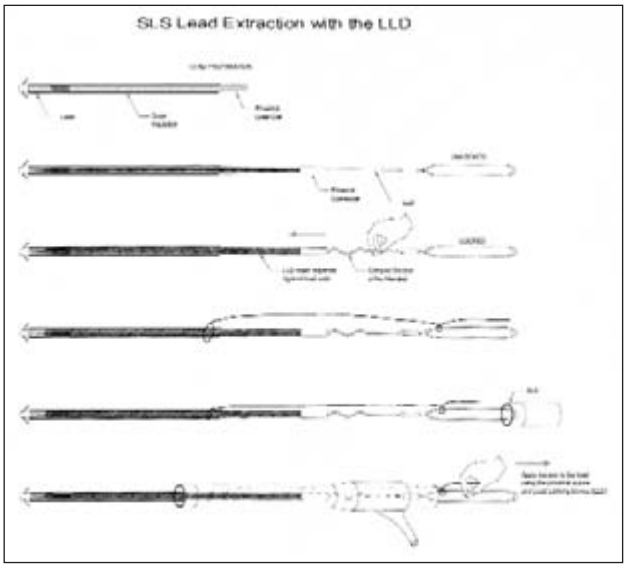


Figure 31.30
The lead locking device (LLD) in the undeployed and deployed configurations. Following successful advancement of the spectranetics laser sheath (SLS) over the LLD, traction to the lead using a proximal suture allows its successful removal.

angioplasty procedures estimated the risk of retained components to be 0.2%.[36] A larger series involving 5400 consecutive PTCA procedures also observed an incidence of 0.2%.[5] Other estimates range from 0.1 to 0.8%.[37,38] Within this system, the most frequently reported retained fragments are angioplasty guidewires[6,9,16,18,23–25,39–44] or rotational atherectomy device guidewires,[45,46] often within the coronary tree. The reasons for this appear to be the delicate structure of the guidewire, possible design weakness,[16] excessive torquing or bending and entrapment or impaction onto a small branch or plaque.[47] Other components include balloon catheter fragments.[8,21,48] Occlusion devices such as embolization coils, umbrella duct occluders and detachable balloons are becoming more widely used and may also become misplaced.[49]

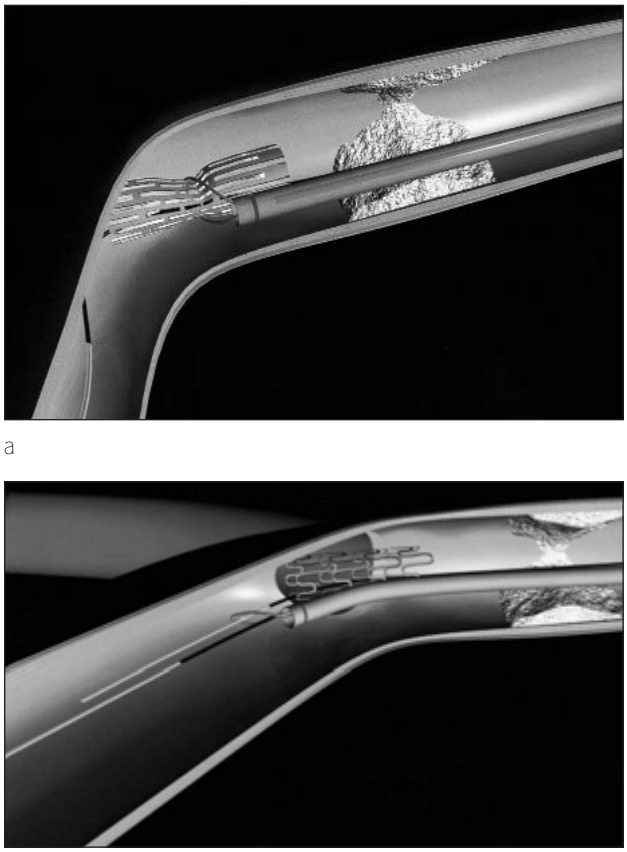
Intracoronary stents

The increasing implantation of intracoronary stents for the prevention of restenosis and the treatment of a suboptimal angioplasty result or acute closure has also heightened an awareness of the need for their capture and recovery if unsuccessfully delivered.[50] Failure of stent delivery or embolization has been widely reported and, although it is not frequent, has been reported in up to 8% of cases.[51–58] However, delivery success rates have improved with more modern premounted, lower-profile, flexible, slotted-tube stents compared to the previous high-profile, hand-crimped, rigid, Palmaz–Schatz stents. Displaced stents, which have not been fully deployed, can be retrieved using snares, baskets and grasping forceps.[7,17,59] Meticulous attention to procedural and periprocedural details is required if stent loss is to be prevented, although such events are usually unpredictable. Although systemic stent embolization does not usually result in clinical sequelae,[55] undeployed stents in the coronary arteries should be removed immediately if at all possible. However, there is surprisingly little literature describing retrieval methods of undeployed stents retained within the coronary tree. Eeckout et al[17] and Pan et al[50] reported on stent recovery after failed intracoronary delivery, but they restricted their report to stents lost from the balloon outside the coronary artery. Using a technique where a second guidewire was twisted around the first, Veldhuijzen et al were unsuccessful in removing an undeployed Palmaz–Schatz stent within a right coronary artery in one patient, although they were successful in retrieving an undeployed Wiktor stent, also within a right coronary artery, in another patient.[22] Foster-Smith et al used a snare to retrieve an undeployed Wiktor stent and a forceps device to retrieve a deployed Wiktor stent from a vein graft, in the same patient.[7] In another patient, an undeployed Gianturco–Roubin stent was removed from the left main coronary artery by inflation of a balloon catheter to 5 atmospheres to trap the stent. It could not, however, be drawn into the guide catheter and was dislodged from the balloon catheter during the attempt. The stent was then retrieved using a multipurpose basket.[7] More recently, Columbo and others have described the use of the Amplatz goose neck snare (Microvena Corp, White Bear Lake MN, USA) to retrieve stents from both within[60] and outside the coronary tree, and the Cook grasping forceps (Cook Inc, Bloomington IN, USA) outside the coronary tree.[61] The goose neck snare may be used in one of two ways (Fig. 31.31). In the proximal grab method, the balloon catheter is removed and the loop of the microsnare is placed over the proximal end of the guidewire. The snare is advanced until the distal end of the microcatheter is positioned just proximal to the stent. The loop is then opened and advanced around the proximal end of the stent. The loop is then closed to grab the stent and removed into the guide catheter. In the distal wire grab method, the balloon catheter is removed and a second guidewire is positioned adjacent to the stent and distal to the original guidewire. The microsnare is looped over the proximal end of the second guidewire and advanced until the distal end of the microcatheter is positioned distal to the stent and original guidewire. The loop is opened to snare the distal end of the original guidewire. The microsnare, both guidewires and the stent can then be withdrawn together into the guiding catheter.

It is important to recognize partial stent detachment and to avoid total slippage of the undeployed stent from the delivery balloon. Radio-opaque stents or those with end-markers are more advantageous in this respect compared to non-radio-opaque, stainless steel stents, which are poorly visualized.

Another advantage of the coiled stents (for example, Wiktor or Gianturco–Roubin designs) which have a wound wire construction, was that they could unravel on traction and this would also facilitate retrieval. When partial slippage of the stent occurs, the guidewire must be maintained within the coronary artery to avoid stent embolization. The next step is the withdrawal of the stent from the coronary artery into the relative safety of the guide catheter. This can be achieved by disengaging the guide catheter from the coronary ostium into the ascending aorta. When the stent is just outside the ostium, a 0.5–1.0 atm balloon inflation then traps the stent on the balloon. The balloon–stent system can then be gently withdrawn into the guide catheter and all are removed from the patient. If the balloon and stent do not enter the guide catheter, then the catheter should be removed from the patient (while maintaining the position of the guidewire within the coronary artery if possible). The balloon/stent should be simultaneously pulled back, maintaining its position just beyond the tip of the guiding catheter. Once the guiding catheter has been withdrawn from the patient, the balloon can be fully deflated and removed from the patient, leaving the stent on the wire close to the femoral sheath. This can then be removed with a snare, basket or retrieval forceps. Figure 31.32 shows an example of successful intracoronary stent retrieval.

An interesting concept proposed by Eigler et al is the intentional removal of an intracoronary stent hours or days following deployment, hence reducing the need for prolonged anticoagulation.[62] This may be achieved using a heat-activated recoverable temporary stent (HARTS device) made from nickel–titanium alloy. Following rapid injection of 3 to 5 ml of Ringer solution preheated to 75–80°C, the expanded stent collapses to its original configuration, gripping onto a catheter, providing a mechanism for its recovery. To date this has been successfully used in dog canine coronary arteries only.



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b

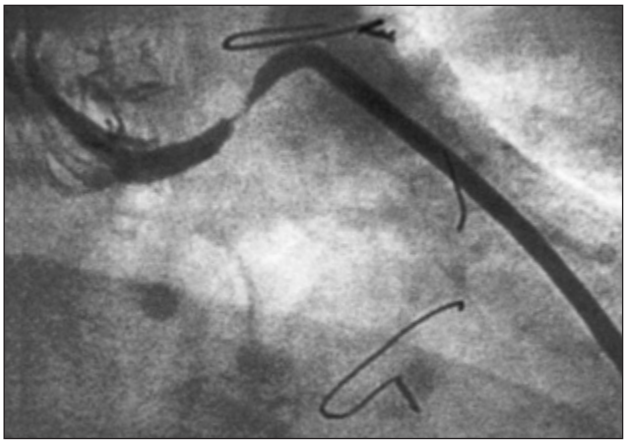
Figure 31.31
Two methods of stent retrieval using the Amplatz 'goose neck' microsnare. (a) The 'proximal grab' and (b) the 'distal wire grab' methods.

Management

The optimal management of retained intravascular fragments has been controversial and remains undefined. It is dependent on the site and situation in which the event occurs and must be tailored to the individual patient's needs and risks. Thus, the retrieval of an undeployed stent within a coronary artery may differ in technique and complexity from that of a pacemaker lead within a great vein.

Although retained components may be removed surgically or percutaneously, they may also be left in situ. There are instances when it may be appropriate and safe to leave a metallic fragment contained within a previously occluded coronary artery, when there is not a clear indication for coronary artery bypass grafting (CABG). In their series, Hartzler et al observed that the intracoronary retention of equipment fragments was at times well tolerated.[5] However, it is worth noting that in this series only one wire fragment was left in situ in a patent coronary artery. Thus the benign clinical course characteristic of the patients in that series primarily reflected detached wire fragments in chronically occluded arteries. The potential for late perforation, dissection,[6,45] infection, arrhythmia and proximal propagation of thrombus resulting in myocardial infarction[9] must be considered as possible risks when this strategy is adopted.[6,9] While there is some evidence that fragments may become endothelialized and remain benign, there are no long-term or pathological data to support this hypothesis.[5]

In some cases, surgery will be required primarily because the initial procedure was unsuccessful and, in these circumstances, the retained fragment can be removed intraoperatively,[6,9,37–44,63] If myocardial ischaemia is present or threatened, surgical removal of components should be considered early.[6] In unstable patients, attempts at catheter extraction may cause unnecessary delay in mobilizing an operative team. When an interventional procedure has failed and the probability of successful dilatation after fragment retrieval is low, a direct surgical approach is advisable.



