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Clinical Pharmacology of Antianginal Drugs

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Preface

When I was asked some years ago by the editors of the *Handbook of Experimental Pharmacology* to edit a new volume on *Antianginal Drugs,* I agreed on the condition that, in accordance with my scientific background, primary emphasis be given to clinical pharmacology and therapeutics. It soon turned out that, due to rapid developments in this field, nothing of the previous volume on *Antianginal Drugs* by Charlier (Vol. 31, 1971) could be retained apart from its basic idea of devoting considerable space to methodology.

Since editors must operate within certain limits, I had to abstain from dealing with acute myocardial infarction in detail despite the well-known overlap between unstable angina, the preinfarction syndrome, and acute myocardial infarction. It was only possible for acute myocardial infarction and the concept of reduction of infarct size to be briefly discussed within the chapter on pathophysiology of acute coronary insufficiency. The chapter on invasive methods provided an opportunity to touch on new approaches to early intervention in acute myocardial infarction. Here, intracoronary streptokinase therapy and PTCA are considered, again with attention to the overlap between mechanical and pharmacological interventions.

Although space was limited, I decided to start with a chapter on the epidemiology of coronary artery disease. It is written by a convinced and very active proponent of the risk factor concept. This was a deliberate choice in view of some controversy, such as the public discussion of the validity of this concept which has taken place particularly in Europe. At the same time this chapter offered the only opportunity in the volume to highlight the importance of both primary and secondary prevention of coronary artery disease.

The other introductory chapter is on the pathophysiology of coronary insufficiency; the principles reviewed here provide the basis for meaningful pharmacological intervention. Emphasis is given to new concepts and results in the biochemical and molecular areas and to information provided by electron microscopic studies. Furthermore, new insights into the regulation of coronary perfusion under normal and pathological conditions are dealt with. The principles of pharmacological intervention derived from these pathophysiological events during coronary insufficiency are subsequently discussed in a short overview by an eminent pharmacologist in this field.

Before dealing with the clinical pharmacology of the various groups of drugs, however, the book presents a relatively detailed set of chapters on methods for testing antianginal drugs. The purpose of this is to provide not only pharmacological information on drugs but also to present the methodological basis for

the results presented later. For those working in this field, these chapters should be of value as a reference source. They should also enable the critical reader to interpret the experimental results in light of the limitations and pitfalls of the methods used. In accordance with the theme of the volume, emphasis is given to clinical pharmacological methods. The chapter on methods in animal pharmacology is written with therapeutic needs in mind and therefore gives special attention to experiments in conscious animals.

In line with this concept, animal experiments are discussed in the pharmacological chapters only where their results are relevant to therapeutics or to an understanding of the mechanisms of action of the drugs concerned. In view of the different scientific backgrounds of the authors, the emphasis placed on pharmacology and clinical medicine varies from chapter to chapter. In addition, the space available did not allow us to deal with all aspects of the basic pharmacology of the drugs concerned. This seems justified in light of some excellent monographs that have been published recently and are recommended to the interested reader, such as volume 54 of the *Handbook* (parts I and II, 1980 and 1981) dealing with adrenergic activators and inhibitors, and the books by Fleckenstein and Roskamm *Calcium-Antagonismus* (Springer-Verlag, 1980) and by Stone and Antmann *Calcium Channel Blocking Agents in the Treatment of Cardiovascular Disorders* (Futura Publishing Company, 1983).

Although it is always difficult, if not impossible, to keep competent and distinguished authors strictly to the general theme of such a book, I hope that the original intent remains evident, namely to present current scientific views on antianginal drugs from the standpoint of clinical pharmacology and, at the same time, to provide a better understanding of the methods used and their limitations. Thus I hope that the book will prove to be a useful source of information for clinical pharmacologists, cardiologists, and internists with an interest in cardiology, and that it will aid both their scientific work and their therapeutic decision-making.

Mannheim U. ABSHAGEN

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General Principles

CHAPTER 1

Epidemiology of Ischemic Heart Disease

S. HEYDEN

A. Preface

Never before in the history of medicine has one single generation of medical practitioners witnessed such dramatic changes of major disease entities as our generation did between the 1950s and 1980s. Whereas, in the western hemisphere, infectious diseases came under control and, subsequently, rheumatic heart disease and syphilitic cardiovascular complications were almost eradicated, rapidly increasing "diseases of civilization" accounted for millions of premature tragedies of morbidity and mortality and led to the epidemic of coronary heart disease (CHD). In the United States and Australia, its peak incidence occurred around the mid-1960s, while the majority of eastern European nations at the present time seem to be heading toward still increasing rates and western European countries are leveling off, either at similar rates to those previously occupied by the United States, or below them.

One of the most hopeful observations in modern medicine has taken place within a period of little more than a decade. Beginning in 1968 and still noticeable in the early 1980s, a 35% decline in coronary mortality has been documented in all age, sex, and race groups in both the United States and Australia. The debate surrounding the reasons for this statistical phenomenon has involved a great deal of speculation, claiming credit for improved drug therapy for the diseased heart patients, a more effective ambulance system and coronary care units, coronary bypass surgery, or new modes of earlier detection through mass screening, primary prevention, and rehabilitation (KANNEL 1982a, b; LUEPKER et al. 1982; NATIONAL CANCER CENTER 1977; US DEPARTMENT OF AGRICULTURE 1977; HEYDEN 1982a; HAMPTON 1982). In this writer's view, we now have evidence that a well-informed high-risk person will act, under the guidance of a prevention-oriented physician, to lower his or her risk substantially and consequently to experience not only better quality of life, but also prevention of premature CHD. Proof that altering life-style over a few years, beginning as late as middle age, can actually lower death rates from CHD has emerged from several indirect sources which will be discussed briefly. The single most impressive piece of evidence, however, was revealed in the results of the Multiple Risk Factor Intervention Trial (MRFIT 1982). For this reason, the most important long-term study of our time will be given top priority in Sect. B.

B. Multiple Risk Factor Intervention Trial

I. Methods, Eligibility, Intervention Strategies, Randomization

Between 1972 and 1973 a total of 361,662 men aged 35–57 years were screened for risk factors of CHD in 22 clinical centers. These volunteers had to be healthy, but they had to qualify for admission to the study by belonging to the upper 10% of a risk score distribution, taking smoking, cholesterol, and blood pressure into the equation, based on data from the Framingham Heart Study (MRFIT 1982). As an example of the application of this criterion, a man whose diastolic blood pressure was 99 mmHg and who reported smoking 30 cigarettes per day was at risk at the 10% level if serum cholesterol was at least 295 mg/dl. Other examples are given in Fig. 1. After excluding patients with a history of electrocardiographic (ECG) evidence of myocardial infarction, angina pectoris, diabetes requiring medication, serum cholesterol level $\geqq 350$ mg/dl, diastolic blood pressure $\geqq 115$ mmHg, or weight $\geqq 115\%$ of desirable weight, 12,866 men were randomized into a special intervention (SI) group or a control group. The latter group was designated usual care (UC), which meant that these men were to be treated by their own physicians. This decision during the planning period proved to be crucial in the interpretation of the results 7 years later. The high motivation of middle-aged men, labeled at high risk for CHD, to participate in a study designed to reduce that risk is evident from the follow-up visit recording (MRFIT 1982).

The missed visit rates (the number of men alive at the time of the specified annual visit but who did not attend, divided by the number of men randomized) were 4.5% for SI and 5.2% for UC men at 12 months. These increased only slightly each year and remained below 10% through six years for *both* groups.

The first man was randomized in December 1973, the last randomization occurred on 28 February 1976, and the trial closed on 28 February 1982, thus exposing each man to the study protocol for a minimum of 6 years (MRFIT 1982).

No intervention program was offered to the UC men, but they were invited to return once a year for a medical history, physical examination and laboratory studies. The results of the screening and annual examinations were provided to their personal physicians, who were informed as to the scientific objectives of the study.

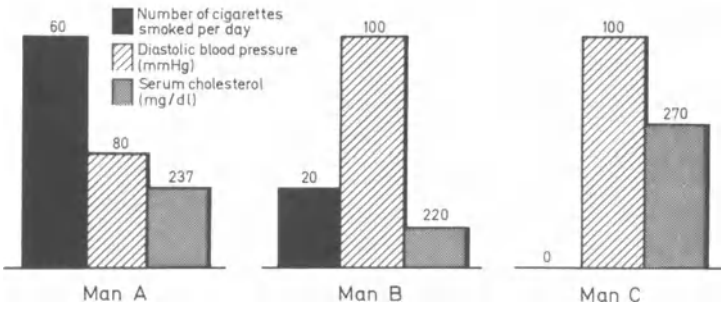

Fig. 1. Examples of risk factor combinations for eligibility (multiple risk factor intervention trial)

Table 1. Mean risk factor levels at baseline and at year 1, 2, 4, and 6 for MRFIT SI and UC men (MRFIT 1982)

	Baseline		Year 1		Year 2		Year 4		Year 6 (Termination)	
	SI	UC	SI	UC	SI	UC	SI	UC	SI	UC
Diastolic blood pressure (mmHg)	91.0	90.9	84.7	88.4	82.5	86.9	81.6	85.6	80.5	83.6
Reported cigarette smoking (%)	59.3	59.0	35.9	55.6	35.2	52.2	33.9	48.2	32.3	45.6
Serum cholesterol[a] (mg/dl)	253.8	253.5	238.4	246.8	238.2	246.0	235.4	243.4	235.5	240.3
Plasma cholesterol[a] (mg/dl)	240.3	240.6			229.9	237.2	227.2	234.7	228.2	233.1
Plasma LDL cholesterol (mg/dl)	159.8	160.3			150.7	157.3	148.1	154.5	148.7	152.9
Plasma HDL cholesterol (mg/dl)	42.0	42.1			42.8	43.3	42.8	43.0	41.7	41.9
Number of participants ar each visit	6,428	6,438	6,112	6,080	5,995	5,919	5,791	5,711	5,754	5,639

[a] Both serum and plasma cholesterol determinations were made; the latter were consistently lower, as reported by others

Each SI man was invited with his spouse or friend to a series of weekly group discussions. Each group included about ten men and met for ten sessions. After the initial intensive phase, individual counseling was carried out as deemed necessary. The participants were seen every 4 months and more often if specific goals established for each person had not been met. The intervention team consisted of physicians, dieticians, and psychologists. Hypertension, defined as diastolic blood pressure $\geqq 90$ mmHg on two consecutive visits was treated by weight reduction and sodium restriction. If higher blood pressure levels were not reduced, medication was prescribed, either hydrochlorothiazide or chlorthalidone. Reserpine, hydralazine, guanethidine, or certain alternative drugs were sequentially added, if the goal blood pressure (10 mmHg below 90 or 89 mmHg diastolic blood pressure, whichever was lower) had not been reached. Apparently, the dosage used in the first year was 100 mg hydrochlorothiazide or chlorthalidone in some cases with higher baseline blood pressure, and was reduced to 50 mg in order to avoid hypokalemia, according to a comment by KOLATA (1982), based on an interview with the associate director for clinical application at the National Heart, Lung and Blood Institute (NHLBI), Dr. William Friedewald. The nutrition intervention aimed at a saturated fat intake to less than 10% of calories, and cholesterol intake to less than 300 mg/day, and increased polyunsaturated fat intake to 10% of calories. In 1976, the nutrition was changed to specify that saturated fat be less than 8% of calories and cholesterol less than 250 mg/day. The 10-week group antismoking sessions at the beginning of the trial were particularly successful, and this success was enhanced by the 5-day clinics held during the final years. The effectiveness of the randomization process in establishing two comparable groups at baseline is demonstrated by the excellent agreement in prerandomization levels of numerous risk factors (Table 1, first column).

II. Results and Interpretations

The first report on the $115 million study, limited to the 6-year mortality data only, was published in September 1982 and produced a surprise result: mortality from CHD was 17.9 per thousand in the SI group and 19.3 per thousand in the UC group, a statistically nonsignificant difference of 7.1% and total mortality rates were 41.2 per thousand and 40.4 per thousand, respectively. It is deemed appropriate to present the key to this apparent paradox in two important observations.

1. The number of deaths in the UC group was substantially short of expectation for the 6 complete years of follow-up as well as for the average follow-up period of 7 years (MRFIT 1982).

Based on design risk factor change assumptions and Framingham risk functions, 442 deaths (including 187 from CHD) were expected by the end of 6 years of follow-up among the 6,438 UC men, only 219 (including 104 from CHD) occurred.

By the end of follow-up for all men, the total of 260 UC deaths (including 124 from CHD) was still well below the number expected for the total of 7 years follow-up period (MRFIT 1982; Table 2).

Application of the logistic function with coefficients estmated from Framingham data to the observed risk factor combinations of the men randomized projected a six-year death

Table 2. By the end of 6 years, expectation of the number of deaths fell short 50%, and by an average of 7 years, the 260 deaths were still slightly less than two-thirds the number expected (MRFIT 1982)

Usual care $n=6438$	Expected deaths after 6 years	Observed deaths after termination	
		End of 6 years	End of 7 years
Mortality from all causes	442	219	260
Death from CDH	187	104	124

rate for *UC men of 29.0 deaths per thousand* men. With a sample size of 12,866 (the number eventually randomized into the trial), a reduction in CHD mortality among *SI men to 21.3 per thousand* could be detected – which means a 26.6% reduction.

With the actual observation of only 19.3 deaths per thousand from CHD among the UC men and 17.9 deaths per thousand among SI men, it must be assumed that either the risk was overestimated or that unanticipated changes took place in the UC group. The answer, in all likelihood, is to be found in both, an estimate of risk for CHD (based on 1960–1965 data) inappropriate for 1976–1982 and substantial reductions of risk factors in the UC group.

2. Whereas it had been projected on the basis of the best information available 10 years ago that this group would exhibit no important changes in blood pressure and cholesterol and minimal changes in smoking habits, the actual findings were very different (NEATON et al. 1981). Sizable reductions occurred in the levels of all risk factors for UC men. Table 1 depicts the risk factor reductions, comparing the SI and UC groups. Remarkably, the only parameter which did not change in either group was the high density lipoprotein (HDL) cholesterol (MRFIT 1982).

By 72 months, diastolic blood pressure reductions were 10.5 mmHg and 7.3 mmHg, respectively. At six years, 58% of SI men and 47% of UC men reported antihypertensive prescriptions. The average percent reduction from baseline to 72 months among all SI men with diastolic bp of $\geqq 95$ mmHg was 12%, a figure exceeding design expectations; however, the corresponding reduction for UC men (unanticipated in the design) was 8%.

At 72 months, 46% of the SI men and 29% of the UC men had become ex-smokers, far exceeding design goals. Mean plasma cholesterol levels after 6 years were 12.1 and 7.5 mg/dl below baseline for SI and UC men, respectively (MRFIT 1982).

These reductions, which primarily represent changes in LDL-cholesterol and not HDL-cholesterol, amount to an SI–UC difference in total cholesterol of 4.6 mg/dl, or 2%. With the less-than-anticipated reduction among SI men and the unexpected decline among UC men, the SI–UC difference was about 50% of goal.

In the conclusion, the authors admit (MRFIT 1982):

It may be relevant that multifactor intervention received a less than optimal test owing, in part, to unexpected declines in risk factor levels and, in part, to lower-than-expected mortality in the UC group. In regard to the former, the UC men thus constituted to a considerable extent a "treated" group.

III. Comments

Although firm evidence for the following observations by the authors is not at hand, it is reasonable to assume (MRFIT 1982) that:

> contributing elements to the risk factor reductions may include the psychological impact on the UC men of enrollment in a trial limited to persons at high risk for heart attacks, the possibility that persons volunteering for a six-year trial are unusually health conscious and motivated to change, sensitization of the UC men to their risk factor status resulting from annual visits to the clinical centers, and the broad influence of health education in the United States aimed at modifying all of the three risk factors. The physicians of the UC men may well have instituted their own preventive programs.

Dr. Claude Lenfant, Director of the NHLBI, introduced the results of the MRFIT (1982) study to the public on 16 September 1982 with a brief review of the background of this trial.