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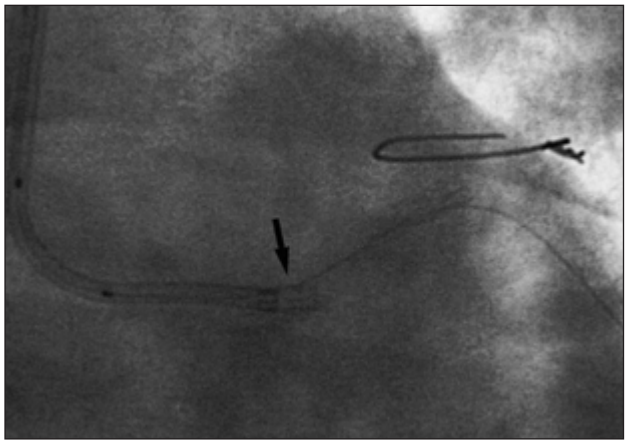

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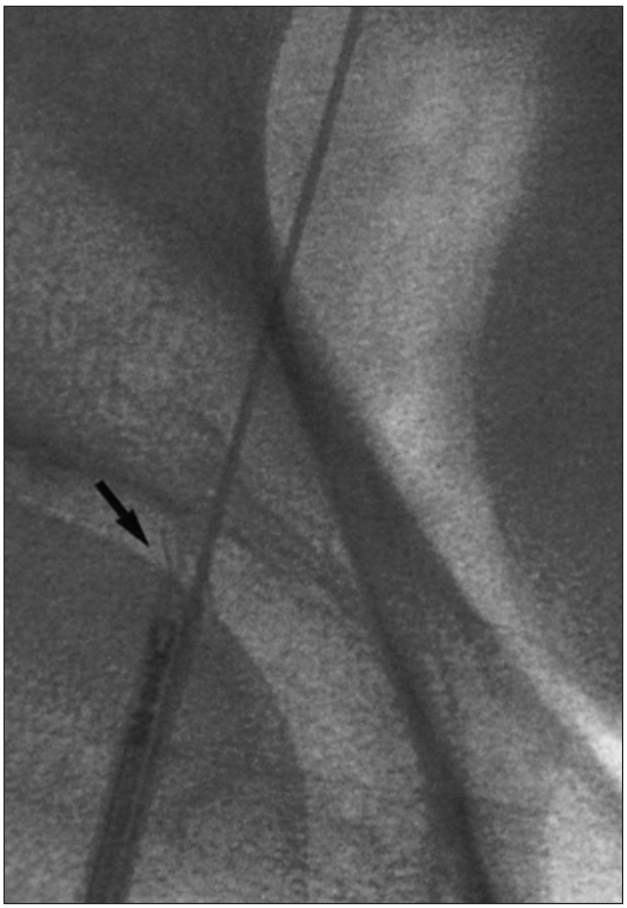

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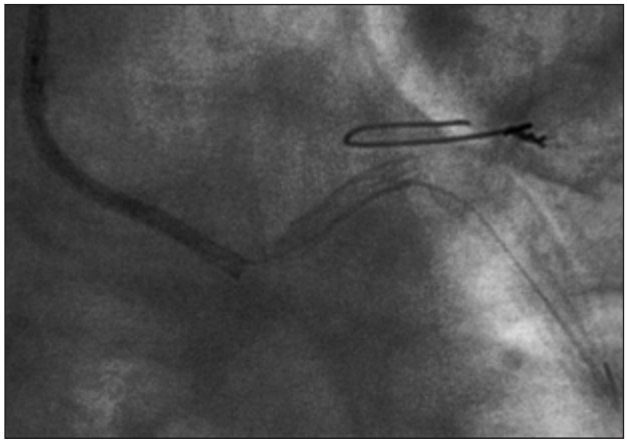

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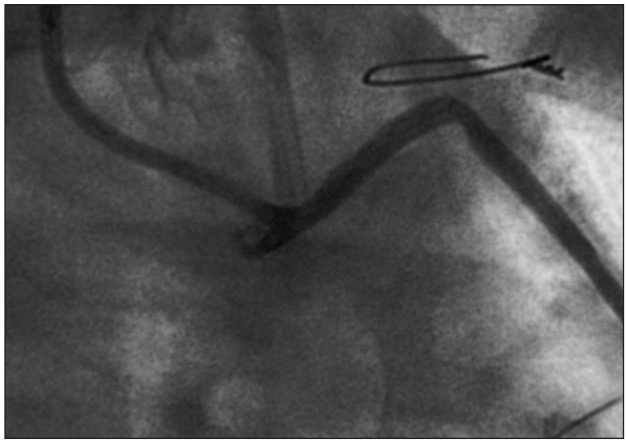

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Figure 31.32

(a) Retrieval of a 16-mm long intracoronary AVE microstent deployed following angioplasty of a severely diseased proximal vein graft to the left anterior descending artery. (b) Although the distal half of the stent was successfully deployed, the proximal half remained on the balloon after its deflation and migrated proximally towards the graft ostium. The reinflated balloon allowed removal of the stent from the vein graft which was partially wedged into the tip of the guide catheter. These were withdrawn down into the femoral artery. (c) Following removal of the guide catheter, the stent was successfully retrieved using grasping forceps (arrowed). (d) Once a new 8.0-mm long AVE microstent was deployed at the proximal end of the lesion, (e) a good angiographic result was obtained. (Courtesy of Dr I Hudson and Dr A Gershlick, Glenfield Hospital, Leicester, UK.)

Although transcatheter removal of retained components may be the optimal solution, it may itself result in serious complications. Thrombus deposition on protruding hardware with subsequent systemic embolization must be considered, although adequate heparinization should reduce this. Wires and retrieval devices may themselves break and become retained. In addition, fragments may slip free during removal and embolize to other locations.[5]

Conclusion

The morbidity and mortality associated with retained intravascular fragments are difficult to assess and it is likely that the literature underestimates the true incidence and early deaths. It is often difficult to implicate retained fragments conclusively as the main cause of death, as this may be ascribed to other causes.

As the applications of conventional angioplasty and intracoronary stenting expand, and newer methods of percutaneous revascularization emerge, the probability of experiencing equipment failure may increase. Therefore, the option of percutaneous extraction of such components in place of invasive surgery will assume increasing importance. Where it can be executed successfully it should substantially diminish clinical risk. In order to achieve this, operators should have a wide selection of retrieval devices and equipment available, and be familiar with their use.

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32

Femoral artery closure devices

Mazhar M Khan

Femoral arterial catheterization is one of the most frequently performed invasive diagnostic and therapeutic procedures. Currently, several million are performed globally each year.[1] Post-procedure the most commonly used management strategy consists of applying manual or mechanical compression including external inflatable compressors such as Femostop™ to promote haemo-stasis.[2] This process is generally considered adequate to manage femoral arterial punctures; however, this is often painful for the patient and time consuming for the attending hospital staff.[3–5] Intervention procedures usually require the use of larger sheaths and are performed in combination with an anti-coagulation regime.[6] For such patients, once the ACT had fallen to a satisfactory level, manual compression was until recently the only way to control bleeding.[4] Early sheath removal is therefore precluded and bed rest of variable duration is needed depending on the anti-coagulation level. In addition, for certain high risk patients who have received aggressive anti-coagulation therapy, indwelling sheaths have to be left in situ for several hours or overnight and compression must be maintained for an extended period of time after sheath removal. Prolonged pressure bandage is also a source of discomfort and hazard since the development of complications, such as haematoma, oozing and arterial bleeding, are concealed and noticed much too late.

The last decade has seen a dramatic increase in percutaneous intravascular intervention, with associated increase in procedural success. Major technical advances in percutaneous therapy and, the concomitant use of newer and more potent antiplatelet and antithrombotic therapies have contributed to this overall efficacy of non-surgical revascularization.[7] However, these major advances have occurred at the expense of an increased incidence of vascular access site complications despite the use of simplified antiplatelet regimens with ticlopidine or clopidrogel instead of warfarin.[8–10] Previous studies have shown that major access site complications requiring surgical repair and transfusion may occur in about 5–10% patients undergoing interventional procedures.[11–13] Access site complications increase the length of hospital stay, adding significantly to the overall procedural cost. If surgical repair is needed, the procedural costs are further increased.[14] Minor complications are also not uncommon and are frequently underreported but do cause significant patient discomfort as well as prolonging hospital stay.[15] Several puncture management devices have been introduced within the past decade. These devices were designed to facilitate early haemostasis, as it is easier and more comfortable to have arterial puncture closure immediately after the procedure, facilitating early mobilization and discharge. It overcomes the need for painful compression late after the procedure when the local anaesthetic effect has worn off. They are also designed to free up staff and catheterization lab time while expediting turnover.[16–18]

Devices for rapid closure of arterial puncture site may be classified according to their mechanisms (Table 32.1).

Percutaneous vascular suture (PVS) devices

This consists of a sheath-like device containing two or four straight, lance-like needles, which are connected at their tips to suture loops to deliver one or two sutures at the arterial puncture site. These devices are available in different sizes, ranging from 6 to 11 French.

Table 32.1 Classification of femoral closure devices based on mechanisms of action.

Mechanism	*Suture mediated*	*Collagen based (collagen plug)*	*Collagen based (collagen anchor)*	*Gel based (gel thrombin-collagen)*	*Gel based (gel thrombin-fibrin)*	*Mechanical disc*	*Radio frequency*[47]
Name of device	*Prostar™ *Techstar™ Closer™ **Sutura™/Super Stitch®	Vasoseal™	Angioseal™	Duett™	Bioseal™[46]	Biodisc™	
Manufacturer	*Perclose Redwood City, CA Sutura Inc/ Sutura BV **Fountain Valley, CA Eindhoven	Datascope Montvale, NJ	Daig/St Judes Medical Minnatonka MN	Vascular solutions Minnesota MN	Global Therapeutics Bloomfield, CO	Bio Interventional Pleasanton, CA	Scimed Minneapolis, MN

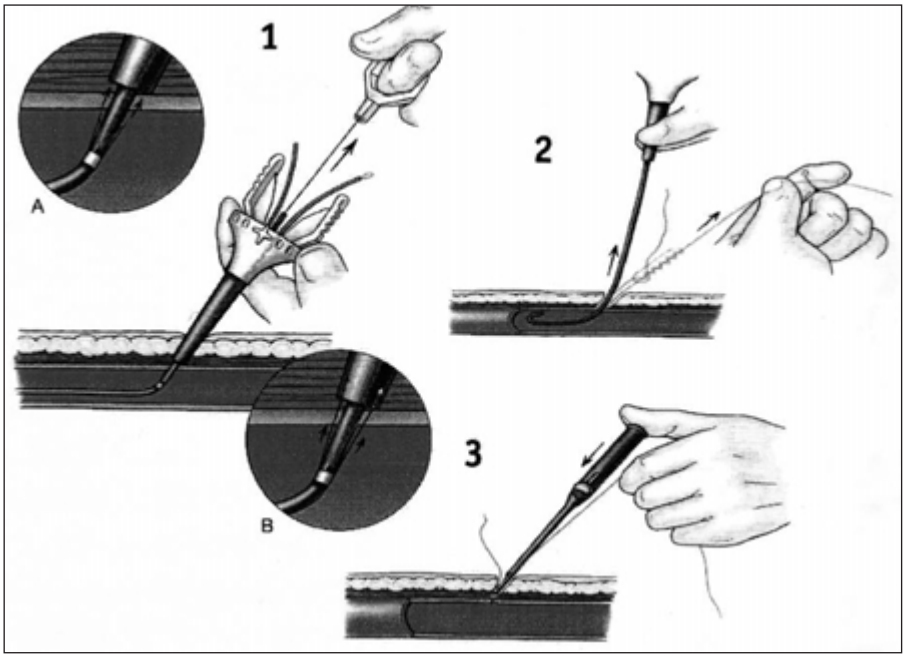


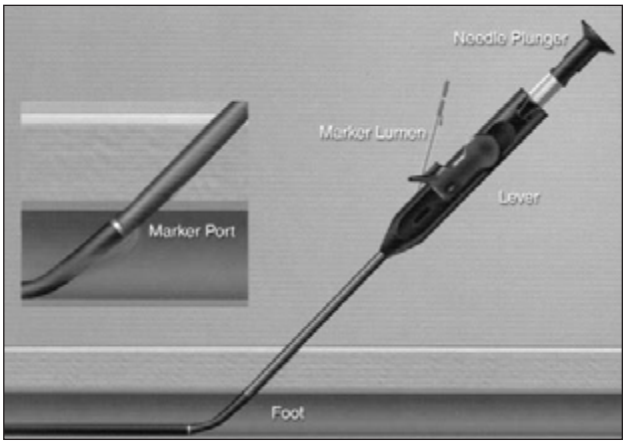
Figure 32.1
Deployment technique of Techstar XL™.

Techstar™/Prostar™/ Perclose™ (Redwood City, CA)

Techstar™ and Prostar™ represent the first generation and contain two or four needles attached to one and two sutures, respectively. They are housed in a flexible sheath, which is positioned in the lumen (Fig. 32.1). The Prostar™ device uses four needles attached to two 4/0 sutures to close 9 to 11 Fr access. Techstar™ has two needles attached to a 3/0 suture to close 6 to 7 French arteriotomy sites. The needles are deployed through the arterial wall and back into the device barrel, pulling the suture loops around the puncture site in an 'inside out' trajectory. Surgical knots are tied and with the help of a knot pusher the knots are pushed on to the arterial wall to achieve haemostasis. Larger Prostar™ devices need a tissue tract dilatation to facilitate device advancement.

Closer 6F™

This is the latest generation device and presents a sheath like profile in which a suture loop is housed. The needles are positioned in the delivery handle and are activated by pushing a plunger. The device positioning is easier and the safety is improved by maintaining the needle outside the arterial lumen. A knotting device is provided to make a more



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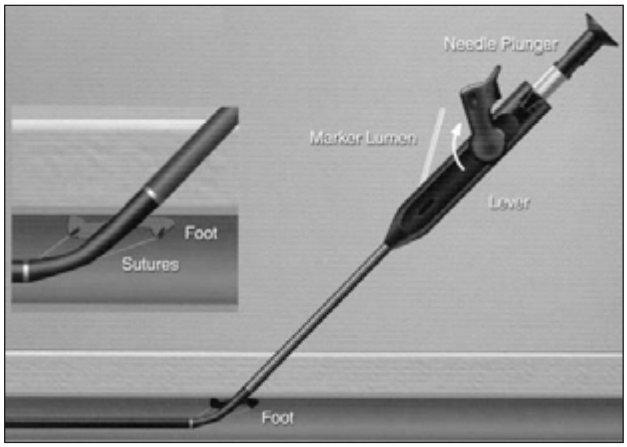
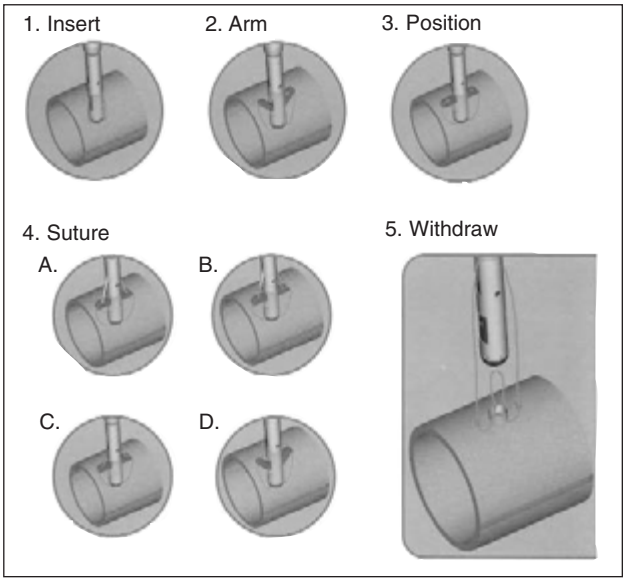


b

Figure 32.2
(a) Position of closure device. Pulsatile blood through the marker lumen indicating the foot and suture are intraluminal. (b) Foot deployment. Foot position is indicated by tactile resistance and cessation of blood through the marker lumen flow.