> MRFIT was conceived by members of the Task Force on Arteriosclerosis in the early 1970s at a time when a so-called coronary epidemic was in evidence. However, during the life of the trial, a dramatic and unanticipated decline in cardiovascular mortality took place in this country. One way of looking at what happened during the 1970s, or at least from 1968 to 1978, is to note the number of deaths that were anticipated on the basis of the death rate in 1968. Let's compare that with the number of deaths that actually occurred – the bottom line. The estimated difference is 335,000 deaths less than was expected.

The interpretations of this complex trial will continue as data on morbidity are coming to light and as more subgroup analyses are shared – examples are to be discussed in connection with the Oslo (HJERMANN et al. 1981) trial and the Belgian Heart Disease Prevention Project (KORNITZER et al. 1983). However, no one has been able to summarize more succinctly than LUNDBERG (1982), in an accompanying editorial, what could be called the essence of MRFIT.

> It would seem that the investigators underestimated the effects of the following: 1. Identifying patients as high risk and informing them of it. 2. Notifying physicians that their patients were in a high-risk control group. 3. Providing original and annual data to the physicians. 4. The quality of practice of the personal physicians of the UC group. 5. The increased knowledge and behaviour change that much of the public at large was experiencing in this arena during the project time. *The interpretation that usual care was nearly as good as special intervention, speaks well for the ability of the patients to change and of practicing physicians to do their jobs effectively* [italics mine].

Or, as ROSE (1982) put it: "It seems now to have been a mistake to base the trial on health-conscious volunteers, who were so ready to catch the prevention message even when they were supposed to be controls."

IV. Multiple Risk Factor Intervention in North Karelia

One is reminded of another community program (PUSKA et al. 1979) to control cardiovascular diseases where the "control" community reduced, quite unexpectedly, the same risk factors, which, in the end, led to insignificant outcome differences between the two groups. "The results of MRFIT are disconcertingly similar to those of a Finish multifactor intervention trial of primary prevention of coronary heart disease" (OLIVER 1982). During the 5-year comprehensive study, two cross-sectional surveys of population samples *not* selected for high risk (as was the MRFIT population) were used. An overall mean net reduction of 17% in men and 12% in women occurred 5 years later with regard to cigarette smoking, blood

pressure, and cholesterol in the North Karelia intervention community. However, the control community in Kuopio, likewise, reduced smoking, lowered blood pressure and cholesterol levels and thus, no difference in CHD could be shown between the two communities. The time for controlled community experiments has passed, since concurrent changes in the behavior of "control" persons in these two studies as well as in future studies will prevent demonstration of a significant intervention effect.

V. The WHO European Collaborative Trial

Only preliminary results are presently available from the four European countries collaborating in a multifactorial intervention study, the United Kingdom, Belgium, Italy, and Poland. Participants were 49,781 men aged 49–59 years working in 88 factories in those four countries. This was a trial of prevention in whole communities. Medical resources were limited, the funds being less than 2% of those used by MRFIT.

Factories (not individuals) were randomized, so that health education could be given to the whole community without influencing controls. The risk factor changes were less than in MRFIT, corresponding over the 6 years of the trial to an average net reduction of 11% in estimated CHD risk. For high-risk men the fall in the intervention group was 22% – the same as in MRFIT. Success in changing risk factors varied widely between countries. The U.K. did well for smoking, but not for anything else. Italy and Belgium did best overall, with average falls of 28% and 16% in estimated overall CHD risk. These differences could be related to differing levels of intervention staffing. The outcome with regard to CHD broadly corresponded to the observed changes in risk factors. CHD mortality was 8% lower in the intervention group as a whole (not significant), ranging from a small but non-significant increase in the U.K. up to a 32% reduction in Italy and a 21% reduction in Belgium. Belgium was a large center and the reductions in both total CHD (24%) and total mortality (17%) reached the 5% level of significance (ROSE 1982).

Table 3. 2-Years changes of risk factors in the Belgian intervention and control group in comparison with the SI and UC groups of MRFIT

Risk factors	MRFIT		Belgium	
	Special intervention	Usual care	Intervention	Control
Smoking (%)				
Baseline	59	59	85	81
Year 2	35	52	69	71
Serum cholesterol[a] (mg/dl)				
Baseline	254	254	265	262
Year 2	238	246	255	263
Blood pressure (mmHg)	(Diastolic)		(Systolic)	
Baseline	91	91	152	153
Year 2	83	87	140	148
Participants				
Baseline	6,428	6,438	8,509	10,900
Year 2	5,995	5,919		
Age (years)	35–57		40–59	

[a] Plasma cholesterol levels were lower!

Table 4. 6-Year cumulative total mortality and coronary incidence in the Belgian heart disease prevention project (BHDPP)[a]

	Intervention (per thousand)	Control (per thousand)	Difference (%)	Significance
Total mortality	33.9	41.1	17.5	(P=0.011)
Coronary mortality	11.4	14.4	20.8	(P=0.072)
Nonfatal myocardial infarction	10.5	14.2	26.1	(P=0.036)
Coronary disease incidence	20.3	26.9	24.5	(P=0.004)

[a] "For 3 out of 4 predefinded end-points the outcome of the BHDPP was favorable with a reduction in coronary incidence almost 25% in the intervention group" (KORNITZER et al. 1983)

The Belgian Heart Disease Prevention Project can be singled out for several reasons:

1. Its 2-year intervention results have been published and can be compared with the 2-year results obtained in MRFIT (Table 3). Clearly, Belgian men at baseline appeared to smoke excessively and both the SI group and the UC group in the United States had a "head start" with only 59% smokers in comparison with 80% in Belgium. Likewise, mean cholesterol levels were 10 mg/dl higher at the beginning of the trial in Belgium. Blood pressures were mildly elevated.
2. The Belgian control group obviously was not "contaminated" by intervention and remained at high risk in smoking, cholesterol, and blood pressure.
3. In addition, the age distribution at baseline is important since it could be expected that, at slightly higher ages (than MRFIT), the CHD incidence would increase.

Table 4 represents a significant contribution to the intervention literature. As ROSE (1982) had pointed out, success in changing risk factors, among others, related to differing levels of intervention staffing. "The Belgian section of the WHO trial gives statistically significant support to the reversibility of risk. Considering the underlying disease in middle-aged men, that is a surprising result." The same could be stated about the excellent results achieved in the Oslo Study.

VI. The Oslo Trial (Primary Prevention)

The bifactorial approach over a period of 5 years in hypercholesterolemic, smoking men (HJERMANN et al. 1981) may be termed the most successful nonpharmacologic intervention trial. The coronary mortality was reduced by 48% in the in-

Table 5. Cholesterol levels in nonhypertensive smokers and nonsmokers with or without hypercholesterolemia [a]

MRFIT Subgroup Analysis I				
Nonhypertensive	Participants		CHD deaths	
	SI	UC	SI	UC
Nonsmokers at S_1				
Serum cholesterol				
<250 mg/dl	102	128	1	1
≥ 250 mg/dl	415	432	3	4
Smokers at S_1				
Serum cholesterol				
<250 mg/dl	846	844	16	11
≥ 250 mg/dl	1,046	1,041	15	29
Total	2,409	2,445	35	45

[a] Presented at the press conference on 16 September 1982 at the National Heart, Lung and Blood Institute, Bethesda, Maryland

tervention compared with the control group. The main credit was given to the 13% fall in serum cholesterol, while cessation of smoking accounted for only 25% of the reduction. The MRFIT provided a unique chance to replicate this observation. Table 5 reflects this attempt in a retrospective subgroup analysis. The numbers of smokers with elevated cholesterol levels at baseline were almost twice as high as in the Oslo trial; the reduction of coronary mortality was, again, almost 50% in the intervention group. What does this mean for everyday clinical practice? A patient who is hypercholesterolemic and unwilling to change either diet, weight (or both), and keeps on smoking, is twice as likely to die from myocardial infarction than one who changes life-style – 6 years seems a very short time period to increase or reverse one's risk.

C. Epidemiologic Observations Confirming the Trend of Decreasing Coronary Mortality in the United States

In the opinion of this writer, multiple risk factor intervention trials in primary prevention of ischemic heart disease are providing the ultimate proof that manifestations of this epidemic disease can be prevented or may be postponed to a later age. Two-risk or three-risk factor intervention experiments thus constitute the evidence required by those who doubt that coronary heart disease is a reversible entity. Their results come closest to the many observations in animal experiments which, particularly in the rhesus monkey, have unequivocally demonstrated reversibility of anatomic changes in the coronary arteries. Later, we shall discuss unifactorial intervention trials which have also shown unexpected benefits for those under active treatment (e.g., diet or antihypertensive therapy) in comparison with control groups under placebo or less aggressive treatment.

Table 6. Changes in food consumption (%) between 1963 and 1980 in the United States and the Federal Republic of Germany

United States (1963–1980)[a]		Federal Republic of Germany (1964–1980)[b]	
Milk–cream	− 24.1	Milk	− 15
		Cream	+ 84
Eggs	− 12.3	Eggs	+ 21
Animal fats	− 38.8	Animal fats	+ 3
Butter	− 33.3	Butter	− 14
Vegetable fats and oils	+ 57.6	Vegetable fats and oils	+ 12
Fish	+ 22.0		

[a] WALKER (1983)
[b] Statistical Monthly Bulletin (1973, 1980)

Among those who have made a study of the issue, opinion is still divided as to how much of the decline in cardiovascular mortality is a consequence of innovations in medical care (i.e., increasing role of thrombolysins and dilatation treatment, introduction of calcium antagonists and β-blockers) or whether this decline has resulted from an altered life-style. We will now attempt to support the latter notion epidemiologically, although the evidence presently available is much more indirect than that previously provided from multiple risk factor intervention trials.

I. Food Consumption Pattern: United States and Germany

A typical example is presented in Table 6 where the eating patterns and their changes over the period 1963–1980 are contrasted between the USA and Germany. Most recent mortality data indicate that CHD is still on a slight increase in Germany, in a country where myocardial infarction during the early postwar years was practically nonexistent and where the death rates suddenly and sharply increased in the late 1950s and early 1960s.

While German eating patterns have not changed significantly over the past 20 years, recent analyses of American food consumption show that the trend has continued since these data were published in 1983. WALKER (1983) cited the following figures: Since 1963, the per capita consumption of whole milk and cream decreased by 24%, the use of eggs by 12%, and butter by 33%. At the same time, the use of animal fat and oil decreased by 39%, consumption of vegetable fat and oil increased by 58%. The decrease in average cholesterol levels among middle-aged men resulting from changes in the quality of fat consumed was from 233 mg/dl in the mid-1960s to 217 mg/dl in the mid-1970s.

II. Development in England

In England and Wales, similar to Germany, no major changes have been recorded in the food consumption over the past 20 years. "Among middle-aged men in 1968 the chances of a CHD death in an American was 40% higher than that of

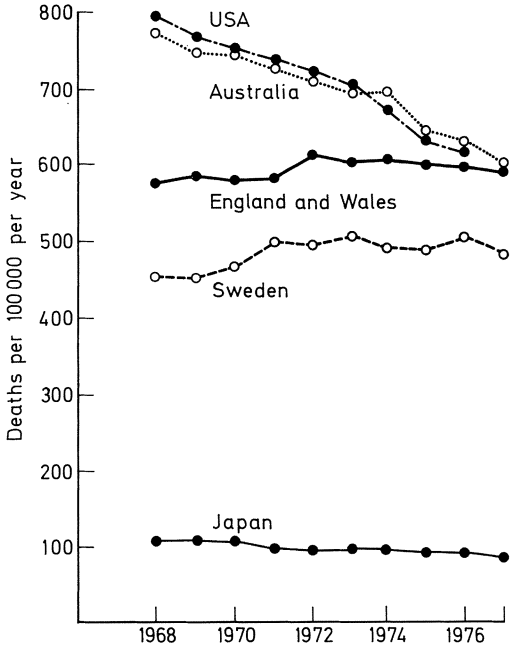

Fig. 2. Age-adjusted death rates from CHD among men aged 35–74 years in five countries. ROSE (1981)

an English man, while by 1976 the American risk had actually declined to below that of the English" (KANNEL 1982a). ROSE (1981) had shown the close proximity of the mortality curves between England–Wales and the United States (Fig. 2). He writes:

In Britain then, we are failing to prevent a preventable disease. If we had shared in the Australian and American decline each year in England and Wales, there would be upwards of 25,000 fewer coronary deaths. One can imagine the outcry if some shortcoming in therapeutic services were to cause even a tiny fraction of this number of unnecessary deaths. Why then, one may ask, do we not as a profession evince a corresponding alarm at a failure of prevention? Why do we not feel that it is our fault?

III. Life Expectancy in the United States

Already, life expectancy shows a rising trend in the United States. The National Center for Health Statistics published the following figures for the all-time life expectancy records of the average American: 1970 70.7 years; 1971 71.1 years; 1972 71.2 years; 1973 71.3 years; 1974 71.9 years; 1975 72.5 years; 1976 72.8 years; 1979 73.8 years; "a total population longevity increase of 3.1 years since 1970, compared with only a 0.8-year increase in the 1960s" (KANNEL 1982a).

IV. Life-Style Changes Versus Improved Medical–Surgical Care

As KANNEL (1982a) has pointed out, "the combined impact of medical and surgical interventions would seem insufficient to produce a 25% improvement. This

suggests that there has been improvement in the incidence or severity of the disease." Even if it could be shown that the aggregate of coronary care units, coronary angioplasty, advances in emergency cardiac care, and the impact of improved therapy are responsible for a portion of the decline, it stands to reason that the changes in risk factors are the major contributors.

V. The Rochester Study

What is apparent from this study as well as from the Minneapolis, Minnesota Study is that more than half of the total decline in CHD mortality rates is due to declining incidence of sudden death. This decline seems primarily due to decreasing prevalence and improved management of coronary risk factors among persons without a history of CHD (ELVEBACK et al. 1981). Unusually comprehensive data are available on CHD in the small twon of Rochester, Minnesota (population 28,000 in 1950 and 60,000 in 1980), because two main hospitals provide the clinical service to a well-defined local population. All hospital case records are available for the past 70 years. Autopsy rate is remarkably high at 60%. The incidence and mortality rates for CHD in this population between 1950 and 1975 were obtained by scrutinizing the records of all patients who were diagnosed with some form of CHD. Follow-up to 1980 was almost complete.

A certain disadvantage is the fact that this study is dealing with a better educated population with a higher than average income, since we recognize the fact that the majority of common risk factors (smoking, hypertension, hyperlipidemia, obesity, sedentary life-style, diabetes) predominantly reside in the lower socioeconomic group of our society. During the study period, 1,321 patients had myocardial infarction, 1,215 developed angina, and 544 cases of sudden, unexpected death were recorded. Most important, the trend in mortality rates in Rochester between 1968 and 1978 parallels that of the United States as a whole. This suggests that the observations made may be generally relevant even if the community is not typical.

The annual age-adjusted mortality rate from CHD was 142 per hundred thousand population in 1960, peaked at 184 in 1969, and then fell steadily to 113 in 1978. This decline was evident in all age groups. The incidence of sudden death declined most. In addition, between 1965 and 1969 the 30-day fatality rate among 300 patients with myocardial infarction was 18%, but between 1970 and 1975 among 385 patients it was only 9.3%. The 5-year survival rate of those alive at 30 days remained unchanged over the whole study period. Therefore, no change in long-term survival after myocardial infarction has been observed. The 5-year survival of patients with angina improved from 75% in the first 20 years of the study to 87% for those developing angina in 1970–1975.