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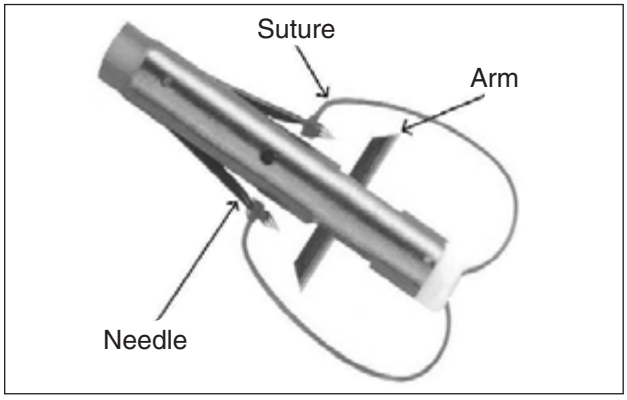

b

Figure 32.3
(a) Five steps of Super Stitch™ deployment. (b) Super Stitch™ ready for deployment.

reliable and consistent sliding of the surgical knot. No subcutaneous dissection is necessary (Fig. 32.2).

Super Stitch™/Sutura (Sutura Inc/ Sutura BV, Fountain Valley, CA)

This recently introduced vascular suturing device is suitable for arteriotomy closure varying from 6 F to 24 F. The design allows consistent positioning and deployment of sutures. The low profile 6 F design also facilitates suture placement in other access sites such as popliteal and brachial arteries (Fig. 32.3).

The vascular suture device is contraindicated in the presence of unresolved haematoma, AV fistula and pseudo-aneurysm, aorto-femoral or ilio-femoral grafts and significant calcification at the puncture site. It should not be used if the femoral artery size is smaller than the dimension of the device. The efficacy of the vascular suture device has been demonstrated in fully anticoagulated patients,[19–22] and same day discharge has been reported in 82% of patients after percutaneous coronary intervention.[23]

The rate of successful deployment of the device varies from 89% to 97%.[18–23] The success rate clearly depends on the operator's experience. Most studies have concluded that the frequency and type of local vascular complications after PVS device are similar to those with manual compression, ranging from 1% to 7% and include pseudo-aneurysms, AV fistula, peripheral ischaemia and large haematomas.[18,19] In one series, minor complications were reduced compared to manual compression, especially in the group of diagnostic patients. A significant reduction was noted in total complications but mainly in the incidence of small haematomas not requiring surgical intervention.[22] Loubeyre et al reported a 9% vascular complication rate despite high volume experience with use of the PVS device following coronary intervention.[24] Additional mechanical compression was required in 23% to achieve haemostasis. The use of larger sheaths or the use of anti-coagulation does not have any major impact on the performance of this device.[19–21] The important aspects of the performance of the device are the reduction in time to achieve haemostasis, time to mobilization and time to discharge when compared with the conventional methods. However, minor bruising due to dilatation of the tissue tract is not uncommon. Rarely, irritation and a dragging pain or numbness occur, particularly in the supply area of the ilio-inguinalis nerve. The new Closer 6 F™ device is clearly a major advance.

Collagen based closure devices

Collagen based closure devices containing bio-absorbable material are used to seal the puncture site after an arterial catheterization to establish rapid haemostasis, even on full anticoagulation.

Internal anchor and outside collagen/sponge (haemostatic puncture closure device)—Angioseal™

This is a bio-absorbent device available in 6 and 8 French sizes (Fig. 32.4). Major components of the device are a small anchor containing a high molecular weight biopolymer, a collagen sponge and a suture. The anchor is a fundamental part of the sealing mechanism and is deployed inside the arterial wall while the collagen sponge is positioned securely on the outer wall of the artery. The suture is used to link the anchor and the collagen together. It is also used to apply tension to the anchor so that it stays attached to the inside of the arterial wall where the puncture was performed. The collagen sponge is firmly secured on the outer wall by the suture, tamper and spring tensioner. The collagen sponge is further focally concentrated on the arterial wall, thereby providing a sandwich of the arterial puncture site between the internal anchor and the outer plug, assuring sufficient collagen seating and sealing. All components are bio-absorbable in 60–90 days. No pressure bandage is necessary.

Vascular haemostatic device—Vasoseal™

This is a collagen based sealing device. It is available in only one size irrespective of the employed introducer sheath. It can be used to seal femoral access with up to 8 French sheath size. Vasoseal™ does not require an intravascular

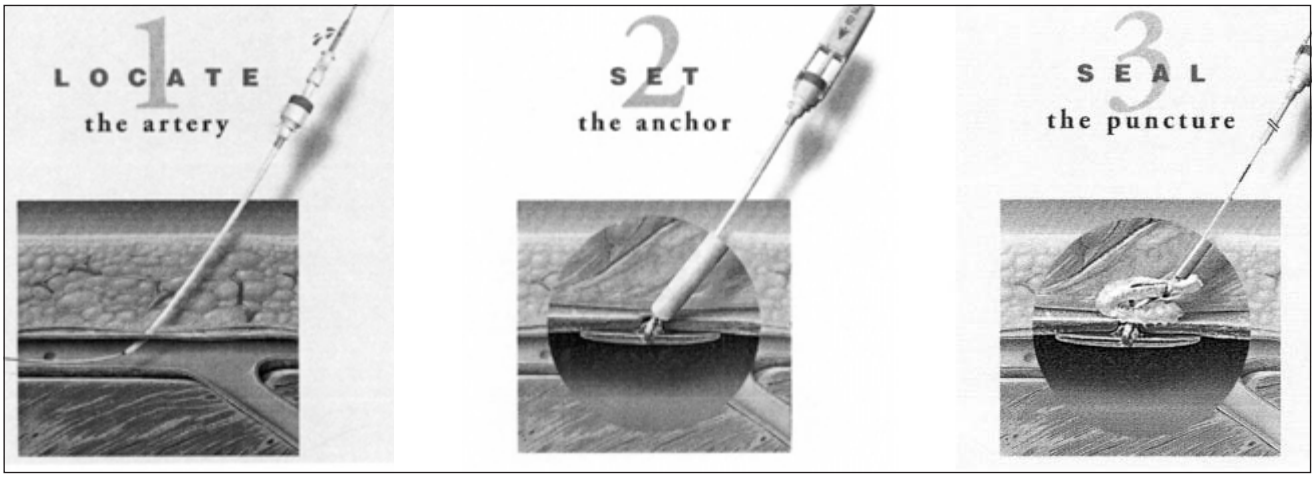

Figure 32.4
Deployment of Angioseal™.

anchor, but a bovine collagen plug is used to seal the access site from the outside of the arterial wall. The older system required measurement of the arterial puncture depth from the skin, but in the latest modification this step is not required. The new version – ES device (Fig. 32.5) consists of a J wire, which is used with the localizer system to help locate the arterial entry point. Depending on the thickness of the subcutaneous tissue, one or two collagen plug applications are delivered. The older product design was not suitable for the superficial femoral artery. It is also not suitable for use if the arterial sheath size is larger than 8 French. Incorrect deployment of the device carries a high risk of bleeding and inadvertent intraluminal entry of the collagen

Collagen based closure devices are relatively safe and effective. They allow earlier mobilization compared to conventional compression techniques after diagnostic and therapeutic interventions. Several studies have confirmed their safety, efficacy and rapid haemostasis. In addition, their application is less painful and better tolerated than manual compression.[25–30] The use of these devices, however, has not substantially affected the rates of major complications. Dislocation of the collagen plug into the distal artery has been reported, leading to stenosis or occlusion of the vessel. Excessive calcification at the access site may predispose to this. Complications may occur with both collagen devices, especially in patients with advanced age, hypertension and superficial femoral arterial puncture, and also where the operator is inexperienced. One series reported a risk of infection in 2% of patients, although others have disputed this increase.

These devices carry the inherent risk of inadvertent intra-arterial collagen placement. In an analysis of 6007 published cases reported by Silber,[31] there was a 0.7% risk of collagen placement intra-arterially with a vascular haemostatic device (Vasoseal™). Recently, intra-arterial collagen displacement complication following use of a haemostatic puncture closing device (Angioseal™) has been reported.[32] There is also no clear evidence that collagen devices decrease the rate of local complications.[30,33–35] Some reports even show a tendency to increase minor local complication.[33,36] Silber concluded that Vasoseal™ and Angioseal™ show comparable success rates for haemostasis[31] although some differences existed regarding local complications, with minor bleeding complications occurring more frequently with Vasoseal™. In contrast, in another report Vasoseal™ was superior and more cost effective than other haemostatic devices including AngioSeal™ and Perclose™.[37] Moreover, the use of Vasoseal™ has been associated with no increase in bleeding events after abciximab therapy[38,39] and in a pilot study, Vasoseal™ was also used to close an arteriotomy site following removal of an intra-aortic balloon pump.[40]

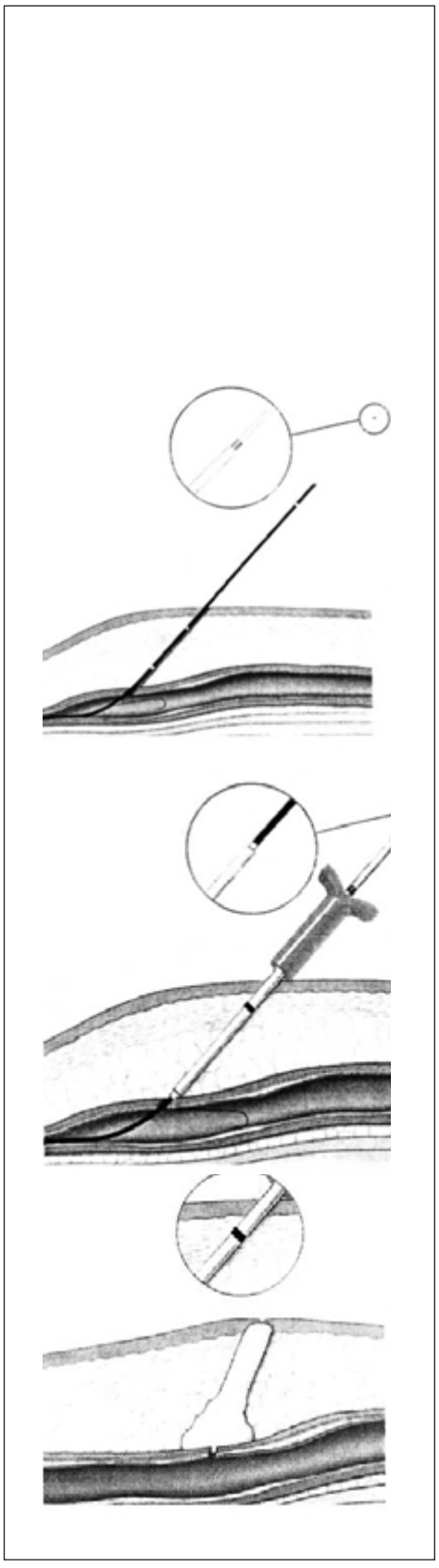

Figure 32.5
Vasoseal™ deployment.