VI. The Minneapolis Study

The other Minnesota study in the metropolitan community of Minneapolis reported on the trend in CHD deaths out of hospital (FOLSOM et al. 1981). The Minnesota Mortality and Morbidity Surveillance Program enumerated coronary

Table 7. Changes in CHD deaths in and out of hospital (FOLSOM et al. 1981)

Deaths	1970		1978		1970–78
	n	Rate/10^6	*n*	Rate/10^6	Change/10^6
In hospital	261	3,972	274	3,654	314
Out of hospital	293	4,458	187	2,493	1,965
All CHD	554	8,430	461	6,147	2,279

Table 8. Changes in cardiovascular risk factors (LUEPKER et al. 1982)

	1973–1974		1980–1981	
n	1,982	2,208	775	879
Diastolic blood pressure (mm/Hg)	79.2	73.6	75.8	71.4
Cholesterol (mg/dl)	207.5	200.4	203.2	197.0
Smokers (%)	40.3	37.0	35.0	34.4

deaths out of hospital and coronary deaths in hospital between 1970 and 1978 from death certificates in seven counties with a total population of 1.9 million. Results for males aged 55–65 years indicate a decline of 27% in CHD death rates overall, with death rates out of hospital and in hospital declining 44% and 8%, respectively. The proportion of CHD deaths occurring out of hospital fell from 53% in 1970 to 41% in 1978.

Declining death rates out of hospital thus constitute much (86%) of the total decline in the CHD mortality rate among men aged 55–64 years (Table 7).

The same group from the University of Minnesota School of Public Health in Minneapolis (LUEPKER et al. 1982) examined the trend in cardiovascular risk factors between 1973–1974 and 1980–1981. To ascertain if total plasma cholesterol, diastolic blood pressure, and cigarette smoking continue to fall, a population sample (age 25–29 years) was surveyed in 1980–1981 and compared with a similar survey in 1973–1974. The same laboratory was utilized and the survey methods were similar. The age-adjusted means are shown in Table 8.

Evidently, major risk factors declined significantly ($P<0.05$ for all parameters) in this population from 1973–1974 to 1980–1981. The decline was seen in both sexes, but was greater in men.

VII. The Chicago Peoples Gas Company Study

Results from the Chicago Peoples Gas Company Study (1960–1980) revealed very similar findings to those reported from the two Minnesota cities. This study used data on 3,203 men from the long-term Gas Company Study which began in 1958. The question posed was whether rates of sudden death from CHD had fallen with both first and recurrent coronary events (ANASTASIOU-NANA et al. 1982). For 1,617 men aged 40–59 years in 1960, age-adjusted first event sudden coronary

death rate was 6.8 per thousand from 1960 to 1964. For 1,733 men of the same age in 1975, the corresponding 5-year death rate was only 1.7 per thousand. This represents a 75% decrease of first event sudden coronary deaths. In contrast, the corresponding rate for *recurrent* sudden coronary death showed little change, being 7.6 and 7.1 per thousand, respectively. The results were similar using several definitions for sudden death (i.e., $\geqq 1$ h, $\geqq 3$ h, $\geqq 24$ h). "These findings are consistent with the concept that broad population changes in life style and life-style-related risk factors have contributed importantly to the sizable recent decline in CHD mortality in the US" (ANASTASIOU-NANA et al. 1982).

VIII. Pathologic–Anatomic Proof that Coronary Atherosclerosis is Decreasing

The quantitative measure of coronary atherosclerosis in two groups of randomly chosen autopsy cases of men aged 25–44 years is of great interest in this context (STRONG et al. 1979; STRONG and GUZMAN 1980). The first group was studied from 1960 to 1964 as part of the International Atherosclerosis Project in New Orleans and the second group between 1969 and 1972 as part of a Community Pathology Study in the same city. The pathologists developed an index to measure the severity of coronary atherosclerosis and used this standard to compare the two groups. The second group of men studied at autopsy between 1969 and 1972 had significantly less severe coronary atherosclerosis. According to STRONG and GUZMAN (1980), "One hundred and ninety-nine white men had more extensive percent coronary intimal surface ($14.2 + 1.31$ age-adjusted mean and standard error) involvement with raised atherosclerotic lesions" in the first period from 1960 to 1964 than the 146 whites in the second period from 1969 to 1972 ($7.0 + 0.84$).

Fatty streaks in the coronary arteries were also less extensive in the second group than in the first group (4.9 ± 0.4 vs 11.4 ± 0.7 for whites). This coronary

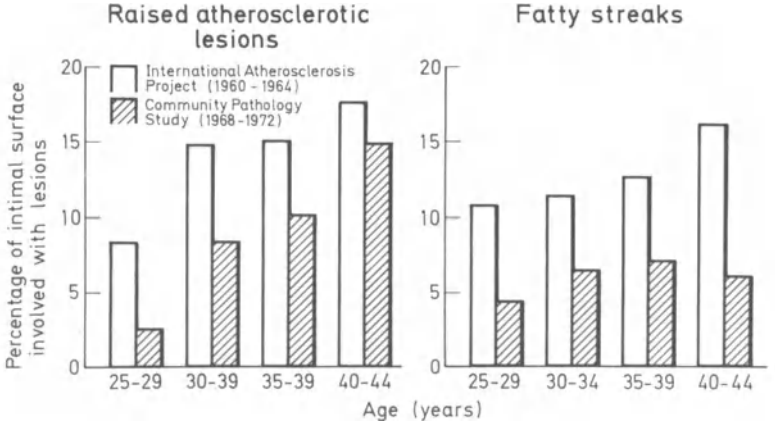

Fig. 3. Atherosclerotic lesions in the coronary arteries of white men at autopsy, by study time period and age. STRONG and GUZMAN (1980)

atherosclerosis index, applied to randomly selected autopsy cases and showing a 50% reduction in the extent of coronary atherosclerosis, is the most objective means possible to measure the decrease in coronary mortality (Fig. 3).

D. Hypertension and Hypercholesterolemia: Unifactorial Intervention for the Prevention of Ischemic Heart Disease

I. Prevention of Fatal and Nonfatal Ischemic Heart Disease Through Unifactorial Intensive Drug Therapy of Hypertension

The predominant opinion in hypertension research in the 1970s was that even intensive treatment could not prevent the so-called atherothrombotic complications of hypertension, in particular, myocardial infarction and ischemic heart disease. The opinion was primarily based on the results of two studies, the United States Public Health Service (U.S.P.H.S.) Hospitals Cooperative Study and the VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS (1967, 1970). The average age in the former study was 44 years at onset with an upper age limit of 55 years. SMITH (1977) stated:

> Pressure lowering conferred no protection against myocardial infarctions, furthermore, angina pectoris, abnormal Master's tests and other ECG abnormalities ascribable to coronary artery disease also occurred with equal frequency in the treatment group.... Since there was no difference in the incidence of "atherosclerotic" events, all of the observed difference in end points incidence are accounted for by reduction in "hypertensive" end points in the group receiving antihypertensive agents.

The results of the second study (Veterans Administration Cooperative Study) were similar and have been summarized by FREIS (1979 b):

> Such complications as hemorrhagic stroke, congestive heart failure, renal functional deterioration, dissecting aortic aneurysm, and accelerated hypertension were entirely absent in the treated group of patients.... On the other hand, myocardial infarction, heart block, atrial fibrillation, and atherosclerotic aneurysm occurred at nearly the same frequency in the control and treated patients.
>
> These results indicated that while treatment was highly effective against hypertensive complications, it was of no demonstrated benefit in preventing atherosclerotic complications, particularly those involving the coronary arteries.... The results could also be interpreted to mean that coronary artery damage occurs only in the course of hypertension, and that once it has occurred, atherosclerosis will progress at an increased rate, irrespective of the degree of control of the hypertension. The differing effectiveness of treatment on hypertensive as opposed to atherosclerotic complications provides an explanation for the diminishing therapeutic benefit seen with decreasing levels of pre-randomization diastolic blood pressure.

FREIS (1979 a) showed that the incidence of morbid events in the untreated as compared with the treated patients was in the ratio 27:1 in patients with the highest diastolic blood pressures (115–129 mmHg); the ratio was 4:1 in patients with blood pressure levels 105–114 mmHg; and it was 1.5:1 in the 90–104 mmHg range. Moreover, Freis emphasized that CHD developed almost exclusively in patients whose diastolic blood pressure was in the range 90–105 mmHg. However, he admits that larger number of hypertensive patients must be studied for longer periods of time before any conclusive statement can be made. Yet in his

state of the art lecture in 1979, FREIS (1979 b) reiterated that: "THE VETERANS ADMINISTRATIONS COOPERATIVE STUDY GROUP (1967, 1970) and the U.S.P.H.S. Hospitals Study (SMITH 1977) have demonstrated conclusively ... the effectiveness of treatment in preventing most complications except myocardial infarction and sudden death."

Obviously, preliminary results were considered as final in establishing this dogmatic hypothesis. In the meantime, a number of critics have voiced their misgivings. KANNEL (1978) noted that all previous studies are characterized by the same defect: they were not started early enough and did not continue therapy long enough to counteract the accelerating effect of hypertension on the atherosclerotic process.

STAMLER (1978) added:

> The V.A. trial was much too small – 264 and 259 men in two groups – to assess the coronary question, even if the study had continued for much longer. The sample size needed for assessing the coronary question was actually more than 10 times the size used in the study. With that problem in mind, it is noteworthy that the treated group in the V.A. study had only half as much mortality from coronary disease as the control group..., the total coronary deaths were 6 and 12, and the major coronary events, non-fatal plus fatal were 11 and 16. Thus there was a trend, and it favored the treated patients.

In another paper, STAMLER (1979) pointed out that distinguishing morbid events induced by atherosclerosis from those caused by hypertension is misleading:

> Stroke in Americans is both hemorrhagic and atherothrombotic and in men of the age in the V.A. study, the majority of strokes are atherothrombotic. Therefore, the view that in the V.A. trial treatment of hypertension did not influence atherosclerotic disease, is in that respect not correct. The evidence is that the treatment of hypertension influences both atherothrombotic and hemorrhagic stroke. Second, the view that the results of trials on the treatment of hypertension are negative in regard to coronary disease is also an incomplete understanding of the data.

The study population in these two studies (V.A., and U.S.P.H.S.) when combined, comprised 457 patients under active therapy and 454 patients in the placebo group. Observation ranged from slightly over 3 years in the V.A. study to 10 years in the U.S.P.H.S. study. Sudden death and fatal myocardial infarction amounted to 8 cases in the active treatment and 15 cases in the placebo group. It is reassuring to see that, although the small numbers prevent statistical evaluation, the prevention of fatal CHD was already apparent, at a time when both the Hypertension Detection and Follow-up Program (HDFP) and the Australian Hypertension Study (MANAGEMENT COMMITTEE 1980) were in their initial stages.

The Hypertension Detection and Follow-up Program (HDFP 1979 a, b) was the longest treatment trial for the largest number of hypertensive patients conducted in modern times. One randomly selected group of patients ($N = 5{,}485$) received intensive antihypertensive therapy in outpatient clinics specifically set up for this purpose (stepped care). Members of the second group ($N = 5{,}455$) were referred to their usual source of care (referred care).

In 1973 and 1974, 158,906 persons between ages 30 and 69 years were screened in 14 communities throughout the United States. The patients were referred to the HDFP clinics if their diastolic blood pressure averaged 95 mmHg at home on two measurements. The Hawksley random-zero device was used in the clinics for

blind measurement; patients with diastolic pressures over 90 mmHg were asked to participate in the long-term study. Patients were then randomly placed in one of two groups:

1. Patients in stepped care were given free drugs in a standardized stepwise fashion. Step 1 was prescription of a diuretic. In step 2, reserpine or methyldopa were added. Step 3 was a vasodilator, and step 4 added an antiadrenergic drug with or without discontinuation of medication at steps 2 and 3. Step 5 was the addition of (or substitution for) further drugs.
2. Patients in referred care had a clinical examination and laboratory tests at the beginning of the trial, as well as after the second, third, and fifth years. The private physician decided whether drug or dietary treatment was indicated for patients referred to their usual sources of care.

Seventy-two % of the HDFP patients (7,825) were grouped as "mild" hypertensives in the range of 90–104 mmHg diastolic blood pressure; 19% had levels between 105 and 114 mmHg (2,052); and 10% had the highest levels $\geqq 115$ mmHg (1,063 men and women). The goal was to reduce the diastolic blood pressure in patients with baseline levels of 100 mmHg or higher, to 90 mmHg. For patients in the range 90–99 mmHg, the goal was reduction to the 80–89 mmHg range. It was decided at the outset that success or failure would be judged by the hardest end point of any study, i.e., the difference in the mortality rate from all causes between the two groups at the end of year 5. Average age was 51 years at baseline.

In order to facilitate understanding of different results in the various long-term trials of hypertensive patients, two facts should be emphasized:

1. In an attempt to represent the full spectrum of hypertension, all hypertensive patients in HDFP were admitted to the study, including patients with a history of myocardial infarction, stroke, angina pectoris, diabetes, kidney disease, and gout.
2. The referred care group was different from control groups in other trials, as no placebo treatment was administered.

As a consequence, the final results of the trial were of great clinical relevance, but less dramatic than might have been expected, especially since many patients in the referred care group were also treated successfully with medication during the fourth and fifth years of the program by their own physicians.

II. Results

1. Death Rates Reduced

The majority of the patients in this trial (72%) had blood pressure values between 90 and 104 mmHg; the mortality from all causes over the 5-year observation period in this blood pressure category was 20% lower in the stepped care group than in the referred care group. The reduction of mortality, for the entire population, in the rigorously treated stepped care group, compared with the group referred to their usual source of care in the community, was 17% (Table 9).

2. Left Ventricular Hypertrophy Reverted

Of the stepped care patients who had left ventricular hypertrophy (LVH) at baseline, 60% reverted to normal ECGs (HDFP 1981). This normalization of a highly abnormal ECG sign led to significantly lower morbidity and mortality rates from myocardial infarction and stroke in the stepped care group as compared with the referred care group.

At the beginning of the study, 726 stepped care patients showed LVH in their ECGs, but after 5 years, the ECGs of 60.3% of these patients were normal. In the control group, 652 referred care patients showed LVH in the ECG at the beginning of the study, and after 5 years, 49.2% had normal ECGs (HDFP 1981; BORHANI 1982). LVH was defined as high R waves, combined with ST segment depression or with T wave flattening or inversion. It had been assumed earlier that, as LVH advanced, parts of the myocardium became relatively ischemic, which in turn would lead to development of necrosis and fibrosis and that this would inhibit proper functioning. Patients with this condition have a higher risk of sudden death, myocardial infarction, and congestive heart failure. So far, only a few studies (SEN et al. 1977) have examined the advantages of antihypertensive treatment for reducing LVH. For many years it was believed that LVH was irreversible once having developed. The new findings of the HDFP study, showing a lower incidence and reversibility of LVH resulting from intensive therapy, have been confirmed by similar results of chest X-rays showing decreased cardiothoracic ratios in stepped care patients in comparison with referred care patients.

3. Myocardial Infarction Rates Reduced Significantly

This trial demonstrated that intensive treatment of so-called mild forms of hypertension prevents fatal myocardial infarction. Among hypertensives with diastolic blood pressure levels ranging from 90 to 104 mmHg, 30 deaths were due to myocardial infarction in stepped care patients in contrast to 56 in referred care patients. Thus, the mortality rate was 46% lower in stepped care patients (see Table 9).

On this clear-cut advantage of a stepped care regimen in the treatment of hypertension over a less intensive drug therapy, FREIS (1982) commented:

> The most controversial question about antihypertensive drug treatment is whether it significantly reduces the incidence of coronary artery disease. Of the various trials, only the HDFP showed a significant reduction of fatal coronary artery disease with treatment. The investigators did not report their experience with non-fatal myocardial infarction.

4. Nonfatal Myocardial Infarction Rates Decreased

The nonfatal myocardial infarction incidence has just been made available (HDFP, 1984). Each participant had completed a standardized Rose questionnaire, which was developed to elicit a history of symptoms of myocardial infarction in a reliable fashion by trained interviewers. These questionnaires were readministered at the termination of the study. At intake, the prevalence of myocardial infarction by Rose questionnaire was identical in stepped and referred care groups. Of 5,485 patient under stepped care, 512 had positive Rose questionnaire

Table 9. Deaths by cause in the stepped care and referred care groups. All strata combined and stratum I (90–104 mmHg) (HDFP 1979 a)

	All strata		Stratum I (90–104 mmHg)	
	Stepped	Referred	Stepped	Referred
Stroke	29	52	17	31
Myocardial infarction	51	69	30	56
Other ischemic heart diseases	80	79	56	51
Heart failure	5	7	5	5
Other hypertension-induced causes	4	7	2	3
Other cardiovascular diseases	26	26	12	19
All cardiovascular diseases	195	240	122	165
Renal disease	15	10	7	5
Diabetes mellitus	5	10	4	8
Cancer	61	74	45	57
(Breast Cancer)	(2)	(5)	(2)	(4)
Gastro-intestinal diseases	11	20	9	15
Respiratory diseases	13	17	9	10
Infections	6	3	4	2
Accident, suicide, homicide	26	25	20	17
Other causes of death	17	20	11	12
All non-cardiovascular diseases	154	179	109	126
Total	349	419	231	291

responses, or a medical history of myocardial infarction (M.I.) or ECG evidence. Corresponding figures for the referred care group were the same, 506 of 5,455 individuals.

Table 10 shows the incidence of myocardial infarction over the 5 years for those who were free of myocardial infarction at baseline (negative response to the Rose questionnaire). Of 4,973 stepped care patients 346 persons with a negative Rose questionnaire at the beginning of the study developed M.I., yielding a 5-year incidence rate of 7,0%. Of 4,949 patients in the referred care group, 413 individuals developed an M.I. within 5 years, with an incidence rate of 8.3%. Thus, there was a relative reduction of 15.7% in the incidence of nonfatal myocardial infarction in stepped compared with referred care. For such a large population (> 10,000 participants), to ascertain proof of myocardial infarction over a 5-year period is much more difficult than in a hospitalized patient whose myocardial infarction may be documented by ECG and enzyme changes over several days or weeks scanning, and clinical course; but, whichever method was applied, standard clinical history, Rose questionnaire, or ECG (with ists well-known Q wave disappearance in at least 14% of myocardial infarctions over time), all these indicators favored the stepped care patients with a lower 5-year myocardial infarction incidence than referred care patients.

Since FREIS (1979 a) mentioned the Australian trial as "further example of a negative outcome as far as coronary heart disease is concerned," it is relevant to

Table 10. 5-Year incidence of nonfatal myocardial infarction (MI) among the HDFP stepped care and referred care participants by diastolic blood pressure strata at entry

Diastolic pressure at entry (mmHg)	Sample size[a]		5-Year incidence				Reduction in incidence among stepped care patients (%)
			Number		Rates/100[b]		
	Stepped	Referred	Stepped	Referred	Stepped	Referred	
90–104	3,553	3,588	250	283	7.1	7.9	10.1
105–114	939	900	68	89	7.4	9.8	24.5
≧ 115	481	461	28	41	5.8	9.0	35.6
Total	4,973	4,949	346	413	7.0	8.3	15.7

[a] Sample size is the population at risk; i.e., those who had a negative Rose questionnaire at baseline, a normal ECG and a negative medical history

[b] Rates are adjusted for age, race, and sex

quote actual figures from this 3.5-year trial. Among the 1,721 hypertensive patients under active treatment, two patients died of myocardial infarction, 18 more suffered a nonfatal myocardial infarction, and 50 patients were classified as angina pectoris and showing ischemic signs in ECG. The control group on placebo drugs consisted of 1,706 patients with the development of 8 cases of fatal myocardial infarction, 17 nonfatal myocardial infarction, and 63 patients classified as showing angina and ischemic signs in ECG. It should be pointed out that in contrast to HDFP, patients with either a history or ECG evidence of myocardial infarction, with stroke, angina, and many other risk factors were excluded from the Australian trial. The total incidence of ischemic heart disease (fatal and nonfatal), again, favored those under active treatment (MANAGEMENT COMMITTEE 1980).

5. Stroke Incidence Reduced Considerably

The prevention of stroke through aggressive antihypertensive therapy has been demonstrated in numerous clinical and epidemiologic studies. Only two subgroups of HDFP deserve our special attention, the elderly with elevated blood pressure and women with hypertension.

A 45% reduction in the incidence of stroke among stepped care participants who entered the study at ages 60–69 years, was rather unexpected. This represents the first demonstration (HDFP 1982a) that stroke can be prevented by an aggressive treatment program in an elderly population 65–74 years old at the termination of the study.

White women were characterized by a very low mortality rate, only 5% in 5 years. In the stepped care group, 58 of the 1,185 women and in the referred care group, 55 of the 1,156 women died (4.9% and 4.8%). White women in the referred care group participated more in the antihypertensive drug therapy than any other race–sex group in which the average diastolic blood pressure remained constantly

under 90 mmHg during each of the 5 years. These two factors, the low mortality from all causes for white women compared with the other three race–sex groups, and the high participation of women in the treatment offered by referred care, are the most important reasons for similarity in the results among white women. However, when stroke morbidity and mortality were combined, white women experienced a 30% reduction of stroke incidence in stepped care compared with referred care over 5 years (HDFP 1982a).

6. The Oslo Trial

Mortality from all causes in 5 years was only 3% among younger patients aged 30–49 years, so that no differences could be expected when comparing mortality between stepped and referred care groups. In contrast, the differences in mortality of patients over 50 years of age were impressive and statistically significant between the two groups. But again, when combining morbidity and mortality from stroke, a 27% reduction in the incidence of stroke was found, even among the younger participants (aged 30–49 years at entry) (HDFP 1982a). It is relevant to emphasize that the mortality *from all causes among the younger patients* ($\leqq 50$ years) was the *same in the stepped and referred care groups* in view of a similar finding in the Oslo trial of mild hypertension (HELGELAND 1980). A total of 406 men between the ages of 40 and 49 years with systolic blood pressure ranging from 150 to 179 and diastolic blood pressure less than 110 mmHg were treated intensively. The 379 men in the control group did not receive placebo tablets, but were referred to their usual source of medical care. The most important findings are:

1. No difference was found between the two groups in either total mortality or deaths due to cardiovascular disease.
2. Left ventricular hypertrophy, fatal dissecting aneurysm, and left heart failure were recorded only in the control group.
3. There were six causes of sudden death in the active therapy group and two cases in the control group. In both groups, eight cases of myocardial infarction were registered.
4. Cerebrovascular events were seen only in the control group.

Unlike the HDFP study, these men were asymptomatic at intake into the trial, just as in the Australian study, and did not have a history of cardiovascular disease, had normal ECGs, did not suffer from diabetes, retinopathy, renal diseases, etc., and were not on antihypertensive treatment for 12 months prior to the beginning of the study.

HELGELAND (1980) commented: "Considering the relatively small study groups and a short observation period, it was not reasonable to expect a significant effect on mortality. Thus, valid conclusions regarding the impact of antihypertensive treatment on mortality should not be drawn."

7. Total Mortality in Mild Hypertension Significantly Reduced

By far the most important finding yet emerging from HDFP may be the recent report on the effect of treatment on mortality in mild hypertension (diastolic

Table 11. 5-Year mortality rates (%)[a] among HDFP participants in stratum I (diastolic blood pressure at entry 90–104 mmHg) by end organ damage status and diastolic blood pressure substrata (HDFP 1982b)

End organ damage at entry	Diastolic blood pressure at entry (mmHg)	Stepped care (SC)			Referred care (RC)			Reduction in mortality for SC $\frac{RC-SC}{RC}$ (%)
		Sample size	Number of deaths	Death rate (%)	Sample size	Number of deaths	Death rate (%)	
Present	90–104	501	78	15.6	460	92	20.0	22.0
	90– 94	173	30	17.4	175	33	18.9	7.9
	95– 99	170	14	8.2	143	22	15.4	46.8
	100–104	158	34	21.6	142	37	26.1	17.2
Absent	90–104	3,402	153	4.5	3,462	199	5.8	22.4
	90– 94	1,301	54	4.2	1,292	74	5.8	27.6
	95– 99	1,220	55	4.5	1,198	65	5.4	16.7
	100–104	881	44	5.0	972	60	6.2	19.4

[a] Mortality rates calculated by life table method

blood pressure 90–104 mmHg). As will be recalled, 3,903 men and women were in the stepped care and 3,922 persons in the referred care group. A subgroup analysis was undertaken for those patients who: (a) were on antihypertensive therapy at baseline or without such therapy; (b) had end organ damage (stroke, myocardial infarction, angina, ECG abnormalities, pathologic creatinine, $\geqq 1.7$ mg/dl, and intermittent claudication) or free of them; and (c) were neither receiving antihypertensive treatment nor had end organ damage at the time of intake into the trial.

Patients receiving antihypertensive therapy on entry had a higher 5-year mortality than patients not on antihypertensive medication at initiation of the trial. Obviously, those patients were placed on drug treatment by their physicians because many of them also had evidence of end organ damage or because of either symptoms or pathologic findings, other risk factors, and comorbidity. Nevertheless, the reduction in cumulative mortality among stepped care patients relative to referred care participants was almost 20% for those who were not on blood pressure drugs on entry. The reduction was 22% for those who were taking antihypertensive medication on entry.

Again, the higher mortality among those with evidence of end organ damage on entry, as shown in Table 11 was to be expected. However, the reductions in cumulative mortality for the stepped care patients are evident. The reduction in cumulative mortality among stepped care as compared with referred care patients without end organ damage was 22%, for those with end organ damage also 22%.

Among the largest group, a total of 5,322 participants with diastolic blood pressure 90–104 mmHg who were not on drug therapy and were free of end organ damage, the 5-year cumulative mortality in stepped care was significantly reduced (Table 12) in comparison with referred care ($P=0.01$). By further subdividing mild hypertensives into those with diastolic blood pressure 90–94 mmHg, the

Table 12. 5-Year mortality rates (%)[a] among HDFP participants in stratum I (diastolic blood pressure at entry 90–104 mmHg) not on antihypertensive drugs and free of end organ damage at entry by diastolic blood pressure substrata (HDFP 1982b)

Diastolic blood pressure at entry (mmHg)	Stepped care (SC)			Referred care (RC)			Reduction in mortality for SC $\frac{RC-SC}{RC}$ (%)
	Sample size	Number of deaths	Death rate (%)	Sample size	Number of deaths	Deaths rate (%)	
90–104	2,619	106	4.0	2,703	151	5.6	28.6
90– 94	1,022	36	3.5	1,023	54	5.3	34.0
95– 99	932	39	4.2	913	53	5.8	27.6
100–104	665	31	4.7	767	44	5.8	19.0

[a] Mortality rates calculated by life table method

mortality rate in stepped care compared with referred care was significantly reduced ($P=0.05$) by 34%. The findings strongly support the HDFP (1982b) conclusion "that in patients with mild hypertension treatment should be considered early and certainly before end-organ damage occurs."

8. Noncardiovascular Mortality Decreased

It is not yet clear how to explain the effect of antihypertensive therapy on mortality from all causes, as was shown in Table 9 from the HDFP, with a significant reduction of noncardiovascular causes of death. Framingham data from the early 1960s, and published by KANNEL and GORDON in 1974, indicate that all causes of death among untreated hypertensives were higher than in age-matched normotensive persons, in addition to the well-known excessive mortality from cardiovascular disease among hypertensive patients without treatment.

In rural Evans County, Georgia, many hypertensive people either remained untreated or were inadequately treated between 1960 and 1969. Compared with normotensive people of the same age, white hypertensive patients suffered an excessively high risk of death from noncardiovascular causes during this period of time. In order to study this phenomenon, the population was divided into two groups. Persons with diastolic blood pressure under 95 mmHg were classified normotensive, and those with levels at or above 95 mmHg were termed hypertensive. The initial blood pressure values were taken in the first examination of the Evans County population between 1960 and 1962. Data on specific causes of death were collected until 1970.

Normotensive men and women had lower mortality rates than expected, with a standardized mortality rate (SMR) of less than one. In contrast, male hypertensive patients in particular showed a high mortality rate from cardiovascular and noncardiovascular causes of death, with the exception of cancer where the SMR was only slightly elevated. As expected, the rate of cardiovascular causes of death was 2.5 times higher for hypertensive than for normotensive men. Noncardiovascular causes of death were 1.5 times more frequent in hypertensive patients

than in normotensive people. It is not surprising, therefore, that the total mortality was nearly twice as high for hypertensive patients, largely left untreated at that time. Women with hypertension showed similar mortality rates.

An explanation for this phenomenon is not available at the present time. The Australian long-term study, for example, did not find a reduction in noncardiovascular mortality among patients in the treatment group, whereas the Swedish intervention study did. It would be equally important to determine the reason for the lower mortality rates from all causes exhibited by normotensive persons in the Evans County study.

III. Prevention of Myocardial Infarction Through Unifactorial Treatment of Hypercholesterolemia

1. Dietary Intervention: Experimental and Observational

a) Experiments with Dietary Intervention

α) *The Minnesota Coronary Survey*. The effect of dietary modification on the incidence of death and cardiovascular events was tested double blind in Minnesota institutions (BREWER et al. 1975). Serum cholesterol decreased 13.8% from baseline levels in the treated group and 0.6% in controls. The average observation period lasted 4 years. Under the cholesterol-lowering diet, in the younger 1,192 men randomized to the treatment group and 1,106 men randomized to the control group, all below age 50 years, significant differences were found for both coronary events and for total mortality (FRANTZ et al. 1975).

In the treatment group, three events of myocardial infarction, sudden death, and stroke occurred (within the 4-year period), and two deaths were registered. In the control group, however, ten persons had a myocardial infarction, died suddenly, or experienced a stroke. Mortality from all causes in the control group amounted to 12 cases. Thus, the cardiovascular event rate in the treatment group was 2.5 per thousand vs 9 per thousand in the control group (FRANTZ et al. 1975). Smokers and diabetics, levels of blood pressure, and number of men with arcus senilis were comparable in both groups (DAWSON and GATEWOOD 1975). Therefore, the difference in the incidence of coronary events and total mortality can reasonably be attributed to the dietary changes over these 4 years of observation. In men beyond age 50 years, risk factors other than diet and cholesterol levels appeared to be of greater importance. The special significance of this experiment is its double-blind nature and the unifactorial approach to CHD with a relatively high total fat intake and almost 15% of the total calorie intake consisting of polyunsaturated fatty acids for the treatment group. Interestingly, the lower cardiovascular disease mortality in the dietary treatment group was not "compensated" by a higher death rate from other causes. The total mortality which includes cancer was 1.7 per thousand in the dietary treatment group and 10.8 per thousand in the control group.

The observation described in the last sentence is rather significant since it could be, and actually has been, argued that other causes of death may automatically increase whenever the CHD is lowered by dietary means. A sufficient number of dietary intervention studies has been reported at this time which allows us

Table 13. Cancer deaths and diet (PEARCE and DAYTON (1971)

Adherence to diet (%)	No. of cancer deaths	
	Diet group	Control group
0–10	10	2
11–20	2	1
(21–30)	(3)	(0)

to examine this important issue (SHEKELLE and PAUL 1981). In particular, in the past few years, concern has been raised that a cholesterol-lowering diet may increase the risk of cancer (BEAGLEHOLE et al. 1980; WILLIAMS et al. 1981; KAGAN et al. 1981). While this hypothesis was examined and dismissed by most nutritionists and cancer specialists, nevertheless the alarm was sounded and led to the following review of the facts.

β) Cholesterol-Lowering Diet: How Much is Safe? The first well-controlled trial was conducted at the Veterans Administration facility in Los Angeles (PEARCE and DAYTON 1971). Among 420 men placed on a diet with increased polyunsaturated fats for 8 years, the reduction of heart attacks, both fatal and nonfatal, was significant in comparison with 420 control men. But in contrast to this expected outcome, a review of the study's figures over a total of 10 years observation revealed a higher cancer death rate in the diet group (31 men) than in the control group (with only 17 men). What had happened? As in every long-term experiment, when people are randomized into a study group, they retain freedom to drop out, or to choose only to participate a fraction of time in the diet. The investigators kept meticulous adherence-to-diet records on each man. A summary of these records, with the adherence expressed as a percentage of the entire time they could have attended the meals served in the special study dining hall, is outlined in Table 13.