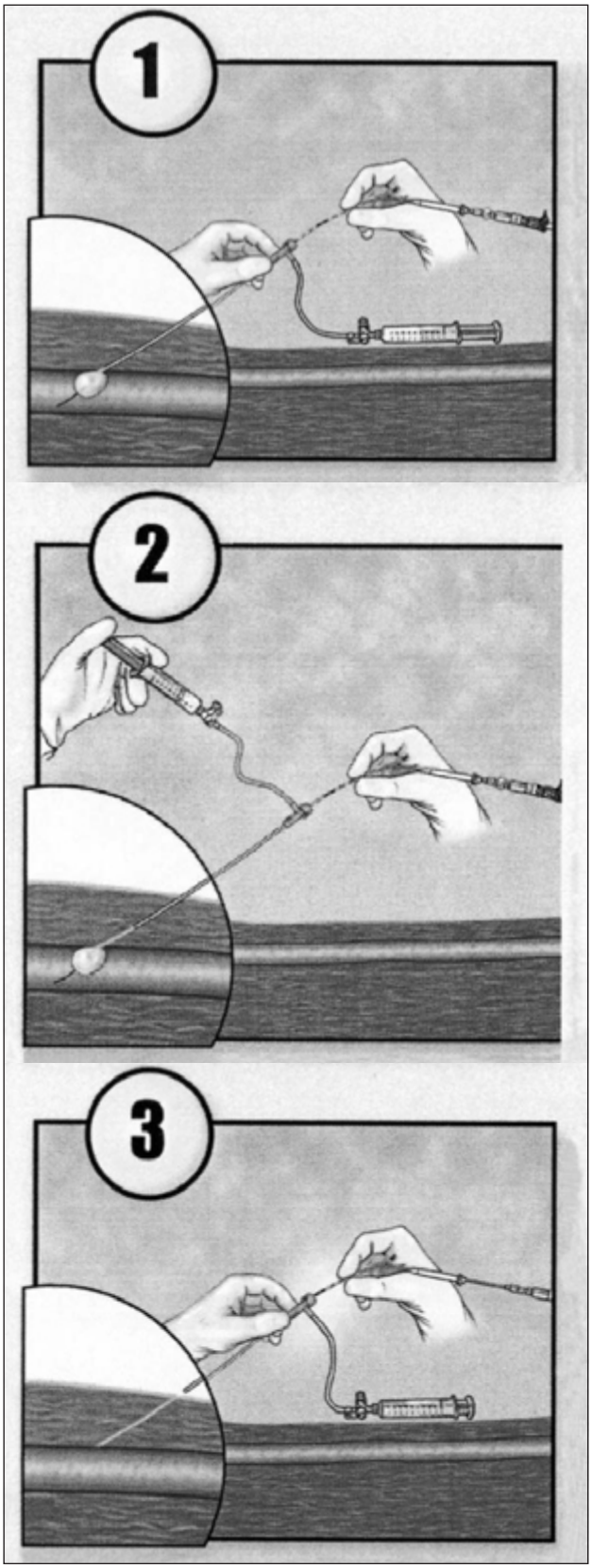

Figure 32.6
Technique of deployment of Duett™ showing a disc shaped short balloon occluding the puncture site.

Thrombin/collagen sealing system—Duett™ (Vascular Solutions, Minnesota, MN)

A new device has recently been introduced to achieve haemostasis following percutaneous arterial catheterization.[41–45] It uses a novel vascular sealing system incorporating a unique, low profile, disc shaped balloon catheter in combination with a biological pro-coagulant flowable mixture containing a bovine microfibrillar collagen and thrombin. Collagen is a potent platelet activating agent. Thrombin promotes effective haemostasis through several mechanisms. It converts fibrinogen to fibrin, accelerates the coagulation cascade and is a potent platelet aggregating and activating agent, thereby acting synergistically with collagen. The balloon catheter is an ultra low profile 3 F catheter incorporating a moveable core wire that allows modification of the balloon dimension (Fig. 32.6). On inflation, the movable core wire is retracted and the balloon alters from a spherical shape to a disc-like configuration with a large diameter and a short balloon length. This configuration provides optimal sealing of the arterial puncture from the luminal side of the arterial wall by ensuring a large surface area of balloon in apposition to the puncture site and at the same time minimizing obstruction to flow through the lumen of the vessel. On deflation, the moveable core wire can be advanced, thereby elongating the deflated balloon and ensuring a low profile for removal of the catheter. A polymeric sleeve is advanced over the deflated balloon to further decrease the balloon profile and abolish any 'winging' effect. The learning time for this device is short. It is simple to use and no change of procedural sheath is required. Another advantage is immediate re-access of the artery after deployment.

The European Multi-Centre Registry comprising more than 1507 patients showed that the Duett™ sealing device is highly effective in achieving rapid and reliable haemostasis with a very low incidence of major complications.[43] Similar results were obtained in another study where the Duett™ was used for percutaneous intervention.[45] It showed reliable and effective haemostasis with a low incidence of complication. In the randomized SEAL trial, the Duett™ was reported to achieve haemostasis with arterial sheaths greater than 8 French and showed a significant reduction in the time to achieve haemostasis and time to ambulation.[44]

Gel thrombin–fibrin—BioSeaL™ (Global Therapeutics)

This also employs a biosealant concept of occluding the vessel puncture by a small balloon catheter on a disc and instillation

of a thrombin–fibrin gel into the outside of the artery to obtain haemostasis. Except for one brief report it has not yet had wide clinical application.[46]

Biodisc™ arteriotomy system

This features a micro-catheter design which incorporates a temporary deployable biocompatible disc. The Biodisc™ microcatheter is placed through the femoral arteriotomy using the existing sheath. The disc is deployed from the microcatheter into the lumen of the vessel. It is designed to be positioned at the inner wall of the vessel, occluding the arteriotomy site. The introducer sheath is removed while the disc is maintained inside the vessel and this allows distal perfusion to the lower extremities. The disc is kept in position at the intimal surface of the femoral arterial wall by maintaining a tension over the catheter. It can be left in situ for 10–15 minutes to achieve satisfactory haemostasis. The Biodisc™ is undeployed once effective haemostasis is achieved without disrupting the naturally formed clot or further injuring the fascial tract. So far, it has not had widespread application in a clinical setting.

Summary

The introduction of arterial closure devices over the past few years has provided a new option for the management of haemostasis at the groin puncture site. They are used in an attempt to reduce complications, improve efficiency, lower costs and enhance patient comfort and satisfaction.

An unfortunate consequence of therapeutic intervention procedures involving femoral artery access is the occurrence of major complications associated with achieving haemostasis. Although their incidence is low, they do cause undue escalation of cost, significant patient discomfort and morbidity. They also have direct impact on patient satisfaction. Major complications are largely due to technique. If a puncture is difficult, needing multiple stabs, or the posterior wall is traversed, then the risk of complication is high irrespective of the device or type of device used. The importance of clean anterior wall puncture cannot be over emphasized.

The use of arterial closure devices has clearly improved patient comfort, especially in those who had procedures with and without previous device usage. Nursing staff show an overwhelming preference for the use of a device. Their benefits are clearly seen in the patients who are unable to lie flat because of chronic back pain, arthritis or respiratory problems. It is also useful in the patient with aortic regurgitation where the use of manual compression to achieve haemostasis is difficult.

New technology should be evaluated as it becomes available in an attempt to improve patient care and reduce complications. There is no doubt about the merits of a femoral closure device, but the data to support its universal use in all catheterization procedures is lacking. There is no clear justification for the use of these devices following all diagnostic procedures where progressively smaller catheters are being used. The time to achieve haemostasis with a 4 or 5 F diagnostic catheter is only marginally longer with a conventional method of manual compression in a patient not on anticoagulation[47] and it may not be possible to achieve 100% successful device deployment.

Effective control of arterial access is a basic principle of any invasive vascular procedure and inadequate haemostasis may turn an elegant result into an unmitigated disaster. Furthermore, increasing demands for improved bed efficiency, shorter hospital stay, judicious use of nurses' time and improved clinical outcome are all increasing the pressure to apply new technology to achieve these objectives. Suture closure has some promise, but the downside is the pain and persistent oozing. The incidence of bleeding complications with collagen devices or with Perclose™ is the same as for manual compression.[48–50] A new complication of infection has been created with all these devices and the need for strict sterility during deployment cannot be over emphasized.[35] The novel thrombin/collagen sealing device, Duett™, which utilizes a balloon, is promising. Further clinical experience will define its potential. It is easy to use with a very high rate of successful deployment. Immediate re-access is possible. The device has been safely used in fully anti-coagulated patients as well as after a IIb/IIIa receptor antagonist.[45] Inadvertent vascular injection of thrombin/collagen suspension is a potential risk, with serious consequence.[51] The merits and limitations of the transradial approach are well established, but a detailed discussion is beyond the scope of this chapter. A recent randomized study, however, showed fewer access site bleeding complications and a lower cost effectiveness of the transradial approach compared to Perclose™ use following coronary stenting.[52]

Conclusion

Arterial sealing devices provide several advantages over manual compression including immediate sheath removal, quick haemostasis and early mobilization and discharge following percutaneous coronary intervention. Their use, however, does not significantly reduce the risk of major complications. They undoubtedly improve patient comfort. They also reduce nursing time and bed occupancy, thereby improving patient turnover. Newer devices appear very promising and it is hoped that a reasonable pricing strategy will make them acceptable for wider use in a cost conscious environment.

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33

The principles and practice of audit in coronary intervention

Anthony Rickards and David Cunningham

Introduction

Until the turn of the 20th century physicians were trained as apprentices basing patient management on experience, supported by a limited understanding of disease process and the effects of treatment. There was no 'optimal management' of disease, except that defined by the teachers in the profession, who in turn based teaching largely on anecdotes.

The development of the mathematics of probability as applied to medicine[1] and the consequent introduction of the randomized trial[2] has changed the basis of medical practice in many disciplines. For common conditions, it is now possible to define contemporary optimal management of disease in terms of the probability of a defined outcome. The probabilities are based on evidence from clinical trials or observational studies. Clinical trials have the advantage of minimizing bias and negating confounding and unanticipated variables, whilst observational studies have the advantage of studying usually larger and more heterogeneous populations of patients more typical of clinical practice.

Cardiovascular disease causes more premature mortality and morbidity in developed countries than any other organ disease.[3,4] It is appropriate that a wealth of information now exists in the common conditions to allow definition of optimal management. When practicing medicine by applying the results of clinical trials and observational studies to an individual patient there is an inherent assumption by both doctor and patient that the outcome defined by such evidence will be achieved. What is usually missing is the measurement of that outcome.[5,6]

Clinical audit may be defined in a number of ways. At its simplest, it is application of the discipline of clinical trials to all medical practice with the requirement to define the patient, disease, treatment and outcome in a way that can be used to compare results against contemporary medical evidence. Clinical audit may also be seen in the context of quality assurance, where it is but one element of a process which results in the identification of both good and bad practice and results in discussion, debate and action whereby all practice is improved and the bad is minimized. The failure of the audit process in the Bristol Cardiothoracic unit,[7] the subsequent pronouncement of the Secretary of State for Health[8] and the NHS Information Strategy[9] make our individual and institutional responsibilities abundantly clear.

The first coronary angioplasty in the UK was performed in 1980 and the operators at that time kept personal records of varying completeness. During the last two decades the British Cardiovascular Intervention Society (BCIS) has undertaken an activity counting exercise with limited patient-based information. BCIS has now defined a dataset which should allow effective clinical audit. Effective clinical audit is difficult to implement; not all of the issues surrounding collection of data, analysis, interpretation of results and subsequent action have been solved although there are currently some spectacular examples of data presentation.[10]

This chapter discusses the requirements of an audit system for interventional cardiology in coronary artery disease but the principles apply to other procedures and disciplines. The illustrations are taken from an institution which in 1999 had implemented data collection according to the nationally agreed standards set by BCIS and implemented by the Central Cardiac Audit Database (CCAD) project.[11]

Medical quality assurance

The process of quality assurance can be seen as a series of steps which start with defining a medical domain of interest for audit.

During the definition of the clinical audit domain, a decision has to be made as to where to 'start' the process. When

auditing the management of coronary disease, the starting point ideally should be the first clinical presentation of the patient with symptoms or signs of the disease. In practice this would require the creation of a medical record which spans primary, secondary and tertiary care. Such a standardized record does not currently exist and whilst not technically complex, the organizational and training issues involved would probably swamp the audit objective. From a tertiary care perspective it might be considered that the coronary intervention audit could start with definition of the coronary anatomy by angiography.

Data definition

The definition of the data to be collected for audit should be considered under the following categories.

Structure

This set of data is concerned with defining the environment in which treatment is being delivered and the quality of the data collected. It should provide adequate data to answer the question as to whether a particular form of treatment should be delivered in a specific environment. Table 33.1 shows some of the 'fixed' variables defining the institutional facilities which need to be collected and collated on an annual basis for comparisons against defined standards. Figure 33.1 shows the completeness of individual patient based data items from which are derived metrics of quality of care. An institution may have the appropriate facilities but without meeting standards of data collection it cannot provide the basics of quality assurance.

Table 33.1 Candidate variables for annual collection from an institution as part of the definition of the structure section of an audit.

Hospital name
Consultant cardiac surgeons
Junior surgical staff
Consultant interventional cardiologists
Junior medical staff
Number of operating theaters
Number of catheter laboratories
Level of equipment available
Level of specialist services available
Annual number of open heart procedures
Annual number of diagnostic caths
Annual number of interventional caths

Appropriateness (Fig. 33.2)

This set of data asks the question as to whether it was appropriate that a particular form of treatment was delivered to a particular patient. Appropriateness can be considered both as indications (eg severity of symptoms or angiographic disease) and as contraindications (eg known risk factors for intervention). Definition of the appropriateness variables is a key step in clinical audit as it should allow comparison of the results of treatment in different institutions in similar groups of patients.

Technique	N	Age	Sex	Indication	Urgency	Shock	CCS	NYHA	LV	Pre Duke	NVess	Les	Post Duke	CKMB
	248	100.0	100.0	98.0	100.0	100.0	97.6	97.6	90.3	99.6	99.2	99.2	99.2	88.7
A. POBA only	30	100.0	100.0	96.7	100.0	100.0	96.7	96.7	93.3	100.0	100.0	100.0	96.7	86.7
B. POBA+Stent	116	100.0	100.0	99.1	100.0	100.0	98.3	98.3	89.7	100.0	100.0	100.0	100.0	93.1
C. Stent only	76	100.0	100.0	100.0	100.0	100.0	100.0	100.0	92.1	100.0	100.0	100.0	100.0	85.5
D. Cutting Balloon	10	100.0	100.0	100.0	100.0	100.0	100.0	100.0	90.0	100.0	100.0	100.0	100.0	100.0
E. X-Sizer	3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
F. Rotablator	1	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	0.0
G. Laser	1	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
H. PTMR	2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	50.0	50.0	100.0	100.0
I. Failed to cross	6	100.0	100.0	66.7	100.0	100.0	66.7	66.7	66.7	100.0	100.0	100.0	100.0	33.3
J. Undefined	3	100.0	100.0	66.7	100.0	100.0	66.7	66.7	66.7	66.7	66.7	66.7	66.7	100.0
	248	100.0	100.0	98.0	100.0	100.0	97.6	97.6	90.3	99.6	99.2	99.2	99.2	88.7

Figure 33.1
Screen shot from an on-line patient database showing the data quality analysis of audit in interventional cardiology. The 248 procedures are categorized by angioplasty technique used and the figures indicate in percentage the completeness of the data for age, sex, clinical indication for the procedure, procedure urgency, whether the patient was in cardiogenic shock at the time of procedure, Canadian Cardiovascular Society angina class, New York Heart Association symptom group, left ventricular function, Duke coronary score pre-procedure, number of vessels and lesions treated, Duke coronary score post procedure and value of CKMB enzyme post procedure. Data completeness ranges from 88.7 to 100%.

Technique	Symptoms	Coronary Score	N	%	Age	Male	Emergent	Shock	Poor LV	123 vd	Vessels	Lesions
			242	100.0%	61.3	86.8	0.8	0.4	3.3	1.5	1.2	1.6
▼ A. POBA±Stent			219	90.5%	61.0	85.8	0.9	0.5	2.7	1.5	1.2	1.7
	▼ Mild symptoms		20	9.1%	56.1	90.0	0.0	0.0	0.0	1.3	1.2	1.7
		Moderate CAD	13	65.0%	56.2	84.6	0.0	0.0	0.0	1.2	1.1	1.8
		Severe CAD	7	35.0%	55.7	100.0	0.0	0.0	0.0	1.6	1.3	1.4
	▼ Mod/Severe symptoms		199	90.9%	61.5	85.4	1.0	0.5	3.0	1.5	1.2	1.7
		Mild CAD	4	2.0%	51.8	75.0	0.0	0.0	0.0	0.0	1.0	1.0
		Moderate CAD	102	51.3%	59.5	85.3	0.0	0.0	2.0	1.2	1.1	1.6
		Severe CAD	93	46.7%	64.1	86.0	2.2	1.1	4.3	1.9	1.3	1.9
▶ B. Failed to cross			4	1.7%	59.8	75.0	0.0	0.0	25.0	1.3	1.0	1.0
▶ C. Other technique			15	6.2%	67.1	100.0	0.0	0.0	6.7	1.4	1.0	1.1
▶ D. PTMR			2	0.8%	56.0	100.0	0.0	0.0	0.0	1.5	0.5	1.0
▶ E. Undefined			2	0.8%	57.5	100.0	0.0	0.0	0.0	1.0	1.0	1.0
			242	100.0%	61.3	86.8	0.8	0.4	3.3	1.5	1.2	1.6

Figure 33.2
Screen shot of the appropriateness section of interventional audit. Of the 219 balloon angioplasty procedures with or without stent insertion, 90.9% of the patients had moderate to severe symptoms (as defined by angina class). Of these patients 98% had moderate to severe coronary disease (as defined by the pre-operative Duke coronary score). No patient with mild symptoms had mild coronary disease. Emergent defines % of non elective procedures, Shock defines % of patients in cardiogenic shock pre-procedure, Poor LV defines ejection fraction <30% and 123vd defined average number of main vessels involved. Vessels and lesions define average number of main coronary vessels and lesions where intervention was attempted.

Shock	Technique	N	%	Age	Male	Lesions	Success	Complete	Scr Time	Pre Duke	Post Duke
		248	100.0%	61.2	87.1	1.6	94.4	90.7	12	3.7	1.1
▼ 1. Not shock or emergent		246	99.2%	61.1	87.8	1.6	94.3	90.7	12	3.7	1.1
	A. POBA±Stent	220	89.4%	60.9	86.8	1.7	98.6	94.5	11	3.7	1.1
	B. Failed to cross	6	2.4%	59.2	83.3	1.0	0.0	0.0	30	2.2	2.3
	C. Other technique	15	6.1%	67.1	100.0	1.1	86.7	86.7	15	3.7	0.9
	D. PTMR	2	0.8%	56.0	100.0	1.0	0.0	0.0	21	2.5	2.0
	E. Undefined	3	1.2%	59.3	100.0	1.0	66.7	66.7	13	3.0	0.0
▶ 2. In shock or emergent		2	0.8%	71.0	0.0	1.0	100.0	100.0	9	5.5	1.0
		248	100.0%	61.2	87.1	1.6	94.4	90.7	12	3.7	1.1

Figure 33.3
Screen shot of the process section of interventional audit. Of the 248 procedures, 0.8% were done as emergencies and 89% of the remainder were treated by balloon angioplasty with or without stent insertion. The process variables listed for each category are the number of lesions attempted, whether at least one attempted lesion was successfully treated (success defined as <30% residual lesion with normal flow), whether all attempted lesions were successfully treated (complete), the screening time and the pre and post procedure Duke coronary scores.

Process (Fig. 33.3)

This set of data defines the process by which treatment was delivered and includes variables related to a particular procedure as well as more resource orientated variables such as waiting times, length of hospital stay and costs.

Outcome (Fig. 33.4)

Any intervention should be associated with well-defined desired and undesired outcomes. These will include key clinical and quality of life variables but could also include resource orientated information such as time off work.

Data security

In implementing a data collection system an institution must be very aware of its responsibility to protect both patients and healthcare professionals without compromising the objective of audit. Anderson in his review commissioned by the British Medical Association has very elegantly laid down the principles of data security and confidentiality.[12] In brief these are:

- all records in a database must contain an 'access control list' which determines who can add to, read or edit the information in that record. Records cannot be deleted;
- all record access for addition or modification of data is both time stamped and electronically signed by the user;

Shock	Technique	N	%	Age	Male	Event Free	Death	Bleeding	Elec CABG	Emerg CABG	ReDo PCI	Non Q	Q wave	CK >x2
		248	100.0%	61.2	87.1	97.2	0.8	0.4	0.4	0.8	0.8	0.4	0.4	1.8
▼	1. Not shock or emergent	246	99.2%	61.1	87.8	97.6	0.4	0.4	0.4	0.8	0.4	0.4	0.0	1.4
	A. POBA±Stent	220	89.4%	60.9	86.8	98.6	0.5	0.5	0.0	0.0	0.5	0.5	0.0	1.0
	B. Failed to cross	6	2.4%	59.2	83.3	50.0	0.0	0.0	16.7	33.3	0.0	0.0	0.0	0.0
	C. Other technique	15	6.1%	67.1	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.1
	D. PTMR	2	0.8%	56.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	E. Undefined	3	1.2%	59.3	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
▶	2. In shock or emergent	2	0.8%	71.0	0.0	50.0	50.0	0.0	0.0	0.0	50.0	0.0	50.0	50.0
		248	100.0%	61.2	87.1	97.2	0.8	0.4	0.4	0.8	0.8	0.4	0.4	1.8

Figure 33.4

Screen shot of the in hospital outcome section of the interventional audit. Note that 98.6% of the balloon angioplasty with or without stent insertion procedures were event free where events are defined as any of the following: death, bleeding requiring intervention or transfusion, elective or emergency coronary surgery at the same admission, repeat angioplasty at the same admission, ECG evidence of infarction or elevation of post procedure CKMB.

- all information within the database whether stored or transmitted is encrypted;
- there is a 'trusted authority' that issues and revokes encryption/decryption keys to individual users;
- institutions have an encryption key with which access to the patient's identification and the operators' name (for interventional procedures) can be limited to users defined by that institution;
- access to anonymized aggregated information is limited and determined as a matter of policy by the institution.

The next steps

Until the creation of the CCAD project, a single cardiac center's ability to collect audit data capable of meaningful analysis has been limited. Although there are many good examples of local record keeping, the limitations for audit of such an approach are:

1 Most centers do not perform enough of a particular procedure in a defined group of patients with the same disease and risk factors. Internal analysis of, for example, performance by time or performance by operator is going to generate such wide confidence intervals that statistically it is unlikely that useful information for audit can be generated.
2 Most centers maintain databases that are procedure rather than patient orientated. Thus a catheter laboratory based PTCA record system is unlikely to record the detail or occurrence of prior or subsequent surgical events.
3 Even when a center does perform a large number of the same procedure on the same patients, comparison with other centers or with the established literature is compromised by the definition of the patient population which cannot be standardized in local databases.
4 In general local centers do not have the time and resources to record patient outcome after leaving hospital following an index event. Late events following angioplasty (including survival, myocardial infarction and re-intervention) are more important in defining performance than in-hospital events but are rarely, if ever, provided by local audit initiatives.
5 Whilst most hospitals are comfortable with providing annual anonymized summaries of activity (such as the BCIS and Surgical registries), such information is essentially useless in determining performance based on patient outcome. Centers are naturally concerned about providing patient-specific data when both patient and medical staff confidentiality may be put at risk.

All of these issues have been important in limiting the good intentions of physicians and surgeons to partake in effective audit. This can only be solved by the sort of solutions offered by the CCAD. Data can be contributed whilst preserving the security of access to patient and staff identification, the definition of procedures and patient populations can be standardized, long term follow-up data can be acquired and large enough numbers can be generated to allow meaningful analysis.

Summary

The CCAD project has been set up to harmonize a variety of contemporary data collection exercises in cardiovascular medicine. It has applied the techniques of medical quality assurance in defining a dataset common to the medical domains of its client special interest groups and categorizing the analysis of these data in terms of structure, appropriateness, process and outcome (the where, when, why, who and what happened of audit). This article describes the implementation of such a system in interventional cardiology in a single institution and sets a standard for intra and inter-institutional medical quality assurance.

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34

Training programmes and certification in interventional cardiology in Europe

Bernhard Meier

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) and percutaneous coronary intervention (PCI) are synonymous and encompass all types of catheter-based interventions for invasive treatment of coronary artery disease. Table 34.1 shows that this technique, introduced in 1977 by Grüentzig, is but an example of a great variety of catheter interventions for heart disease constituting the discipline of interventional cardiology.[1–17] However, in contrast to the other listed interventions, PTCA has evolved to become one of the most common medical interventions in industrialized countries.

Table 34.1 Milestones in the history of interventional cardiology.

Year	*Author*	*Technique*	*Reference*
1953	Rubio-Alvarez	Pulmonary wire valvuloplasty	1
1966	Rashkind	Atrial septostomy	2
1966	Porstmann	PDA closure	3
1974	King	ASD closure	4
1975	Gianturco	Coil occlusion of shunt	5
1977	Grüentzig	PTCA (= PCI)	6
1979	Semb	Pulmonary balloon valvuloplasty	7
1981	Singer	Coarctation angioplasty	8
1982	Gallagher	His bundle ablation	9
1983	Lababidi	Aortic balloon valvuloplasty	10
1984	Inoue	Mitral balloon valvuloplasty	11
1986	Puel	Coronary stent implantation	12
1987	Simpson	Coronary atherectomy	13
1990	Palacios	Pericardial balloon fenestration	14
1994	Sigwart	Transluminal ablation of septal hypertrophy	15
1997	Oesterle	Percutaneous transmyocardial laser revascularization	16
1997	Teirstein	Brachytherapy against coronary restenosis	17

ASD = atrial septal defect; PCI = percutaneous coronary intervention; PDA = patent ductus arteriosus; PTCA = percutaneous transluminal coronary angioplasty.

Percutaneous transluminal coronary angioplasty is applicable to all stages of coronary artery disease without age limit. Over 80% of PTCA procedures worldwide have always been single-vessel interventions. The application of PTCA to multivessel disease in a single session is common but, despite widespread opinion, is not increasing. In true triple-vessel disease involving all large arteries, the role of coronary bypass surgery is unchallenged.

The advent of alternative or complementary devices to the balloon has had no palpable impact on indications, complications, or long-term results of PTCA, with the exception of stents which have proved invaluable for clinical purposes and result in a reduction in restenosis. While the training requirements to handle these devices may include prolonged training periods, standard PTCA has become easier as a result of refined balloons, guidewires and guiding catheters, and the availability of stents.

Training

The result of the training of an individual is determined both by the trainee and the training programme. The more important factor is the trainee. Table 34.2 lists some of the character traits that are positive or negative in a candidate. It has been said that all one has to do in PTCA is advance, retract or rotate left or right one or perhaps two instruments at a time. In fact this is not far from the truth but the hidden skills lie in knowing what to tackle, when to do it, how to look, what to

Table 34.2 Positive and negative personality traits for interventional cardiology.