Thus, 12 cancer cases occurred among men in the diet group who adhered less than 20% of the time to the diet. We now recall that of all men assigned to the diet group, 31 later died from cancer. However, the 12 men who died from cancer and who only rarely or never ate the meals in the study dining hall can hardly be called dieters. They were not exposed to any significant degree to the diet enriched with polyunsaturated fats, and must have eaten the "control meals." If we now deduct these 12 men from the 31 cancer cases, only 19 cancer patients remain in the experimental group; there is no longer any significance in the difference in cancer frequency among the two groups. In fact, we can now add to the original 17 cancer patients on "control food," the 12 men who were supposed to, but hardly ever consumed the diet! (HEYDEN 1974, 1982a, b; HEYDEN and WILLIAMS 1982).

The combined experience of the dietary studies among men in Oslo, London, Helsinki, and Faribault (EDERER et al. 1971), all of them with increased consumption of polyunsaturated fats, was reported immediately following publication of the PEARCE and DAYTON (1971) study. The incidence of cancer during the years

of diet and the so-called postdiet phase was lower in the dietary experimental groups with 7.7% in comparison with the control groups with 10.9%.

The 13-year results from the "Anti-Coronary Club" in New York deserves special attention (SINGMAN et al. 1973, 1980). Results indicated a significant decrease in coronary mortality which was in part explained by unexpected confounding factors in the diet group. These men also lost weight and thus considerably decreased blood pressure levels. SINGMAN et al. (1973) wrote: "Our observations lend no confirmation to the alleged association between cancer mortality and high polyunsaturated fatty acid diet." A slightly lower risk of the active dieters to develop cancer agreed well with the previously quoted results from three European and one American dietary intervention studies.

The bifactorial 5-year intervention study from Oslo (HJERMANN et al. 1981) not only confirmed the 47% lower frequency of both heart attacks and sudden death in the diet group, but also took cancer mortality into consideration. The total death rate was 26 per thousand in the diet intervention and 38 per thousand in the control group, cancer death rates were 8 per thousand and 13 per thousand, respectively. Again, unequivocally, cancer was not increased in men placed on a diet with polyunsaturated and saturated fat in the ratio of 1 : 1 – if anything, cancers occurred less frequently among dieters.

b) Observations of Dietary Fat Consumption

α) *The Chicago and Zutphen Studies.* Although only an observation, not an experiment, the 19-year follow-up of 1,900 men in the Chicago Electric Company is important in this context (SHEKELLE et al. 1981). There was a 30% reduction of CHD deaths in men who had reported low consumption of dietary cholesterol and a relatively high intake of polyunsaturated fats at the beginning of the 19-year follow-up. At the Conference of the National Institutes of Health in Bethesda, May 1981 (NIH 1981), the cancer incidence in five different cholesterol groups in this population was presented and showed no difference in the frequency of cancer over the 19-year period in men with either low, medium, or high cholesterol levels at baseline.

Another observational study from the town of Zutphen, The Netherlands (KROMHOUT et al. 1982), reported on the cause-specific 10-year mortality of 871 middle-aged Dutch men. At the beginning of this study, information was collected about the usual food intake. During the 10-year follow-up period, 107 men died from all causes, 37 from CHD, and 44 from cancer. The differences in the intake of energy and macronutrients in 107 men who died from all causes and 764 survivors were all highly significant, i.e., in polyunsaturated fat: 18.5 g in men who died and 20.2 g in survivors ($P = 0.007$) and in dietary fiber 26.9 and 30.9 g, respectively ($P = 0.001$). Again, as in all the previously reported studies, the higher intake of polyunsaturated fats, presumably over a lifetime, did not predispose these men to a higher death rate, but rather appeared to be "protective." The authors of the Zutphen study emphasize the influence of the high fiber intake (in combination with a higher consumption of poly- and mono-unsaturated fats, *and* vegetable protein, *and* polysaccharides) on the mortality from all causes. Figure 4 demonstrates the fiber–CHD mortality relationship. The apparent interaction

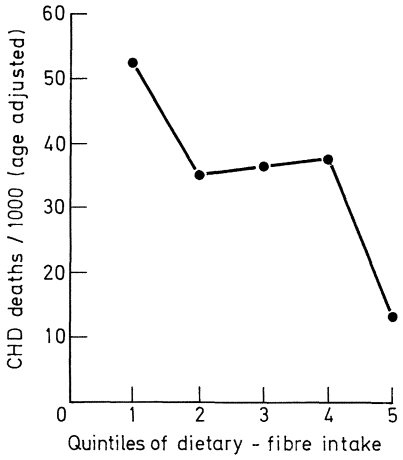

Fig. 4. Relationship between dietary fiber intake and 10-year CHD death rates. KROMHOUT et al. (1982)

between intake of polyunsaturated fats and fibers and effect on coronary mortality was shown first in the British Diet–Heart Study.

β) The British Diet–Heart Study. Between 1956 and 1966, MORRIS et al. (1977) conducted detailed week-long dietary studies of 337 healthy working men aged 30–67 years. The men were representative samples of British banks, and London Transport drivers and conductors. By the end of 1976, 45 of them had developed clinical CHD. The follow-up study disclosed an inverse association between the ratio of polyunsaturated fatty acids to saturated fatty acids (P/S) and coronary incidence – the higher this ratio, the lower the CHD rate. The association with P/S ratio was significant, both in the first 5 years ($P=0.05$) and in the later 24-year follow-up (LEWIS 1980). This is particularly interesting since the "P/S ratio in the diets was small, and the highest ratio was smaller than is often regarded as optimal" (MORRIS et al. 1977). At a remarkably low P/S ratio of only 0.16–0.28, which constituted the upper range among English men between 1956 and 1976, the CHD deaths were one-half of that seen at a P/S ratio of 0.09–0.18. Simultaneously, the self-selected total fiber content of the diet, as recorded at the initiation of the study, was related to the incidence of CHD: low intake with more disease, and high intake with relative freedom from it. On further analysis, however, the association was found only with fiber from cereals; the other and equally large part of dietary fiber, derived from fruit or vegetables, pulses, and nuts was not related to CHD.

In order to compare actual numbers with those revealed from the Zutphen study, low dietary fiber intake was defined in the range from 5.6 g/day to 15.4 g/day. This was associated with a fivefold higher CHD incidence that at the highest fiber intake, defined as 16.9–56.1 g/day. (Mortality from all causes was not reported.) MORRIS et al. (1977) speculate that:

> among cereals, not only does wholemeal bread containing three times, and brown bread twice, as much dietary fiber as white bread (8.5, 5.1, and 2.7 g/100 g respectively),

but the fiber in white and brown bread also differs. Whole grains carry polyunsaturated fat (linoleate) in the wheat germ.... The linoleate is only one possibility that cereal fibre may be the vehicle of other effectual nutrients.

γ) *Conclusion.* Univariate analyses with data for the years 1954–1969 from 20 economically advanced countries showed that a combined dietary lipid score based on per capita consumption of saturated fat, cholesterol, and polyunsaturated fat and the consumption of refined and processed sugars were both highly correlated with age-adjusted CHD mortality rates for the years 1969–1973 for both men and women aged 35–74 years. Fiber intake, estimated as the sum of calories available from vegetables, fruits, grains, and legumes, yielded a significant inverse correlation with CHD mortality rates. These three dietary variables are highly intercorrelated (LUI et al. 1982).

The lowering of blood cholesterol levels through changes in the fat quality which has proven beneficial in the prevention of heart attacks has had no undesirable side effects. Even more important, the reports on the frequency of cancer in ten international dietary studies (Minnesota, Los Angeles, Oslo (LEREN 1970), London, Helsinki, Faribault, New York, Oslo (HJERMANN et al. 1981) Chicago, and Zutphen) between 1970 and 1982, have demonstrated a slight (and insignificant) reduction in cancer deaths, an unexpected bonus for those replacing animal fats with vegetable fats and oils in their diets. Positive results as far as CHD is concerned in these studies were obtained among men either below age 50 years or between 40 and 49 or 40 and 55 years of age, and, in the British study, with a few men beyond age 55 years.

From population studies, it is well documented that in Japanese and among people living in the Mediterranean countries either on low fat in the fomer or on a fairly high fat diet in the latter, the life expectancy is higher than in other industrialized western nations (BLACKBURN et al. 1979); both the Japanese and the Mediterranean diets are characterized by a low percentage of animal fat and a high percentage of mono- and polyunsaturated fatty acids with a high P/S ratio. The AHA (1982) report points out that "the crucial atherogenic factors are saturated fats and cholesterol and not percent total fat. In Crete, e.g., fat intake is 40% but saturated fats make up only 8% and CHD mortality rates are extremely low."

2. Primary and Secondary Prevention of CHD Through Lipid-Lowering Drugs

a) The Coronary Primary Prevention Trial

January 20, 1984 will be remembered as a historic date in the 70-year struggle for verification of the "lipid infiltration theory" or "lipid hypothesis." On that day, the results of a 10-year intervention study of 3,806 men with hyperlipoproteinemia type II were released. After proper randomization, 1,906 men were followed for a minimum of 7 years under cholestyramine therapy plus modest dietary changes with the aim of reducing cholesterol levels (baseline 265 mg/dl). The control group of 1,900 men received placebo treatment plus the same modest dietary restrictions.

In the past, the supporters of the lipid hypothesis could point to successful animal feeding experiments, biochemical examinations of plaques, genetic studies,

metabolic investigations, and epidemiologic surveys in different nations and continents. The missing link was the decisive experiment in humans to answer the question: does lowering cholesterol concentrations in the serum lower the risk of CHD? A major contribution to this chain of evidence was provided by the Lipid Research Clinics Study, which can be regarded as one of the most meticulously planned and executed intervention trials ever conducted (CPPT 1979, 1984a, b). The essential features of the trial were randomization, double-blind testing (the patients were asked not to obtain lipid determinations outside the Lipid Research Clinics for 7–10 years), large numbers of participants, with many years of follow-up, and excellent adherence to the study regimen (only 27% dropped out within 7 years). There were no side effects of the drug except minor gastrointestinal problems. The results can be briefly summarized: (a) a 19% reduction in fatal and nonfatal heart attacks occurred; (b) a reduction in the incidence of angina pectoris by 20% in the active treatment group was observed; (c) annual exercise ECG showed after 7 years an incidence of 25% less positive tests among the men in the treatment group; (d) coronary bypass surgery became necessary in some men in both groups over the 7-year period, but in 21% less in the active treatment group compared with the placebo group. These differences in primary and secondary end points became apparent within the second year of the study. From this point on, the gap between the treatment group and the placebo group in terms of cumulative CHD incidence widened progressively.

Did any other known risk factor influence the results? The 7-year comparison of risk factors revealed no difference between the two groups. Blood pressures were 122/78 mmHg in both; weight was the same, the proportion of smokers was 26% in the placebo group and 27% in the treatment group; the number of cigarettes smoked per day was 25 and 26, respectively; the proportion of men on regular exercise was 27% and 28%, respectively, and alcohol intake was 51 and 53 g/week, respectively. Aside from the incidence data, the most important conclusion from this study came from the relation of the reduction in cholesterol to reduction in CHD risk, according to cholestyramine intake as the measure of compliance (Table 14). For each 1% of cholesterol reduction, a 2% reduction in CHD incidence was observed. The relation of reduction in total and low density lipoprotein (LDL) cholesterol to reduction in CHD risk is shown in Table 15. The results are particularly striking because the mean age at intake was 48 years in both groups. It can be assumed that many of the patients must have been exposed to the hypercholesterolemic levels for 10–20 years. Obviously, this first ex-

Table 14. Relation between reduction in cholesterol and reduction in CHD risk

Cholestyramine intake (sachets)	No. of men	Total cholesterol lowering (%)	Reduction in CDH risk (%)
0–2	439	4.4	10.9
2–5	496	11.5	26.1
5–6	965	19.0	39.3

[a] Each 9-g sachet provides 4g anhydrous cholestyramine

Table 15. Relation between reduction in total and LDL cholesterol and reduction in CHD risk

	Reduction of		Reduction in
	Total cholesterol (%)	LDL cholesterol (%)	CHD risk (%)
Study average	8	11	19
Full dose	25	35	49

perimental trial in men with unequivocal findings lends support to the notion that atherosclerotic involvement of the coronary arteries is a reversible process.

Apart from constipation and heartburn, the side effects of long-term treatment with cholestyramine were negligible; equal numbers in cancer incidence (57 for each group), prove that cholestyramine is not carcinogenic over a 10-year period. The number of hospitalizations was the same and the diagnosis of gallstones was made with equal frequency in the two treatment groups.

b) The WHO Clofibrate Study

In the WHO Clofibrate Study (OLIVER 1981; COMMITTEE OF PRINCIPAL INVESTIGATORS 1978), three groups with 5,000 patients each were compared. Group I had average cholesterol levels of 250 mg/dl and was treated with 4×400 mg clofibrate. Group II had the same cholesterol level and was given placebo tablets. Group III was a second control group that received placebo tablets, but the cholesterol levels for this group averaged 180 mg/dl. In the clofibrate group, the cholesterol levels were reduced by 9% and the myocardial infarction rate was decreased by 20%.

The benefit of this treatment could be seen in patients with multiple risk factors, for example hypertension and smoking in addition to hypercholesterolemia. The incidence of nonfatal myocardial infarction was reduced by 35% among these patients. Since reviewers of this WHO study found a higher rate of total mortality in the clofibrate group, sales of clofibrate were temporarily prohibited in the Federal Republic of Germany, even though the original article stated that no statistically significant difference was found in the age-adjusted mortality from all causes within the three groups. The authors also found no significant difference in the cancer incidence when the three groups were adjusted for age. OLIVER (1981) mentioned: "In the first report, it was noted that pathology of the hepatobiliary–intestinal systems was in excess in the clofibrate-treated group but during the follow-up the proportionate difference, although still evident became less."

The results of this drug trial indicate that pharmacologic therapy to lower lipids can be valuable in the prevention of CHD. The medication that is chosen should, however, lower the lipid level by at least 10%. This therapy is particularly beneficial to patients who have a high CHD risk due to other risk factors or who have a positive family history of myocardial infarction. In the meantime, a second article on the WHO study was published on 23 August 1980 (COMMITTEE OF PRINCIPAL INVESTIGATORS 1980). Since certain interpreters of this study have made ex-

cerpts out of context, it seems appropriate to quote the original authors of the clofibrate study directly, especially because they obviously found it difficult to explain differences in the mortality rates of the three treatment groups.

On page 384 of the Lancet article, they state (COMMITTEE OF PRINCIPAL INVESTIGATORS 1980):

1. There is no evidence of any relationship between the excess mortality in Group I and the time in the trial, i.e., length of exposure to Clofibrate.
2. Nor is there any evidence of tissue specificity either in malignant or non-malignant causes of death (this is also true for liver, gall bladder, and intestines).
3. The excess mortality in the Clofibrate-treated group is spread in small numbers over a remarkable range of ordinary everyday causes.
4. Such general effects on mortality are exceedingly rare and call to mind aging or low social class.
5. The evidence of adverse effects is thus entirely "statistical" and without "biological" corroboration.
6. Presumably the small amounts of olive oil in the placebo tablets (of Group II) are unlikely to afford any protection, and the possibility of a chance effect therefore needs particular consideration.
7. There are rather curious features of mortality in Group II, compared with Groups I and III to which attention should be drawn.... Eleven deaths were classified as due to non-malignant "regional pathology" (liver, gall bladder, intestines) in Group III but, remarkably, only one in Group II. These aspects of the behaviour of Group II are odd.

c) Secondary Prevention Studies

DORR et al. (1978) conducted a 3-year drug intervention trial of 2,278 hypercholesterolemic patients. A significant reduction of cholesterol levels and of deaths due to ischemic heart disease, as well as of total mortality, was achieved in the active treatment group as opposed to the placebo group. Such a reduction was accomplished even in those men who had already developed manifestations of ischemic heart disease. When the men were divided into two groups according to their baseline cholesterol levels, a higher coronary mortality rate was found in the group with baseline cholesterol levels above 300 mg/dl than in the group with levels below 300 mg/dl.