Positive	*Negative*
• Readiness for comprehensive responsibility	• Anxiety
• Stress tolerance	• Reluctance
• Calmness	• Cowardliness
• Patience	• Obsession
• Decisiveness	• Stubborness
• Perseverance	• Arrogance
• Humility	

use, how to push and pull, how to torque and last but not least when to stop.

Many authorities have established and regularly update recommendations for training and the infrastructure required for PTCA.[18–37] Individual authors have also expressed opinions on training and quality assessment in interventional cardiology.[38–47] Even for the specializing nursing staff, quality control guidelines[48] and a textbook[49] are available.

Recommendations vary significantly and it is obvious that in many countries a substantial number of operators (if not the majority) do not meet the relevant national requirements. Consequently, it is important both to improve the training status of operators and to create guidelines that are realistic. Table 34.3 relates the average training requirements of European authorities for interventional cardiology to reasonable recommendations. This projects about 7 years of training after graduation from medical school, of which 3 years should be spent in cardiology, involving invasive procedures. One additional year dedicated to interventional cardiology is warranted before independence. The structure of the programme, the volume of the teaching facility and the ratio of number of cases to number of trainees correlate with the quality of the individual training. A dedicated board exam for interventional cardiology has been introduced in the United States and is in the planning stage in many European countries.

Training in PTCA should only be offered by institutions staffed with at least two full-time interventional cardiologists with at least 1 year's experience. They must perform an average of over 200 procedures per year per trainee and include facilities for in-house cardiac surgery.[30] These are minimum requirements. The ideal ones are more than 1000 procedures per year with at least 300 cases and one teaching faculty per trainee. For a centre of this magnitude, daily or at least weekly conferences, where easy and complicated cases are demonstrated and discussed are generally recommended, as is a dedicated data bank. Moreover, the performance of the centre as a whole and of each individual instructor and trainee are regularly analysed.

For continued specialized medical education, 50 cases per year are the minimum, 100 a reasonable goal. Regular updates at dedicated meetings are essential. It has been repeatedly demonstrated that it is not only operator experience but also the size of the institution, that have a significant effect on the outcome of cases. Low volume operators operate with higher mortality (Fig. 34.1). This disadvantage can be overcome if they perform within a high volume institution, where they only differ from high volume operators by having more restricted access to investigational devices (Fig. 34.2).

Table 34.3 Curriculum of interventional cardiologists before independence.

	Published recommendations	*Reasonable proposal*
General (internal) medicine (years)	3	2
Clinical cardiology (years)	2	3
Invasive cardiology (years)	1	0.5
• diagnostic cases		
– as assistant	100	50
– as operator	200	100
Interventional cardiology (years)	1	1
• PTCA cases		
– as assistant	50	50
– as operator	75	50
Practical courses	2	1

PTCA = percutaneous transluminal coronary angioplasty.

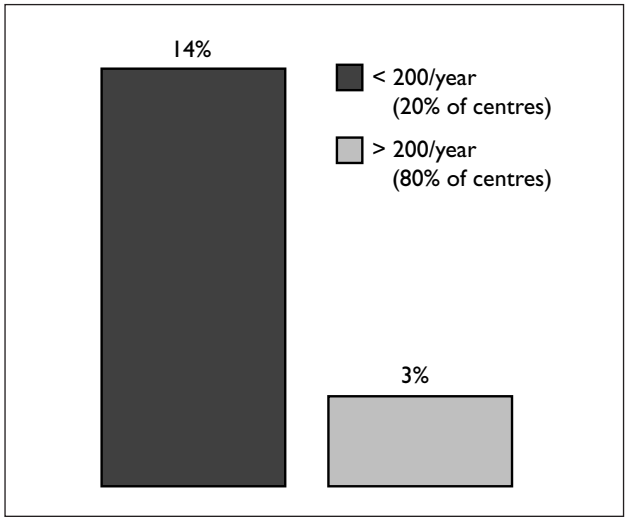

Figure 34.1
Mortality of approximately 150 000 PTCA cases in California, USA, in 1995 stratified according to the experience (number of cases per year) of the operators (Brown, personal communication).

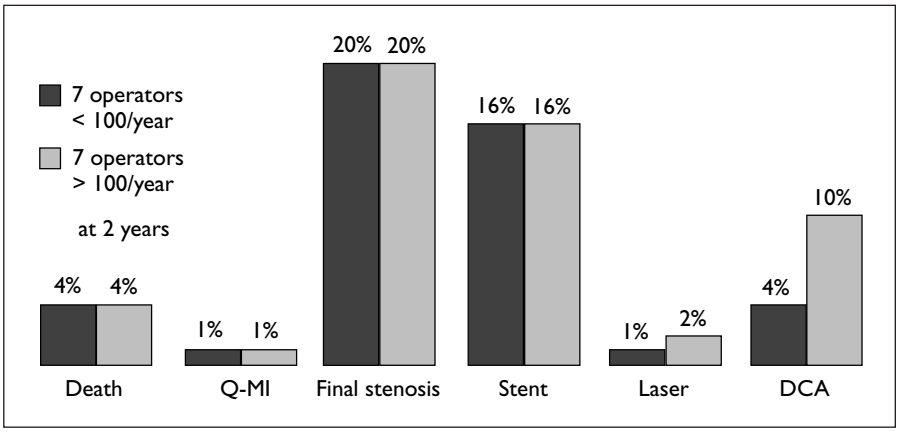

Figure 34.2
Outcome variables of PTCA cases at the Cleveland Clinic stratified according to the experience (number of cases per year) of the operators. DCA, directional coronary atherectomy; Q-MI, Q-wave myocardial infarction (Ellis, personal communication).

Staff and equipment required for certification for PTCA

Holland is the only European country with a high patient volume that restricts the activity of PTCA to state-certified centres. Yet, all PTCA centres should honour minimum requirements regarding personnel and equipment.[30]

Two physicians capable of performing PTCA, one of them contactable around the clock, and at least one additional physician with some experience in assisting during the procedure should be on the staff. At least one non-physician who is experienced in routine PTCA and management of complications should be present throughout the PTCA intervention. This person should also be aware of the material stocked and the place where it is kept. An additional physician experienced in life support measures (resuscitation, intubation) has to be available within minutes.

A state of the art catheterization laboratory with digital image enhancement, cine loop and adequate storage facility is mandatory.[50] An additional fluoroscopy unit, capable of angulated views, must be available within the institution as a back-up. On-line monitoring of vital signs, including pressures, within the laboratory and during transport, and an on-site intensive care unit are required.

The laboratory has to be stocked with a comprehensive pharmacy of cardiovascular drugs, a variety of basic PTCA materials such as balloons, guidewires, guiding catheters and stents as well as temporary pacing wires, pericardiocentesis equipment, and intravascular foreign body retrieval devices. Equipment for defibrillation, cardioversion and artificial respiration has to be at hand, and an intra-aortic balloon pump is recommended.

In-house surgical standby is the ideal background.[51] However, if this requirement stands in the way of a well indicated ad hoc PTCA or leads to disqualification of patients from timely treatment, PTCA without standby should be tolerated on condition that there are no local legal objections, the operator is well experienced with prior training in an institution with standby, the case selection is scrutinized based on the absence of surgical standby,[30] and the patient is informed that, if necessary, a distant cardiac surgery centre would perform an emergency operation.

Institutional policies

At first glance it would be desirable that every catheterization laboratory performing diagnostic coronary angiograms should be capable of immediately adding a PTCA to any diagnostic study. This is convenient for the patient and economical regarding disposable material. Yet, the advantage of ubiquitous ad hoc PTCA has to be weighed against the disadvantage of the dilution of PTCA experience. Under the following circumstances ad hoc PTCA is recommended:

- the PTCA team is experienced;
- the situation is entirely clear and premeditated;
- the patient has been informed about this possibility before the diagnostic study and consented to it provisionally;
- the patient is awake enough to reconsent to it after the findings of the diagnostic part of the intervention have been explained;
- an adequate place in the hospital for aftercare is organized (particularly in the case of outpatient angiography);
- ad hoc cases are regularly scrutinized by the operators and uninvolved peers to avoid abuse of self-referral.[30]

The protocol of the intervention and the medical report, preferably depicting a graphic rendering of the situation before and after PTCA, have to be kept for several years. A dynamic angiographic document[50] should be stored either with the patient or at the facility where it was created, or both.

Conclusions

Official rules for training and certification of physicians, non-physicians and institutions involved in interventional cardiology (PTCA in particular) in Europe are still largely non-existent. The general quest for quality control and cost containment is likely to remedy this before long. It is to be hoped that the rules will be assessed for their practicability before they become legal and result in sanctions. Regulations that place responsible physicians outside the law are an even worse scenario than rationing, which is already a bad enough threat.

The quality control of PTCA as a procedure in general and the respective training and education in particular have to remain in the hands of the cardiac societies. It is important that they act before regulatory agencies feel compelled to intervene. Some restraint and perhaps small sacrifices by individual interventional cardiologists are likely to bear dividend and keep politicians from imposing negative restrictions. On-site peer visits for assessment of centre quality have been organized by national cardiac societies in Austria[52] and Switzerland,[53] and by the European Society of Cardiology in Europe.[54]

It is advisable that rules for training facilities and certifications should for the present concentrate on PTCA and ignore the number of other catheter-based cardiac interventions which are rarely performed. Exceptions to this are electrophysiological procedures such as pacemaker implantations and ablations. They are common and are performed by a different specialist and are beyond the scope of this chapter. However, a new wave of procedures performed by interventional cardiologists common enough to invoke official rules are at the doorstep. They include carotid angioplasty,[55] device closure of the patent foramen ovale in patients with cryptogenic stroke,[56] septal ablation in hypertrophic obstructive cardiomyopathy, mitral balloon valvuloplasty, percutaneous myocardial laser revascularization and brachytherapy.

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35

Training in interventional cardiology in the United States: program accreditation and physician certification

Daniel M Kolansky and John W Hirshfeld Jr

Health care governance in the United States

In the United States' health care system, governmental regulation takes place at the level of the individual states. For the most part, these state agencies confine their regulatory control to the granting of a general license to practice medicine and surgery. Responsibility for credentialing and privileging for specialized medical and surgical procedures lies within the individual health care organizations such as hospitals. These organizations are empowered to develop criteria for the granting of privileges and are responsible for monitoring the quality of medical practice.

The United States has a longstanding voluntary (non-governmental) process for assuring standards of specialty medical practice. Two related organizations chartered by the American Medical Association have an interlocking responsibility to maintain high standards of specialty medical care. The American Board of Medical Specialties (ABMS) is an organization composed of individual boards that represent all of the medical disciplines. These individual boards are responsible for setting standards for certification in their respective specialties. The American Council on Graduate Medical Education (ACGME) is an organization that represents graduate medical education training programs. It is responsible for determining standards that training programs must meet to receive accreditation. The Residency Review Committee is the ACGME's arm for evaluating programs in order to grant accreditation. The ABMS and the ACGME, although separate organizations, have an important interaction. In general, the individual specialty boards require that candidates for certification must have received requisite training in an ACGME accredited program.

In order to achieve certification, an individual must complete a specified training experience in an ACGME accredited program and must achieve a passing score on the examination given by the respective specialty board. Thus, while certification by a medical specialty board does not carry any legal weight, it is tangible evidence that an individual practitioner has met a certain standard of competence. Most United States health care organizations require board certification or its equivalent for the granting of specialty medical privileges.

There are numerous professional organizations of medical specialists in the United States. In general, eligibility for membership of these organizations requires board certification. These organizations collaborate with the specialty boards to determine the standards of education, training and practice for their respective disciplines. The American College of Cardiology (ACC) is the United States' professional organization for board-certified cardiologists and cardiovascular surgeons. The Society for Cardiac Angiography and Interventions is a professional organization of invasive cardiologists. Fellowship in the Society requires the completion of at least 1000 cardiac catheterization procedures.

Jurisdiction for governance of interventional cardiology

The American Board of Internal Medicine (ABIM) is the parent board for internal medicine and its subspecialties, one of which is cardiovascular disease. Interventional cardiology is considered a subdiscipline of cardiovascular disease. Consequently, interventional cardiology as a discipline falls under the purview of the Cardiovascular Board of the American Board of Internal Medicine and the Residency Review Committee for Internal Medicine.

Evolution of the discipline of interventional cardiology

As the discipline interventional cardiology has developed and evolved, there has been a gradual evolution in the structure of training programs. The earliest angioplasty experience was obtained in Europe. The technique quickly spread to the rest of the world, particularly the United States. Early training was obtained by individual observation of the practices of a single operator. This early time period was also notable for the development of live angioplasty training courses. Dr Andreas Gruentzig offered the first training to many interventionalists from around the world in a series of live demonstration courses in Switzerland. Interestingly, despite the development of formal training requirements in later years, this practice of live demonstration courses continues as a major adjunctive experience for many operators today. Individual practitioners of cardiac catheterization then brought these experiences to their own laboratories and developed their skills.