ROSENHAMER and CARLSON (1980) treated patients who had experienced myocardial infarctions after they were discharged from the hospital between 1972 and 1979. Group I was treated with a combination of nicotinic acid and clofibrate, while Group II was treated by diet only, but it is not clear from the report whether patient compliance to dietary advice was good. The cholesterol levels were reduced by 14% in the drug treatment group and remained unchanged in the control patients, triglyceride levels were reduced by 19%. Deaths due to ischemic heart disease were significantly less in the drug therapy group with only 31 deaths ($P=0.01$) than in the diet group which had 53 deaths. Nonfatal myocardial infarctions occurred far less frequently ($P=0.05$) in the drug therapy group (2.5 per 100 patient years). There were seven cases of cancer in the drug therapy group and six in the diet group. This study thus demonstrated the benefit of lowering lipid levels, even after myocardial infarction.

IV. Summary

In the 1970s, rather emotional arguments weighed down the discussion concerning the significance of hypercholesterolemia in the etiology, and the role of lower-

ing cholesterol levels in the prevention of CHD and potential carcinogenesis. I have therefore focused on clarifying the scientific views on this topic by discussing the position taken by the NIH workshop in Bethesda, Maryland, 1981 which ended on a similar note (NIH 1981):

> The panel of experts ... concluded that although there was considerable divergence of findings among the various studies, there was sufficient suggestion that there was a somewhat inconsistent weak relation between very low cholesterol levels and cancer of the colon.... This association is not similar to the kinds of relationships observed between cholesterol and cardiovascular disease – it appears to be present only in men, it tends to be more prominent at older ages, it is of smaller magnitude and it does not show a graded effect over the range of cholesterol levels. The panelists noted further that no data was available to relate these associations to diet.... The panelists concurred that the correlations observed did not substantiate any direct cause and effect relationship between low blood cholesterol levels and cancer.... It was the unanimous opinion of the panelists that the data did not preclude, countermand or contradict the current public health message which recommends that those with elevated cholesterol levels seek to lower them through diets.

On the basis of data from the dietary intervention trials in Los Angeles, London, Helsinki, New York, Oslo, and Minneapolis, a cause and effect relationship can be established between long-term adherence to a sensible diet and reduction of serum lipid concentrations as well as of cardiovascular mortality. The recommendations for dietary intervention have led to desirable results both on a community level (in Finland) and in control studies measuring HDL and LDL cholesterol levels and can therefore be applied to individual patients. A dietary approach must be applied to hypercholesterolemia (above 220 mg/dl) and every subgroup of hyperlipoproteinemia, even if drug therapy is indicated at the same time.

The great controversy of the past decade surrounding the role of lipid-lowering drugs has been eliminated by the most recent results of the Coronary Primary Prevention Trial (CPPT 1984a, b). Despite the fact that side effects must be anticipated and watched for carefully when lipid-lowering drugs are prescribed, it must also be clearly understood that epidemiologic data show elevated lipid levels to be a significant risk factor. The opposite finding that decreasing cholesterol levels by diet or medication does not increase the risk of other noncardiovascular diseases or cancer was described in a review of eight experimental, three observational, and three drug studies in which the latest research results were incorporated (CPPT 1984a, b).

E. Cigarette Smoking and Obesity: Unifactorial Intervention

I. Smoking

There is growing evidence that cessation of smoking is followed by a decrease in lung cancer mortality, first shown in British physicians who had quit the habit in large numbers. The apparent time interval between the termination of smoking and the observation of a decreasing incidence of lung cancer was relatively short, probably in the neightborhood of a decade.

No data are available to demonstrate reduction of both bladder and pancreas cancer in persons who have quit smoking and it is rather unlikely that such evi-

dence will ever be put forward. It is certain that emphysema is not reversible once it is established. Secondary oral cancer is said to recur with a high degree of probability in patients who continue to smoke after successful surgery or radiotherapy of the first cancer of the oral cavity. Symptoms of peripheral vascular disease, intermittent claudication, are definitely reversible among ex-smokers and the incidence of myocardial infarction is markedly declining among ex-smokers within a short period of time. How short this period is, clearly depends on the health status of the person who decides to give up the habit. If a patient who has already sustained a myocardial infarction or suffers from angina pectoris quits smoking, chances for secondary prevention of another heart attack or reversibility of angina are, of course, limited in contrast to a younger person who gives up cigarettes in top physical condition and who is embarking on a program of physical activity. We therefore have sometimes conflicting reports in the literature pertaining to the prevention of ischemic heart disease among ex-smokers. Another important consideration is the presence or absence of associated risk factors at the time of cessation of smoking, notably: (a) obesity; (b) diabetes; and (c) hypertension.

1. Smoking and Obesity

In the Evans County study (HEYDEN et al. 1971) a 7.5-year follow-up of 471 smoking and 308 nonsmoking white men in three different weight groups revealed these results. The rate of myocardial infarction among nonsmokers ranges from 51 per thousand in normal weight men to 30 per thousand in moderately overweight to 64 per thousand among the obese. Nonsmokers thus showed unpretictable, insignificant differences in the incidence rates of myocardial infarction, regardless of their weight. On the other hand, current smokers who were of normal weight, moderately overweight, or obese showed markedly increasing incidence rates, from 80 to 90 to 150 per thousand, respectively. It is obvious that the risk of the two factors smoking and obesity for ischemic heart disease is not simply additive, but exponential. To patients who still might ask their physicians "what is more dangerous, smoking or obesity?" the answer is that it would make little sense to attend an antismoking clinic without undertaking some dietary changes and, even worse, to check in a weight reduction program while continuing the smoking habit.

2. Smoking and Hypertension

In HDFP, the mortality from all causes for smokers was compared with that of nonsmokers during a 5-year observation period. The two groups were part of the intensive treatment (stepped care). In the largest subgroup, patients with diastolic blood pressure values between 90 and 104 mmHg, the total mortality (not adjusted for age) after 5 years was 8.1% for the 1,383 smoking hypertensive patients and only 4.6% for the 2,411 nonsmoking hypertensive patients. The mortality from all causes for smoking hypertensive patients is twice as high as for nonsmoking hypertensive patients, despite intensive antihypertensive treatment (mortality from all causes).

3. Smoking and Diabetes

Clinically, the danger for a diabetic patient who smokes is well recognized as far as myocardial infarction and intermittent claudication are concerned. Unfortunately, no long-term epidemiologic study has systematically examined the issue of a potential interaction effect. The relatively large University Group Diabetes Program (UGDP) study represents an example of an opportunity missed. The UGDP study showed an increased coronary mortality in diabetic patients treated with tolbutamide. However, two important factors were not taken into account when the results were made public:

1. The patients were not asked about their smoking habits. POFFENBARGER and SCOTT (1980) described the case of a female diabetic patient who developed significant cardiac arrhythmias when she used tolbutamide while smoking cigarettes, but did not develop them if she did not smoke while taking the drug.
2. The majority of the patients in the UGDP study, 70%, were women. Seen retrospectively, it is difficult to understand why only 30% of the diabetics allowed to participate in the study were men. For reasons that still escape full explanation, women with diabetes are more likely to die from ischemic heart disease than nondiabetic women compared with a much smaller difference between male diabetics and nondiabetics. This finding first reported from the Framingham study was confirmed in the Evans County study (HEYDEN et al. 1980). The results of the UGDP study therefore need to be qualified in view of these two aspects, smoking and gender.

Against this background one becomes aware of the complexity of studies in ex-smokers.

Experiences of Ex-Smokers

The largest and longest prospective study on the effects of smoking cessation comprised over 50,000 American veterans. (Dr. Harold Dorn initiated the study on 1 January, 1954, with males between 55 and 64 years of age and concluded 16 years later on 31 December, 1969.)

Mortality from all causes among ex-smokers who quit smoking less than 5 years ago was found to decrease right in the middle between the mortality curves of current smokers (highest rates) and nonsmokers (lowest rates). The mortality from all causes of ex-smokers is thus clearly less than that for current smokers. However, the total mortality among ex-smokers could not be expected to be lowered to that for nonsmokers, since some of the ex-smokers were forced to quit owing to smoking-related diseases such as angina pectoris, myocardial infarction, emphysema, chronic bronchitis, intermittent claudication, bladder cancer, and stomach ulcers. Once smokers have quit for at least 15 years, the mortality curve of ex-smokers completely resembles that of nonsmokers.

II. Obesity

The results of some epidemiologic studies have puzzled countless physicians in the past. Weight, in particular overweight, cannot be regarded a risk factor for the

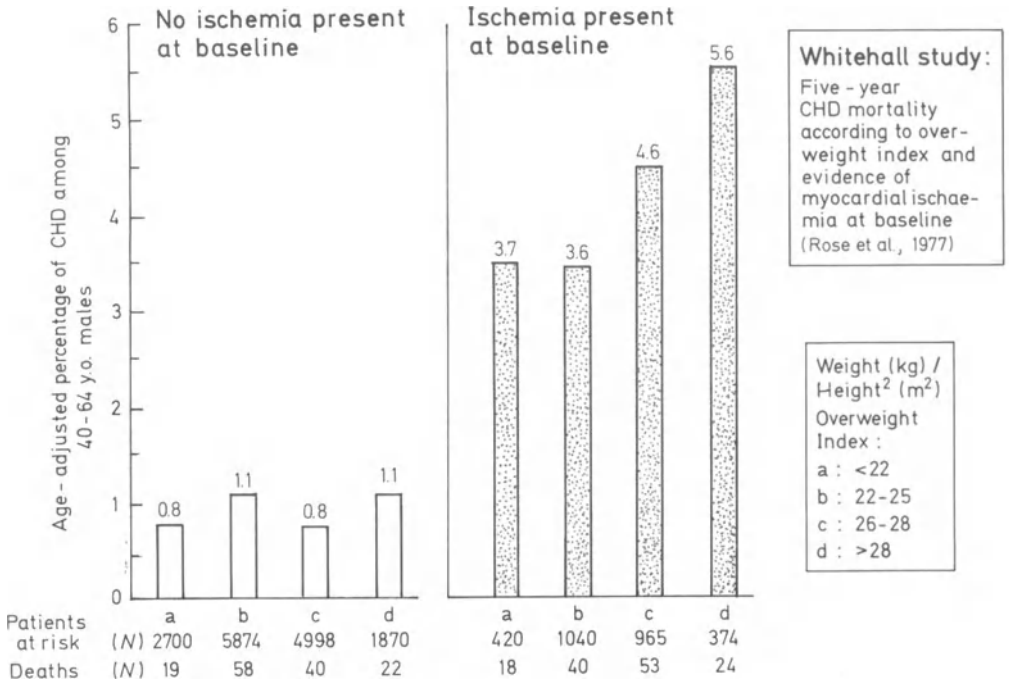

Fig. 5. 5-Year CHD mortality as a function of overweight index and evidence of myocardial ischemia at baseline. Overweight index = weight (kg)/height^2 (m^2); values of index are: *A* <22; *B* 22–25; *C* 26–28; *D* >28. ROSE et al. (1977)

development of ischemic heart disease. Mention was made in Sect. D.II.8 of findings from the Evans County white male population. *Nonsmoking* normal weight, moderately overweight, and obese men have a similar low risk for myocardial infarction. ROSE et al. (1977) presented data from the British Whitehall study among government employees. Divided in four subgroups ranging from normal to severely overweight, the 5-year follow-up of this population demonstrated no increase in incidence of CHD with increasing weight. However, this was only true for persons who were free of overt CHD (i.e., normal ECG) at baseline. A different picture emerged when patients were followed in increasing weight categories, patients who had already pathologic ECGs at baseline. With each increment in weight classification, there was an increase in CHD mortality (Fig. 5).

Crude estimates would associate obesity with a number of risk factors, i.e., 85% of the noninsulin-dependent (so-called adult onset) diabetics are overtly obese. Approximately 70% of gout patients are moderately to severely overweight. The HDFP revealed that 60% of the hypertensive men and women were more than 20% above their desirable weight. An equal percentage of the obese population is thought to have lipid abnormalities, ranging from hyperlipoproteinemia type IV, to lowered HDL levels which, in turn, are usually associated with high serum triglyceride levels. LDL cholesterol levels are mostly elevated, while total cholesterol is commonly found to be normal or only mildly increased, reflecting

Table 16. Peripheral insulin delivery in diabetics and nondiabetics (SKILLMAN and TZAGOURNIS 1982)

	Insulin (IU/day)
Nondiabetics	
Lean	31
Massively obese	114
Diabetics	
Juvenile	4
Lean adult	14
Obese adult	46

the opposing directions of HDL and LDL cholesterol levels. Additionally, physical inactivity is the most frequent condition seen among the obese, contributing heavily to the development of obesity in the first place. Reviewing those five primary and secondary risk factors for ischemic heart disease and their prevalence in the obese population, it remains an enigma why obesity is not emerging as a risk factor in its own right in the majority of epidemiologic studies.

The present medical director of the Framingham study, Dr. William P. Castelli, was interviewed by E. R. SHALL (1982):

> A more startling finding received considerable press attention when first reported 2 years ago. According to the data, the thinnest Framingham subjects died youngest, even before those who were grossly overweight. This led to speculation that a few excess pounds could prolong life. But Castelli points out, there was a confounding factor that, once discovered, quickly overturned this theory. Shortly before death many people lost a lot of weight. The abnormally low weights which had been measured shortly before death were skewing the curve. Once this group was weeded out, the statistics confirmed the common belief that thin people tend to outlive their fat counterparts. It is equally interesting to observe the ease with which weight reduction, even of modest degree, can eliminate risk factors – which should not come as a surprise to those who have witnessed the decline of risk factors (diabetes, hypertension, hyperlipidemia, and physical inactivity) in the postwar years of WW II in European countries.

1. Diabetes and Weight Reduction

The importance of weight control in the diabetic and in the prediabetic individual (Table 16) is shown in the peripheral insulin delivery among a large number of normal persons, and type I diabetic (insulin-dependent) and type II diabetic (noninsulin-dependent) patients, studied by Genuth (see SKILLMAN and TZAGOURNIS 1982).

In order to increase the number of insulin receptors one must: (a) decrease total calories; (b) reduce weight; (c) increase exercise; and (d) use sulfonylurea drugs in the noninsulin-dependent type II diabetic patients. Their diabetes is a receptor deficiency and they should not be mistreated with insulin.