In the early 1980s, university and large non-academic medical centres in the United States began to offer a dedicated year of angioplasty training to cardiologists who had completed their traditional Fellowship training in general cardiology and diagnostic catheterization. This became the major source of training of new practitioners, who typically completed this third Fellowship year. During this time period, other experienced angiographers continued to acquire training and skills in angioplasty without benefit of a dedicated training year. This practice declined as the pool of experienced angiographers acquired sufficient skills, and as sufficient new trainees were produced. By the late 1980s most new interventionalists completed a dedicated training year.

The need for an organized strategy for training in interventional cardiology was promptly recognized by the major cardiovascular societies in the United States. In 1986 a joint American College of Cardiology/American Heart Association task force first formulated the concept of a dedicated additional year of training for interventional cardiology. It recommended that cardiovascular trainees who planned to perform coronary angioplasty undertake a dedicated fourth year of fellowship training in interventional cardiology, with specifications as to minimum numbers of procedures to be performed.[1] Alternative routes of training for established angiographers were also recommended. Subsequently, the Society for Cardiac Angiography in 1988 also recommended completion of a formal 1-year fellowship in coronary angioplasty,[2] and the ACC reaffirmed its endorsement of the dedicated year of training in its 1988 version of guidelines for coronary angioplasty.[3]

Following these recommendations, training programs gradually expanded to 3 years for general cardiology and diagnostic catheterization, with a fourth year dedicated to coronary intervention.

Development of standards for training in interventional cardiology

The current standards for training in interventional cardiology are derived from the COCATS (COre CArdiology Training Symposium) document, published by the American College of Cardiology in 1995.[4] This document was based on a conference convened by the College to examine all aspects of training in cardiovascular disease. By design the document is terse and specifies only the general outlines of a training program. However, its significance is that it formalized the concept that training in interventional cardiology required a dedicated fourth year of training in addition to the standard 3 years for general cardiology. The document specified little as to how the training was to be conducted other than to specify that a trainee should participate in a minimum of 300 coronary interventional procedures during training.

Subsequently, the American Board of Internal Medicine determined that the discipline of interventional cardiology had matured to the point that it merited separate recognition within cardiovascular disease and proposed to ABMS that an added qualification examination be developed. A key component of this determination was the recognition that interventional cardiology is a cognitive as well as a technical discipline. Practitioners of interventional cardiology must hold a unique highly specialized cognitive knowledge base in addition to the technical skill required to execute the procedure. The cognitive knowledge base governs, among other things, case selection, technique selection, adjunctive pharmacotherapy and post procedure management. This aspect of the discipline of interventional cardiology constituted the ABIM's rationale to develop a program for a certificate of added qualification in interventional cardiology.

The ABIM achieved approval for this initiative from the ABMS. It then developed a syllabus that compiled the topics of the interventional cardiology cognitive knowledge base. Subsequently it developed the interventional cardiology certifying examination. The first examination was administered in October 1999. At the time that this examination was administered, there was considerable heterogeneity in the training experience of the population of physicians who were performing interventional cardiac procedures. Consequently, the initial eligibility criteria for the examination were very inclusive. Two pathways to board eligibility were specified – a practice pathway and a training pathway. The practice pathway was for experienced interventional cardiologists who may not have undertaken a formal training program. This pathway required that the candidate have performed either 150 coronary interventional procedures in the 2 years prior to the examination or 500 procedures over a career. The training pathway required that the candidate have completed a dedicated fourth year of interventional training and a requisite number of cases. More than 2200 physicians took the 1999 edition of the examination.

Concomitantly, in consultation with ABIM, the ACGME developed criteria for accreditation of interventional cardiology training programs. It announced its interventional cardiology training program certification and in 1999 issued a call for applications. The first round of applications was reviewed and the first program approvals were granted in the spring of 1999.

With the development of program accreditation, the ABIM determined that, beginning in 2003, completion of formal training in an ACGME accredited program would be required for eligibility. Thus, this officially closed the program accreditation – physician certification loop.

The characteristics of an optimal interventional cardiology training program

The ACGME's accreditation criteria development process constituted an opportunity to examine the procedure for training in interventional cardiology. This process recognized that proper training required both a systematized didactic curriculum to present the interventional cardiology cognitive knowledge base and a practical experience performing procedures in order to develop the technical expertise and accumulate a requisite clinical experience. The ACGME identified four basic elements that characterize a training program:

- Training program goals and structure. This includes the program goals and requirements and qualifications for faculty, requirements for facilities and requirements for the patient population.
- Training program didactic curriculum. This includes the curricular requirements for the didactic educational curriculum and conferences.
- Duration and conduct of training. This includes the process for procedure training (including numeric standards), the types of procedures included, the standards for structured conferences and trainee participation in research.
- Trainee evaluation. This includes the conduct of the trainee evaluation process.

The accreditation requirements for interventional cardiology training programs are viewed by ACGME as threshold requirements that a program must satisfy in order to achieve accreditation. The development of these standards led the American College of Cardiology to examine the interventional cardiology training process. A writing group constituted by the College examined the ACGME requirements as a point of departure to identify the programmatic qualities and curricula that would optimally enhance a program's educational and training environment. The writing group endorsed the ACGME standards. Thus, this process identified the qualities and features that a training program should endeavour to achieve in order to provide optimal training in interventional cardiology. The outcome of this process was published by ACC in the *Journal of the American College of Cardiology*.[5]

The basic elements of the ACGME accreditation criteria are presented along with the ACC suggestions for enhancement in Table 35.1. This summarizes the standards required by ACGME to achieve accreditation. The enhancements suggested by the ACC define desirable attributes over and above the ACGME criteria. These suggested enhancements may be summarized below:

(1) *Program activity level and faculty complement.* The ACC concluded that larger programs have the potential to offer a better training experience. In a larger program, the trainee is more likely to be exposed to a greater variety of types of cases and more likely to achieve a satisfactory activity level. Similarly, larger programs with greater numbers of faculties can provide a broader perspective on technical strategies. Thus, whereas ACGME requires a minimum of 400 procedures per year, ACC recommends that the number be greater than 600. Similarly, the ACC recommends that the faculty responsible for training be higher volume operators. Whereas ACGME requires that program faculty perform a minimum of 75 procedures per year, ACC recommends that this number be more than 125. The rationale behind this recommendation was that the faculty responsible for training should be held to a higher standard of accomplishment.
(2) *Trainee procedure experience.* Both the ACGME and the ABIM recommend that a trainee perform a minimum of 250 procedures during the training year. The ACC suggested that 250 procedures represented a minimum and that 400 procedures during training was a more optimal value. The ACC also recognized that a trainee could become overloaded with coronary interventional procedures to a degree that the balance of the cognitive aspects of training would be compromised. Consequently, the ACC recommends that a maximum of 600 procedures be conducted in a training year.

Future directions

Over the past 20 years, interventional cardiology has matured from an investigational technique to a widely applicable and extensively utilized clinical service. As the discipline has matured, the standards and criteria for education, training and performance evaluation have become systematized. The United States, through its training program certification

Table 35.1 Standards for training in interventional cardiology.

		ACGME minimal core requirements	*ACC additional recommendations for optimal program*
Educational program	Programmatic relationships	Integral component of an accredited subspecialty residency in cardiovascular disease	
	Training prerequisites	Completion of accredited 3-year cardiology training program	Trainee must achieve COCATS level II competence in diagnostic catheterization
	Training duration	One year	
Faculty	General qualifications	• ≥ 2 clinically active faculty (>75 procedures/year) • No more than 1.5 trainees per faculty member • Board certified in interventional cardiology	• ≥ 3 (More recommended) • Board certified in interventional cardiology • >125 annual procedure volume • >500 procedure career experience
	Program director		• Board certified in interventional cardiology • >1000 career procedure experience
	Expertise	• Balloon angioplasty • Coronary stents • Coronary atherectomy • Intravascular ultrasound • Coronary Doppler and pressure measurement	• Not all skills need be represented in each faculty member • Cardiac valvuloplasty expertise desirable but not mandatory
Facilities and resources	Equipment	One appropriately equipped cardiac catheterization laboratory	Cardiac catheterization laboratory must have digital video processing with roadmapping and gap-fill
	Activity level	≥ 400 procedures per year	• >600 is optimal • >100 diagnostic catheterizations per year for intrinsic cardiac valve disease
	Coexisting facilities	• Cardiac care unit • On-site cardiac surgery • Cardiac surgical intensive care unit • Outpatient cardiac care program	• On-site cardiac ultrasound • On-site cardiac nuclear medicine • On-site clinical electrophysiology
Program content	Clinical experience (evaluation, management)	• Clinical experience with chronic and acute ischaemic heart disease and with valvular disease • Bleeding complications • Care of patients pre- and post interventional procedures • Cognitive knowledge base of clinical decision-making • Outpatient follow up of patients who have undergone interventional procedures	
	Technical and other skills	• Cardiovascular pharmacology and other adjunctive therapeutic skills • Interpretation of diagnostic haemodynamics, angiography, intravascular ultrasound and Doppler • >250 coronary interventional procedures performed • Participation in a case includes: pre procedural evaluation, performing the critical manipulations of the procedure and being actively involved in post procedure management	• 250 procedures during training is a bare minimum; at least 400 is optimal • Core skills include conventional balloon angioplasty, coronary stents, coronary atherectomy, primary angioplasty for acute myocardial infarction, intravascular ultrasound, intraaortic balloon counterpulsation and other mechanical circulatory support • Optional skills include cardiac valvuloplasty, endomyocardial biopsy, Doppler coronary flow measurement and transcatheter closure of congenital cardiac defects.
	Formal Instruction	• Platelet physiology and blood coagulation • Mechanism(s) of restenosis • Role of gene transfer for treatment of restenosis • Regulation of the coronary circulation • Coronary artery anatomy • Radiation physics, biology and safety • Critical analysis of interventional cardiology clinical research data	• Didactic seminar series to cover core topics of cognitive knowledge base • Weekly interventional cardiology conference to review and critique instructive cases and complications

From Hirshfeld et al,[5] reproduced with permission from the *Journal of the American College of Cardiology.*

process, now has a well organized system for assuring standards of quality in the education and training of interventional cardiologists. As interventional cardiology promises to continue to be a rapidly moving field, the standards for program accreditation and for physician certification will need to evolve to be commensurate with the developing knowledge base. The infrastructure of the ABIM, ACGME, and ACC will assure that that evolution takes place.

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What's on the horizon?

Spencer B King III and Mahomed Y Salame

Although many advances led to the development of interventional cardiology, this discipline was fully borne in 1977 when Andreas Gruentzig performed the first coronary angioplasty procedure.[1] Since then, the specialty has been largely driven by advances in technology. The era 1977–1986 was dominated by the improvement in guide catheters, the development of guidewire technology and the improvement of balloons with a lowering of profile while increasing the tolerance to higher inflation pressures. The mid 1980s through the mid 1990s was an era of device development, including lasers, directional atherectomy, rotary ablation and stenting. In the latter part of the 1990s, the discipline became dominated by stenting, first with the early designs and then second and third generation devices.

Interventional technologies for the future

Despite impressive advances detailed in this volume, a number of issues remain for future technologic improvement. The principal failures of percutaneous intervention continue to be restenosis (including the difficult problem of in-stent restenosis), the inability to open an appreciable percentage of chronic total occlusions, the occurrence of distal embolization especially in degenerated saphenous vein graft disease and the difficulties in managing bifurcation lesions and diffuse small-vessel disease. However, novel interventional approaches are currently being developed and evaluated to meet these challenges. In addition, more accurate plaque characterization for assessment of plaque stability will emerge making possible the stratification of lesions subject to spontaneous plaque rupture or the prediction of distal embolization during percutaneous intervention.

Improvements in the percutaneous management of chronic total occlusions should be given a high priority since this condition remains a major limitation in performing interventional procedures. The guidance of the mechanical device is critical to opening total occlusions. Thought to be addressable in only 50–60% of cases,[2] chronic total occlusions are now opened more consistently by highly trained operators. Colleagues in Japan have reported 80–90% success in chronic total occlusions. This effort is accomplished by using very stiff guidewires but it remains a relatively crude technique and new approaches to opening total occlusions are greatly needed. There are developments including laser wires, forward looking ultrasound catheters and ablative devices using various energy sources that may address this problem.

Lesions subject to distal embolization are receiving interest since distal emboli can cause microinfarction even with patency of the parent vessel. Devices capable of capturing distal embolic material have been developed for carotid arteries and are being evaluated. However, the technical challenge for utilizing these devices in native coronary arteries remains to be investigated. A subset of particular interest is degenerated vein grafts which are very susceptible to distal embolization. Current trials are evaluating both balloon occlusive devices and umbrella-shaped filters with pores from 75–100 microns.

Potential interventional devices

Although the new device era of the late 1980s and early 1990s has given way to the balloon and stent, interesting devices continue to be developed. Improved directional

atherectomy catheters may reignite a largely abandoned technique. Plaque modification by sonotherapy or thermal methods, be they hot or cold, will be tried. Of particular interest is the photosensitizing therapy using the compound antrin, which is taken up by macrophages in plaque and, when subjected to light, destroys them.