2. Hypertension and Weight Reduction

It is common knowledge that weight reduction leads to lower blood pressure and, in combination with a sensible NaCl restriction to less than 5 g/day (preferably

Table 17. Relationship between weight changes and changes in serum glucose, cholesterol, and uric acid over 2 years under diuretic antihypertensive medication (HEYDEN et al. 1985)

Weight change (kg)	Percentage of participants	Casual glucose			Cholesterol			Uric acid		
		Baseline	2-Year	Change (%)	Baseline	2-Year	Change (%)	Baseline	2-Year	Change (%)
Stepped care										
−9 or more	6.3	121	118	− 2.48	230	221	−3.91	6.40	6.57	2.66
−8.5 to −3	32.2	114	116	1.75	239	232	−2.93	6.14	6.78	10.42
−2.5 to +2.5	44.9	110	113	2.73	235	231	−1.70	5.99	6.68	11.52
+3 to +8.5	14.8	108	113	4.63	229	230	0.44	6.05	6.81	12.56
+9 or more	1.8	109	121	11.01	232	231	−0.43	6.15	7.14	16.10
Total	4,796[a]									
Referred care										
−9 or more	5.4	123	124	0.81	238	223	−6.30	6.39	6.43	0.63
−8.5 to −3	26.2	115	116	0.87	237	228	−3.80	6.12	6.38	4.25
−2.5 to +2.5	48.4	110	113	2.73	236	230	−2.54	6.05	6.42	6.12
+3 to +8.5	17.7	107	112	4.67	232	228	−1.72	6.05	6.50	7.44
+9 or more	2.3	114	123	7.89	227	224	−1.32	6.13	6.69	9.14
Total	4,455[a]									

[a] The total number (not %) of patients who had blood pressure and these laboratory measurements recorded at baseline and at the 2-year follow-up

Table 18. Relationship between weight changes and blood pressure changes after 2 years on diuretic antihypertensive therapy (HEYDEN et al. 1985)

Weight change (kg)	Percentage of participants	Diastolic blood pressure			Systolic blood pressure		
		Baseline	2-Year	Change (%)	Baseline	2-Year	Change (%)
Stepped care							
−9 or more	6.3	101	81	−19.80	161	125	22.36
−8.5 to −3	32.2	101	84	−16.83	160	127	−20.63
−2.5 to +2.5	44.9	101	85	−15.84	158	128	−18.99
+3 to +8.5	14.8	102	86	−15.69	160	132	−17.50
+9 or more	1.8	102	86	−15.69	158	131	−17.09
Total	4,796[a]						
Referred care							
−9 or more	5.4	102	88	−13.73	160	137	−14.38
−8.5 to −3	26.2	102	90	−11.76	160	141	−11.88
−2.5 to +2.5	48.4	101	91	− 9.90	157	141	−10.19
+3 to +8.5	17.7	101	93	− 7.92	155	142	− 8.39
+9 or more	2.3	103	95	− 7.77	160	147	− 8.13
Total	4,455[a]						

[a] The total number (not %) of both groups represents those patients who had blood pressure and all laboratory measurements recorded at baseline and at the 2-year follow-up

3 g/day), to complete normalization. However, we feel the role of weight reduction in antihypertensive drug treatment is not yet recognized in its full potential. We have recently analyzed the impact of weight changes among hypertensive patients in the HDFP on biochemical parameters known to be influenced in long-term therapy with diuretic drugs. The findings from this 2-year study suggest that the increases of uric acid, glucose, and cholesterol associated with most diuretics may be prevented or attenuated by concurrent weight loss. Specifically, among stepped care patients, more rigorously treated with diuretic drugs than referred care patients, there was a 10% increase in serum uric acid (SUA) levels over a 2-year observation time. The increase in SUA rose in a stepwise fashion from 2.6% to 16% with increasing weight gain (Table 17). But weight losers showed a reduction of SUA levels from baseline.

Mean serum cholesterol was 235 mg/dl at baseline and declined at 2-year follow-up to 231 mg/dl in stepped care. The percentage decline was 2.5% for all stepped care patients and there was a slight, but consistent, trend of greater decrease with greater weight loss, reaching 4% from baseline levels in stepped care participants who lost more than 9 kg. Casual glucose increased at approximately 4% in the stepped care treatment group from baseline to 2-year follow-up and rose in stepwise fashion with increasing weight gain to 11% in patients who gained more than 9 kg, but, again, weight loss was actually associated with a decrease of glucose levels from baseline.

We also observed a stepwise decrease in diastolic blood pressure at 2-year follow-up in stepped care patients, ranging from 86 mmHg for participants gaining

9 kg or more to 81 mmHg for those losing 9 kg or more. Similar findings were obtained for systolic blood pressure with a stepwise increase in 2-year systolic blood pressure with each decrease in amount of weight gained or of increasing weight loss (Table 18).

It may be recalled that the HDFP was not designed as an experiment in weight changes. Weight losses occurred spontaneously, as Table 17 and 18 show, in a minority of this population, 32% losing between 2.5 and 8.5 kg, and 6% losing 9 kg and more in stepped care (26% and 5%, respectively, in referred care). However, the advantage of large numbers in this trial (4,796 patients in stepped care and 4,455 in referred care) has allowed us to make an extraordinary observation. While the changes in uric acid, cholesterol, glucose, and systolic as well as in diastolic pressure may seem small in ordinary clinical interpretation, the percentage changes over 2 years represent the statistical mean of several thousand patients. Here, then, is a biologically important observation, the significance of which is made even stronger considering:

1. The monotonic progression of laboratory and blood pressure levels with weight change; i.e., there is a uniform stepwise change of blood pressure and biochemical values from maximum weight loss to maximum weight gain.
2. A remarkable regularity of the stepwise relationships in both stepped care and referred care.
3. The consistent findings of this trend for all five parameters is further evidence of the importance of weight changes.

3. Hyperlipidemia and Weight Reduction

We have recently shown (NELIUS et al. 1982) that a short-term modest weight loss of only 9 kg among 90 obese women and 12.5 kg among 39 obese men resulted in normalization of highly abnormal lipid values. Thus, total cholesterol decreased from 241.6 to 198.8 mg/dl, which represents a decline of 43.6 mg/dl (−18%). Triglycerides, as expected, declined from 192.0 mg/dl to a normal level of 129.1 mg/dl (−65.2 mg/dl or −34%!). LDL cholesterol paralleled changes seen in total cholesterol: from 159.1 mg/dl to 129.8 mg/dl (−29.9 mg/dl or −19%). Very low density lipoprotein (VLDL) levels came down from 35.2 to 25.4 mg/dl, representing a decrease of 10.0 mg/dl (−28%). A significant relationship was demonstrated between the amount of weight loss and increase in HDL cholesterol levels from pretreatment to posttreatment ($P=0.05$). This latter finding is of considerable interest since the obese patient is usually found to display very low HDL cholesterol levels; in our female patients 48 mg/dl and in our male patients 34 mg/dl at baseline. MRFIT data, published in an interim report in 1981 after 4 years, are relevant in this context. The greatest increase of HDL cholesterol over 4 years was reported in those 1,391 men who lost a minimum of 4.5 kg. But it is equally relevant that the 4-year interim report (CAGGIULA et al. 1981) has documented for the first time the confounding factors which may influence HDL levels among smokers. "At baseline, smokers as a group reported higher intakes of total calories, saturated fat, dietary cholesterol, and alcohol, and lower intakes of polyunsaturated fat than non-smokers." The authors presented a table where

substantial increase in HDL cholesterol was evident only in the nonhypertensive subgroups, and the greatest increase was noted in the smokers who quit during the first 4 years *and* lost 4.5 kg.

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CHAPTER 2

Pathophysiology of Coronary Circulation and of Acute Coronary Insufficiency

W. SCHAPER, J. SCHAPER, and H. M. HOFFMEISTER

A. Regulation of Coronary Blood Flow

I. Overview

It has been known for a long time (ANRER 1926; GREGG 1950; GREGG and FISHER 1963; ALELLA 1954; GOLLWITZER-MEIER and KROETZ 1940) that the heart regulates its own blood supply according to its own needs in a very precise way. The classical way to test whether blood flow is regulated by a control system is to produce a step change in one of the two variables (pressure or flow) and to observe the response of the system. In the case of stable conditions for myocardial oxygen consumption, a step change of perfusion pressure (i.e., a sudden increase) will at first result in an increased blood flow, but this response is of short duration; blood flow returns to its previous value in spite of the elevated perfusion pressure (Fig. 1). The system resists the change, it does not tolerate overperfusion, and it is tightly controlled by a feedback control system. This is, of course, only valid when the sudden change in pressure is artificially imposed and not generated by the heart itself. The latter condition would have required more oxygen and hence a decreased vascular resistance. These experiments are best carried out in isolated hearts not performing any external work. The fact that the control system works so perfectly in an isolated heart suggests that regulation of blood flow takes place in the heart itself and not elsewhere, i.e., not in the autonomic or central nervous system. We know that the autonomic nervous system has some modulating influence on regulation. Its influence seems to be indirect in normal physiology, but it may play a more direct role in pathophysiologic states. The indirect influence is easily felt during states of altered emotions, i.e., when psychogenic tachycardia leads to increased cardiac metabolism and hence to increased coronary blood flow. The autonomic modulation becomes quite obvious in pharmacologic studies when inotropic actions of catecholamines are blocked, but the vascular actions are not. Blockade with propranolol and infusions of norepinephrine at the same time lead to coronary vasoconstriction (FEIGL 1983) which overrides metabolic autoregulation.

The nature of the control system, its operation, and the transmitters between cardiac metabolism and vascular tone are unknown. The close correlation between blood flow and oxygen consumption and the relative constancy of coronary venous PO_2 (XHONNEUX and SCHAPER 1969) focused the attention of nearly all investigators on oxygen as the most important agent of regulation (Fig. 1). All too often it is neglected that certain oxidation fuels (or the lack of them) cause

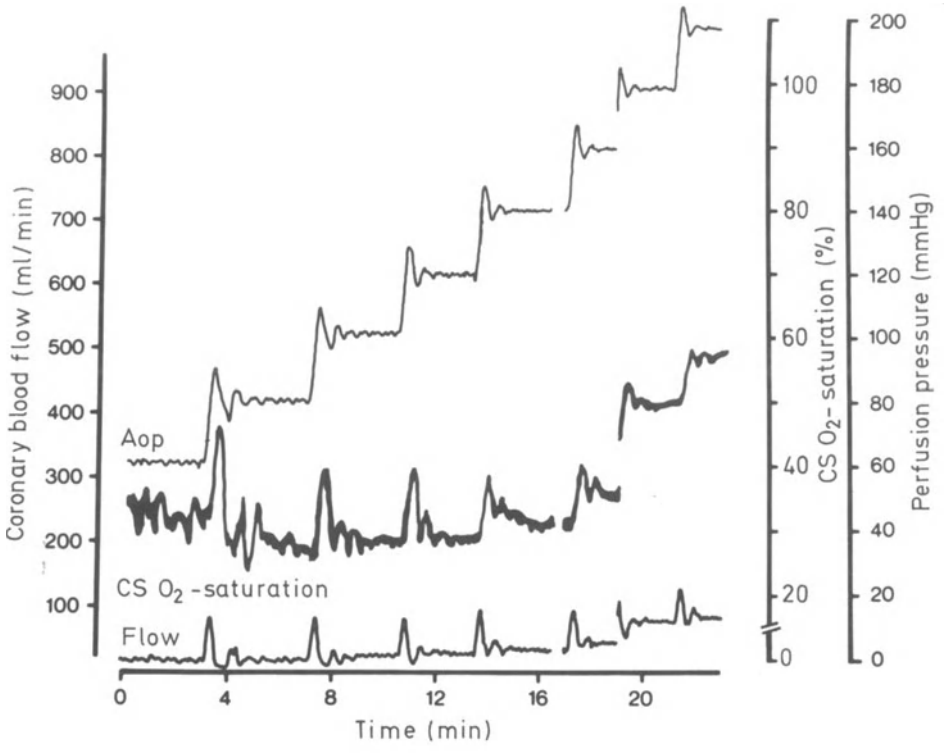

Fig. 1. Autoregulation in an isolated blood-perfused dog heart. When blood pressure (AoP) is stepwise increased, blood flow shows only a transient rise and a quick return to previous flow levels. Only at pressures above 140 mmHg does blood flow tend to increase together with coronary sinus (CS) O_2 saturation

autoregulatory responses. A sudden drop in blood glucose by insulin overdosage causes coronary vasodilation (K. J. HENRICHS 1983, personal communication). Substrate-free perfusion of isolated hearts leads to a progressive coronary vasodilation when endogenous stores of glycogen are nearing exhaustion. An abundance of fatty acids in diabetic hearts also causes coronary vasodilation. Changes in pH, PCO_2, and the osmolality of the extracellular space cause coronary vasomotion, and all these modulating influences are observed in the abundant presence of oxygen. As already said, there is no unifying theory explaining the regulatory system and its modulating influences.

The refinement of biophysical research tools has even cast doubt on the nature of the effector organ of regulation. The classical viewpoint was that arterioles and small arteries, i.e., the class of vessels between 10 and 100 μm, regulate blood flow by their change of tone. The number of these vessels, their cumulative diameter, and the number of their muscle layers makes these vessels ideally suited to produce large changes in blood flow by small changes in contractile energy which, in engineering terms, is an amplification effect. More recent observations (HENQUELL and HONIG 1976) claim that capillaries may significantly contribute to

regulation. Contractile material in endothelium may completely occlude the lumen of the capillary, and precapillary sphincters exert a similar effect. Both reactions have been observed in the vascular periphery, i.e., subcutaneous vessels of the rabbit and omentum of cold- and warm-blooded animals (WEIGELT et al. 1980), but not yet in the coronary circulation. Some authors (HONIG et al. 1980; HONIG and ODOROFF 1981; HONIG and BOURDEAU-MARTINI 1973) believe that, under conditions of low myocardial oxygen consumption, not all capillaries are open and "recruitment" takes place in coronary vasodilation. Although the coronary microcirculation was made visible in vivo in small rodent hearts by BING et al. (1972), HONIG and BOURDEAU-MARTINI (1973), TILLMANNS et al. (1976), and STEINHAUSEN et al. (1978) there is no clear-cut evidence for recruitment of "dormant" capillaries as a mechanism of coronary vasodilation.

The large epicardial coronary arteries have recently become the focus of attention because spasm may be a cause of anginal attacks and of myocardial infarction. Studies by BASSENGE (1984) have shown that the epicardial coronary arteries of the dog change their diameter with blood flow, i.e., they become somewhat larger with increased flow and vice versa. It is believed that this reaction is mediated by endothelium which, under the influence of viscous drag, releases a relaxing agent into the smooth muscle layer of the tunica media.

II. Metabolic Autoregulation and the Adenosine Hypothesis

The control system which resists changes in flow with a stepwise increase in pressure at unchanged $M\dot{V}O_2$ and which regulates blood flow according to the energetic requirements of the heart muscle is believed to be linked with adenine nucleosides, i.e., adenosine. Independently, GERLACH et al. (1963) and BERNE (1963) showed that ATP breakdown in the heart proceeds from AMP to adenosine rather than from AMP to IMP as in skeletal muscle (BERNE 1963). The observation by DRURY and SZENT-GYORGI (1929) showed adenosine to be a potent coronary vasodilator. It was implied that ATP is converted into adenosine in ischemia or with the sudden onset of increased cardiac work load. This hypothesis was deceptively simple and elegant because it linked mitochondrial metabolism or ATP cleavage at the sarcomere level with coronary vascular tone. However, many important arguments mitigate against the adenosine hypothesis. It was shown that the enzyme 5′-nucleotidase, which converts AMP to adenosine and inorganic phosphate, is inhibited by ATP (BURGER and LOEWENSTEIN 1975). Significant adenosine production will therefore only occur at low ATP levels. This was, however, not a very conclusive argument because it was observed that adenosine is indeed produced in measurable quantities early in ischemia when there is very little fall in ATP. The situation became even more confounded when it was discovered that ADP also inhibited 5′-nucleotidase in vitro, but this was also obviously not a major argument because adenosine was measured at ATP and ADP levels which in vitro would have inhibited 5′-nucleotidase. It became quite obvious that adenosine production occurs in a compartment which is inaccessible to the inhibiting ATP and ADP concentrations in mitochondria and at sarcomeres and also inaccessible to cytosolic adenosine deaminase, i.e., adenosine was believed only to exist in the extracellular space.

Earlier work unrelated to the coronary problem had shown (BRAKE et al. 1975) that 5′-nucleotidase is a "marker enzyme" of cell membranes and this information revived interest in the adenosine hypothesis although the elegant direct link between cardiac muscle metabolism and coronary vascular tone had vanished: adenosine may be produced at the cell membrane and in the extracellular space, but information has to be passed from the locus of metabolism to the locus of adenosine release. DEPIERRE and KARNOWSKI (1974) discovered that 5′-nucleotidase is an "ectoenzyme" with the active sites sticking out from the cell into the extracellular space and exogeneous AMP is easily converted into adenosine and inorganic phosphate. The blockade of this ectoenzyme with a derivative of ADP (AOPCP) (FRICK and LOEWENSTEIN 1978) inhibited adenosine formation from exogenous AMP in the guinea pig heart, but hypoxic perfusion and adenosine accumulation and release remained unchanged. This meant that the ecto form of 5′-nucleotidase had nothing to do with adenosine formation associated with coronary autoregulation with the possible exception of the rat heart (FRICK and LOEWENSTEIN 1978). Difficult problems also arose from pharmacologic experiments. Many years ago, KÜBLER et al. (1970) showed that the coronary vasodilator dipyridamole, which potentiated exogenous adenosine, inhibited the transport of adenosine out of globally ischemic hearts. Kübler reasoned that coronary vasodilation cannot be transmitted by adenosine when agents which inhibit adenosine transport out of the cell and hence reduce the adenosine concentration at the vascular receptor site not only fail to cause coronary vasoconstriction, but are rather potent coronary vasodilators themselves. BERNE (1980) countered this argument by the equally well-known effect of dipyridamole and several other drugs on the inhibition of inward transport. When inward transport of adenosine is more inhibited than outward transport, the effect of concentration at the receptor site is increased. Although this asymmetric transport inhibition remains speculative, there are experiments to support this hypothesis. Another pharmacologic experiment also casts grave doubt on the adenosine hypothesis: blockade of the adenosine receptor with xanthine analogs (theophylline, aminophylline) blocked the actions of exogenous adenosine, but not physiologic test responses like hypoxic vasodilation or reactive hyperemia (AFONSO and O'BRIEN 1970).