Solving restenosis

The major shortcoming of interventional procedures is the tendency for the stenosis to recur. Historic efforts at controlling restenosis have largely failed. Recent emphasis has been placed on control of cell proliferation through a very potent weapon, endovascular radiation. The use of radiation has been successful in blocking cell proliferation in non-malignant conditions such as keloids on the skin[3] or pterygium in the eye.[4] Animal studies have demonstrated inhibition of smooth muscle cell proliferation and neointima formation in coronary arteries following balloon injury.[5,6] Multiple clinical trials have now shown that endovascular radiation therapy is highly effective in reducing late renarrowing following angioplasty and stenting.[7–9] Potential downsides have also been identified, especially the delayed healing of the endothelium and increased thrombogenicity.[10] Recently completed trials, SMART and INHIBIT, using a prolonged anti-platelet therapy and avoiding unnecessary stenting, have shown a dramatic decrease in late thrombotic problems.

Small vessels are less attractive for percutaneous coronary intervention since they typically have relatively high restenosis rates. However, subgroup analysis of the SCRIPPS trial suggested that smaller vessels might derive benefit from radiation in lowering the restenosis rate.[11] The SMART (Small Artery Radiation Therapy) study, a multicenter, double blind, placebo controlled non-randomized trial in 180 patients, will be evaluating the safety and efficacy of ^{192}Ir for the prevention of restenosis with provisional stenting in vessels less than 2.75 mm in diameter. The primary endpoint is MACE at 6 months and 2 years and binary restenosis at 6 months.

Another difficult condition that needs addressing is the management of SVG restenotic lesions with percutaneous intervention because of the relatively high rate of restenosis. The WRIST-SVG trial, a randomized, placebo controlled trial, focuses on in-stent restenosis in saphenous vein grafts.

Bifurcation lesions continue to have a high restenosis rate requiring new solutions that have not yet been solved by stenting. Newer generations of bifurcating stents are being developed, but it is too early to say whether they will have an impact on restenosis rates.

The strategy of pharmacotherapy continues to be evaluated for restenosis prevention. Large trials are currently underway using tranilast (an anti-keloid medication) and paclitaxel (a microtubule-stabilizing agent with potent antiproliferative activity). Tranilast has been shown to reduce neointima formation in the pig coronary angioplasty model[12] by inhibiting vessel wall cellular proliferation,[13] and is being evaluated in the PRESTO trial in over 11 500 patients. Paclitaxel has been shown to decrease smooth muscle cell proliferation and migration in in vitro studies and to reduce neointima formation in animal studies.[14,15]

Recently, a polymer-coated stent has been engineered to release the drug sirolimus, which is an anti-rejection compound used in transplant patients. An initial feasibility study showed no significant intimal proliferation at 4 months by angiography or intravascular ultrasound.[16] These were relatively short de novo lesions but, if this observation holds, then drug-eluting stents may become a potent device for many patients.

In the future, gene therapies may be targeted to control cell migration and proliferation. It is likely that local delivery of agents will find its place. The problems with local delivery in the past have been inefficient transfer of agents, and because of the rapid circulation in the tissues, a diffusion and lack of persistence of the agents in the local environment. These problems may be solved by encapsulating the agents in slow release formulations or tagging agents chemically.

Late lumen loss after angioplasty has been an invariable component of angioplasty and stenting. Stent placement is currently performed for two reasons. The first is to avoid acute closure, which has now become unusual in the interventional laboratory even with balloon angioplasty, and second, to achieve a very large final diameter of the vessel in order to make room for significant late loss. However, the ability to freeze the result with radiation or other agents has the potential to change the current attitude toward a successful interventional result. Others would argue that stenting is so ingrained in the mind of the interventional cardiologist that no change will occur. This is probably dangerous thinking, as evolution seems to rule in the world of interventional cardiology.

Imaging and hemodynamic adjuncts

Although intravascular ultrasound (IVUS) entered the interventional cardiology arena several years ago with great promise, its use has remained limited. One may wonder why ultrasound has not become a more integral component of interventional cardiology. The answer probably lies in the fact that the technologic development of intravascular ultrasound has been inhibited because industry is unwilling to invest more resources in a technology that seems to be uncommonly used. On the other hand, cardiologists seeing little improvement in intravascular ultrasound are still reluctant to use the older technologies. Certainly it should be possible to create very small IVUS devices, even to the size of guidewires

that could image arteries routinely during interventional procedures to more fully and accurately characterize the lesion as well as to measure the adequacy of the interventional procedure performed. New devices will emerge to better characterize coronary plaques. These involve use of energy such as heat and light and importantly, magnetic resonance. Magnetic resonance angiography, using endovascular catheters and guidewires as the MR antennae, can image arteries with a high degree of precision and provide excellent characterization of lesions, perhaps providing a way to discriminate vulnerable from stable plaque. Other plaque imaging techniques being investigated are near infrared spectroscopy, optimal coherence tomography and temperature sensing catheters. If high risk plaques can be identified, this could lead to a new revolution in interventional cardiology – treating non-obstructive but threatening disease.

Hemodynamic measures, such as obtained with Doppler flow wires and pressure transducer wires, have been shown to be valuable adjuncts in interventional cardiology. The cost of these devices, combined with the confidence in the angiogram (sometimes misplaced), limits the use of such devices. Pressure devices such as fluid filled catheters may provide equally valuable data, but at lower cost.

The era of non-invasive coronary arteriography is about to dawn. Although EBCT (electron beam computed tomography) has been used primarily for detection of vascular calcification, it can also be used for contrast enhanced angiography. Vein grafts and IMA grafts can be visualized quite well. Multislice spiral computed tomography may give even higher resolution. Magnetic resonance angiography, although commonly used for peripheral studies, can image myocardial function and perfusion and eventually will be used for coronary arteriography. Direct invasive coronary arteriography, however, will remain the diagnostic method for many years to come.

Anti-thrombotics

The platelet has now been recognized as central to arterial thrombosis, a fact that has been strengthened by the results of a large number of trials of anti-thrombotic therapies. The trials of three GP IIb/IIIa receptor blockers have shown a dramatic reduction in acute coronary events, especially non-Q-wave myocardial infarction. Low molecular weight heparin has also improved results and ADP receptor blockers combined with aspirin have become the standard following stent placement. Future research will undoubtedly concentrate on establishing the value of reducing microinfarction. This is a critical question because while there are therapies available to reduce this event, it remains unclear what the value of decreasing the enzymatic leak in otherwise uncomplicated cases is. Perhaps the use of IIb/IIIa agents will become routine in interventional procedures and the price will become more competitive. On the other hand if the price remains high, efforts will be made to select patients most likely to benefit. It is also likely that other anti-thrombotic efforts will be developed such as direct anti-thrombins and tissue factor inhibitors.

Approach to specific disease states

Diabetic patients with coronary artery disease have been identified as a group of patients who are a significant challenge for percutaneous coronary interventions. The long-term outcome of multivessel patients with diabetes treated with angioplasty was inferior to those treated with surgery in the BARI trial,[17] the EAST trial[18] and the CABRI trial.[19] Observational databases have also shown this effect. Current efforts to test angioplasty versus surgery in the ARTS trial and the SOS trial may improve the outcome of diabetics, but this is unclear. An important future investigation will be BARI II, which will examine revascularization versus optimal medical therapy for the diabetic population and will also test whether replacement of insulin or improvement in insulin sensitivity is a preferred method for dealing with type II diabetic patients undergoing treatment for coronary artery disease. It is clear that heightened surveillance and optimized secondary prevention are critical in the diabetic patients undergoing interventional procedures.

Acute myocardial infarction

Primary angioplasty for acute myocardial infarction has been demonstrated to provide excellent TIMI 3 flow and improved survival compared to thrombolytic therapy in formal randomized trials.[20] The prompt availability of primary angioplasty, however, is suboptimal and the debate rages over whether there should be regionalization of interventional therapeutic centers for acute myocardial infarction or whether there should be wide dissemination of interventional procedure laboratories. There is certainly no agreement on this subject; however, quality of delivered care should be the overriding concern. Trials of therapy of thrombolytics with or without IIb/IIIa inhibitors combined with PCI in patients whose arteries do not open are beginning. Ultimately, systems of integrated acute MI therapy must be developed and the competition between thrombolytics and interventional therapies eliminated. Undoubtedly the economics of medicine will enter into the discussion, but it is critical that the profession provides leadership in determining the best approach to making optimal acute infarction therapy available. This will vary from region to region in the future and one would hope that clinical

judgment would prevail. There is a danger that decisions of this sort will be made by third party payers and/or government agencies. The role of professional societies, such as the American College of Cardiology and the European Society of Cardiology, should be central in protecting the profession and the patients.

The unrevascularizable patient

With the aging population and the wide application of surgery and angioplasty, there will be many patients who are significantly symptomatic yet unrevascularizable by conventional approaches. These problems are being addressed with new investigational techniques such as laser myocardial revascularization,[21] angiogenesis[22,23] and enhanced extracorporeal counterpulsation devices. All of these techniques have shown significant symptomatic improvement in open label trials. The placebo effect of such therapies is undeniable in such a desperate population and therefore it will be important to establish mechanisms and to identify whether the improvements will be sustained. Randomized trials currently underway should identify whether symptomatic improvement is due to other mechanisms or not. Perhaps most promising is the use of angiogenic compounds. Current trials with intracoronary application of VEGF or bFGF have not proved very successful and may yield to more direct intramyocardial or intrapericardial delivery and one would expect significant effort to be applied in this direction in the years to come.

The coronary venous circulation has been suggested as a conduit for delivering retroperfusion from arterial sources or as bypasses around arterial obstructions in patients who are not otherwise candidates for revascularization due to extensive disease.

Congestive heart failure has not in the past been the purview of the interventional cardiologist; however, the potential for regrowing myocardium using stem cells or skeletal muscle cells directly implanted into the heart muscle could become procedures that would require interventional cardiology expertise.[24,25] Guidance systems for precise delivery of these agents, including radiofrequency triangulation methods, may aid in precise positioning of both angiogenic substances and myocardiogenesis efforts.

Applying what we know

The Dartmouth Atlas of Cardiovascular Healthcare, 1999 edition,[26] highlights the uneven application of diagnostic and therapeutic procedures in the United States. Randomized trials have clearly identified therapies such as the use of aspirin[27] and beta blockade[28,29] following acute myocardial infarction. In this population, the use of beta blockade following myocardial infarction ranged according to region from a low of 5% to a high of 92%. Many other aspects of secondary prevention, such as lipid management, have not been applied to best advantage in interventional patients. It is highly likely that more standardization of care will occur as more evidence-based documentation becomes available. It will be important, of course, for proper judgment to be applied in individual patients. There will always be exceptions to the rules but undoubtedly more rules are coming in the future. It will be critical for professional societies to ensure the development of guidelines rather than leave this to other parties.

Preserving the profession

The perception that there are presently an excessive number of interventional cardiologists in the US is borne out by data from the *Dartmouth Atlas of Cardiovascular Healthcare*. In 1996, among 16 620 cardiologists who could be classified, 38% were interventional cardiologists, 22% general cardiologists who did some invasive work, 34% general cardiologists who did no invasive work and 6% electrophysiologists. This distribution of physician workforce may not be appropriate for the future. On the other hand, the total number of cardiologists currently being trained would project a gradual decrease in all cardiologists from the 2000 average of just over 6 per 100 000 to a 2020 level of less than 5 per 100 000. With the aging population this may not be adequate. Interventional cardiology will be strengthened by the formal recognition of the discipline with its own certification. In the future, trainees completing approved programs in interventional cardiology will be eligible to take this examination and, by virtue of doing so and maintaining their activities in interventional cardiology, may have less emphasis put on absolute numbers of cases to maintain their local credentialing. Many practices have concentrated the interventional activities into the hands of fewer of their members, improving the quality of interventional cardiology performed by those practices.

The future for interventional cardiology remains extremely bright. The development of technology will not diminish and will likely accelerate. The revolution in the information age will likely be followed by a revolution in the biotechnology age. The latter will undoubtedly be driven by venture funding and large pharmaceutical and device companies more than by charitable or governmental agencies. Whereas such entrepreneurial development is most efficient for economic growth and technologic expansion, it is not adequate for delivery of medical care. As long as there is a significant proportion of the population without medical insurance, or

there is state or hospital rationing of the number of interventional procedures performed, the interventional cardiology community will be hampered in delivering adequate care to our patients. In the future, some form of healthcare system will have to be developed which provides adequate coverage for all citizens. This also will mean that some degree of triage will be practiced in deciding which therapies are most effective and cost effective.

Universal coverage will be mandatory as we expand genetic testing and therapies. As interventional cardiologists, we have been focused for the past 20 years on the development of technology without major concern for the application of that technology for the common good. As physicians, that certainly has been our major responsibility. In the future, however, we must participate in the planning of whatever health system emerges in order to ensure that the technologic advances that have characterized interventional cardiology will not be inhibited. As we develop these technologies, we must also pay close attention to critics such as Stephen Klaidman who concluded his book, *Saving the Heart. The Battle to Conquer Coronary Disease,*[30] with this admonition, 'We must find a way to transform medicine from the industry it has become in to a caring profession again'.

Interventional cardiologists who are focused on technology must remember this, however, more than most disciplines of medicine, our specialty has great potential to lead in developing innovative and effective therapies for the benefit of all cardiovascular patients.

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