The inconsistencies of the one-compartment systems (i.e., the earlier intracellular and the later extracellular production of adenosine) stimulated the search for the site of the intracellular adenosine compartment. Work in a number of laboratories showed that adenosine exists intracellular as a complex with the enzyme *S*-adenosylhomocysteine hydrolase (SAH hydrolase). Although the adenosine bound to this enzyme can serve as a substrate for the synthesis of *S*-adenosylhomocysteine when the second substrate, L-homocysteine, is supplied (SCHRADER et al. 1981), it appears to be insensitive to hydrolysis by the high adenosine deaminase activity present in dog heart muscle. In the dog heart, the intracellular compartment accounts for over 90% of the cardiac adenosine pool (SCHRADER et al. 1981). Concentrations of the extracellular compartment, about 0.2 μM, are below the threshold of adenosine's coronary vasoactivity, which explains why sustained intracoronary infusion of adenosine deaminase and/or the adenosine receptor antagonist theophylline do not affect basal coronary resistance (E. O. FEIGL, personal communication).

Recent work by SCHÜTZ, SCHRADER, and GERLACH (1981) showed (in addition to the presence of ectonucleotidase) intracellular 5′-nucleotidase. Adenosine so produced is bound to SAH hydrolase and released into the extracellular space in response to hypoxia. The difficulty with this hypothesis is that these authors could not show directly that increased adenosine levels in hypoxia originated indeed from the SAH fraction. Additionally, SCHÜTZ et al. (1981) showed that blockade of outward transport of adenosine by 6-(4-nitrobenzylthio)purine riboside (NBMPR) increased intracellular adenosine concentrations in hypoxia, but failed to change the vasodilator response to hypoxia.

Furthermore, when L-homocysteine is offered during hypoxia, adenosine is rapidly converted to *S*-adenosylhomocysteine, but again the vasodilator response is unimpaired. Our own studies with L-homocysteine (HENRICHS et al. 1982) point in the same direction: the reactive hyperemia response after coronary occlusion, varying between 5 and 20 s, proceeds with and without L-homocysteine (thiolactone form), but an area reduction of 30% was noted with homocysteine, indicating that ischemia-related adenosine production is responsible for about 30% of the reactive hyperemia response. Similar findings were observed with intracoronary infusions of adenosine deaminase (HENRICHS et al. 1984 a) which also reduced the reactive hyperemia response by 30%.

Our own studies in isolated guinea pig hearts (TROMPLER et al. 1983) make it very unlikely that hypoxic vasodilation is causally related to adenosine. We tested first the vasodilator response of a pharmacologically untreated isolated heart to hypoxia and subsequently added L-homocysteine to trap adenosine intracellularly, added NBMPR to block outward adenosine transport, added further theophylline to block the vascular receptor, and perfused the heart with a buffer containing adenosine deaminase. None of these maneuvers alone, in combination, or all together, significantly altered the vasodilator response to hypoxia.

Neither reactive hyperemia following coronary artery occlusion nor hypoxic perfusion of isolated hearts is a physiologic situation and extrapolation to known physiologic reactions may prove inadequate. A recent very elegant experiment by OLSSON and GEWIRTZ (1984) used a situation of pathophysiologic relevance to test the adenosine hypothesis: coronary artery stenosis produces peripheral coronary vasodilation to maintain blood flow. If adenosine deaminase is infused before induction of a stenosis, one would expect a diminished vasodilator response if adenosine were the mediator. However, peripheral vasodilation proceeded as if no deaminase was given, making it very unlikely that adenosine plays a role in this type of metabolic autoregulation.

III. Alternative Hypotheses Explaining Metabolic Autoregulation

1. Chemoreceptors

LOCHNER et al. (1956) and LOCHNER and NASSERIE (1959) were probably the first to suggest that the regulation of coronary blood flow is controlled by chemoreceptors similar to those in the glomus caroticum. Injections of nicotine, lobeline, and cyanide into the coronaries induced vasodilation in the same range of concentrations that produced reflex activity originating from the glomus. From the point of view of efficiency, an oxygen sensing mechanism outside the myocardial cell

is only second best because the metabolic rate of the myocyte has to be sensed by this separate structure and transformed into a signal for the blood vessels. This would lengthen the chain of command with the inherent danger of faulty information transfer. Two different structures were implied for the extracellular chemoreceptor, the vascular smooth muscle cell itself and a specialized perivascular cell (BORGERS et al. 1971) equipped with the enzymes of purine nucleotide breakdown and synthesis.

HONIG and BOURDEAU-MARTINI (1973) advocated the precapillary sphincter cell (smooth muscle) as a likely candidate for the oxygen sensor. With sufficient oxygen the smooth muscle contracts, the capillary empties, and the tissue PO_2 falls, which causes smooth muscle relaxation and capillary perfusion. This in turn will lead smooth muscle contraction, etc. The difficulty with this hypothesis is that the existence of precapillary sphicters is unproven in the mammalian heart. Regulation as proposed by this theory would proceed according to the needs of vascular smooth muscle rather than providing for cardiac muscle. The possibility that both metabolic rates are identical is indeed very remote. Published values (PAUL 1980) of oxygen consumption of maximally stimulated vascular smooth muscle (0.5 $\mu mol\ g^{-1}\ min^{-1}$) differ by a factor of 30 from that of maximally stimulated isolated rat heart preparations (15 $\mu mol\ g^{-1}\ min^{-1}$). Our own work (BORGERS et al. 1971) has shown that the enzymes of purine nucleotide degradation and salvage are most active in a perivascular cell with unusual features. This cell is in close contact with the smooth muscle of small arterioles and of capillaries. The area of contact is suggestive of a synaptic cleft (Fig. 2) and the cell body sends

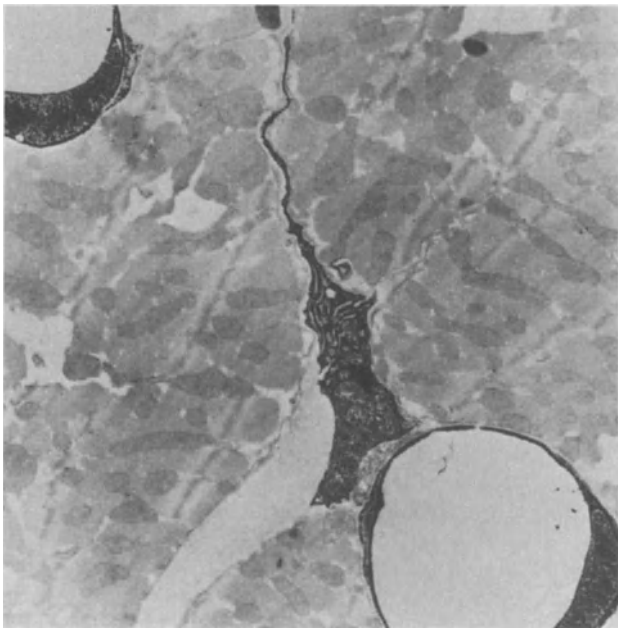

Fig. 2. A pericyte with a long "dendritic" extension between two myocardial cells is stained for nucleoside phosphorylase. Endothelium also shows a strongly positive reaction

very long dendritic extensions into the myocardium. These dendritic extensions of several perivascular cells come together and form a network which bridges intercapillary distances. It is tempting to speculate that these extensions which form a web around myocytes are the oxygen sensors and that the signal that is produced in the transduction process becomes operational in the synaptic cleft. The very high enzymatic activity in these cells suggests a purinergic receptor and transmitter. We therefore suggested that the adenosine hypothesis is indeed applicable, but the origin and mechanism of action of adenosine are confined to the purinergic perivascular cell. The differences between exogenous (injected) adenosine and endogenously released adenosine can also be explained. Exogenous adenosine reaches smooth muscle mainly via the endothelium and it is very likely that injected xanthines (theophylline, aminophylline) block mainly the receptors at the endothelial side of the smooth muscle layer. We believe that xanthines do not reach the synaptic cleft, but when they do the local concentration of adenosine is much too high to be effectively blocked. Experiments by SCHRADER et al. (1977) with protein-bound AMP support our view: since the protein complex is too large to leave the vascular compartment, its measured action (vasodilation) was achieved by attaching to the receptor from within the vessel. The fact that the complex left the vascular compartment uncleaved is another piece of evidence: if the complex had appeared in the interstitial space it would have been attacked by ecto 5′-nucleotidase which was not the case. It is quite conceivable that coronary endothelial cells transmit the message (adenosine, AMP) to underlying smooth muscle because BORGERS et al. (1971) as well as NEES et al. (1980) and RUBIO and BERNE (1980) have shown the extraordinary activity of endothelial nucleoside phosphorylase as well as other enzymes of purine nucleotide breakdown and synthesis. In conclusion, we arrived at a hypothesis which assumes two types of receptor, i.e., an endovascular that senses injected or blood-borne transmitters which can be blocked by injected antagonists. Physiologic regulation (work hyperemia, hypoxic dilatation) is the task of perivascular receptor cells which sense myocardial PO_2 with their long dendritic extensions and which most probably use adenosine as a transmitter which cannot be easily blocked because of the high concentrations in the synaptic cleft.

2. The Autonomic Nervous System

Sympathetic nerve stimulation and injections of catecholamines lead to both increased contractile cardiac activity and increased coronary blood flow. If the latter effect is blunted by β-blocking agents, these stimuli lead to coronary vasoconstriction (HOLTZ et al. 1976, 1977). With these experiments, it was shown that coronary arteries are not fundamentally different from those of the remainder of the body, but the practical importance of sympathetic α-mediated vasoconstriction remains nuclear. FEIGL (1983) believes that sympathetic vasoconstrictor tone may be necessary to balance metabolic vasodilation. Intracoronary injections of norepinephrine causes metabolic net vasodilation, but venous oxygen tension falls, indicating an even greater myocardial oxygen extraction. This "checking" mechanism does not limit oxygen supply in such a way that the heart produces lactate. It is difficult to envisage the role of the sympathetic nervous system under more

physiologic circumstances, e.g., no stellate stimulation, no intracoronary norepinephrine. Experiments by HOLTZ et al. (1977) with regional sympathetic denervation of certain areas of the heart with 6-hydroxydopamine showed significantly, but not markedly higher blood flows in the denervated areas. α-Blocking agents such as phenoxybenzamine abolished these differences. This experiment suggested the presence of an α-adrenergic constrictor tone in the normal heart under basal conditions which could be blocked with α-blocking agents or with chronic denervation. On the other hand, phenoxybenzamine alone is not known to dilate coronary arteries. In a similar experiment, CHILIAN et al. (1981) produced a similar regional denervation by local phenol application. This type of denervation (which included parasympathetic nerves) did not produce regional differences in coronary blood flow.

From a pathophysiologic point of view, it is of interest that BUFFINGTON and FEIGL (1981) demonstrated competition between α-receptor coronary vasoconstriction and metabolic autoregulation, even in the presence of coronary stenosis. The vasoconstrictor response was again not powerful enough to drive the heart into lactate production. Of some practical importance is the fact that so many patients suffering from coronary heart disease are under chronic medication with β-blocking drugs. Increased levels of catecholamines in these patients may increase the severity of their coronary stenoses, especially when they are treated with non-β_1-selective agents like propranolol. The role of catecholamines in the pathophysiology of the disease is, however, much more evident as an important cause of dangerous arrhythmias and by oxygen-wasting effects than by their influence on coronary tone. The beneficial role of β_1-selective blockers in these areas is hardly disputed.

B. Coronary Artery Stenosis and Spasm

I. Overview

It is known that coronary resistance vessels exhibit high basal tone, i.e., there is a large difference between blood flow at basal tone and blood flow at maximal coronary vasodilation. In a typical canine heart, minimal coronary resistance is 0.16 mmHg ml^{-1} min^{-1} per 100 g heart muscle, which means that at a perfusion pressure of 16 mmHg, 100 ml blood perfuse 100 g tissue or that at 160 mmHg the ratio of perfusion volume to tissue volume is 10:1 (SCHAPER et al. 1976) (under normal working conditions it is about 1:1 and under low basal conditions it is 0.5:1). It is therefore not surprising that coronary artery disease must be far advanced before it becomes symptomatic: peripheral coronary vasodilation compensates for the reduction in blood flow that would otherwise have been caused by the stenosis. It is not surprising that angina pectoris, the ischemia-related precordial pain, is usually felt for the first time during physical or emotional exertion, i.e., situations which cause a higher myocardial oxygen demand.

The concept of supply and demand and the assumption that atherosclerotic lesions are rigid flow-limiting structures was for a long time the prevailing view of clinicians and pathologists. This concept in essence was the thesis that blood flow through a rigid stenosis is fairly constant under most hemodynamic con-

ditions, but the demand for blood flow can vary widely. If stenotic blood flow changes at all it will decrease because most high-demand situations are associated with tachycardia which, because of the shortened diastolic intervals, decreases stenotic blood flow. This concept was supported initially by in vivo coronary cineangiography, but in recent years the rediscovery of coronary artery spasm has softened the views of the rather rigid concept of constant supply versus a variable demand. Not all atherosclerotic lesions of coronary arteries are rigid stenoses. About two-thirds of arterial narrowings do have some normal wall segments (HORT 1979) (see Fig. 2) and may hence participate in vasomotion. Dilating stimuli or drugs may increase the stenotic cross-sectional area and vice versa. Coronary artery spasm is reported to occur even in angiographically normal coronary arteries. The frequency of occurrence of coronary artery spasm in normal and stenosed coronary arteries is a matter of dispute. Angiographers report as little as 2% (ARBOGAST and BOURASSA 1973) and as high as a 12% (GENSINI 1978) incidence of spasm. Some believe that a spastic component plays a role in all patients with coronary heart disease (CHIERCHIA et al. 1978). It looks as if clinical coronary cardiology, like Reaganomics, has switched to supply-side economics.

The widening of eccentric (elastic) stenoses under the influence of vasodilating drugs is also a matter of dispute and may be a problem of the reference base. Coronary artery spasm as a pathophysiologic concept underlying angina pectoris and infarction has had an interesting history. A symposium on angina pectoris held in Vienna under the chairmanship of WENCKEBACH (1924) presented three views on the etiology of angina. The pathologists found a very high association between coronary artery stenoses at autopsy and angina before death. However, most clinicians believed that angina was caused by coronary artery spasm because of the association with anxiety states. Wenckebach himself believed that it was a disease of the aorta because surgical removal of the aortic depressor nerve "cured" the symptom in most patients. Although this proved not to be a tenable viewpoint, WENCKEBACH reported a few observations that are of interest even today. First, angina pectoris was a rare affliction in 1924: Wenckebach observed only a handful of cases in 10 years. He reasoned that the cause of the symptom cannot be spastic or stenotic coronary artery narrowing because that would cause myocardial ischemia and ischemia would lead to failure. He differentiated his anginal patients from those with latent failure by walking with the patient briskly around the hospital block: those with a "typical" angina did not get dyspnea, i.e., no cardiac failure and hence no ischemia. We must conclude from this observation that WENCKEBACH probably selected exclusively primary spastic angina. Another interesting observation in 1924 was that this type of angina can be provoked by ergot alkaloids. The concept of spasm as the origin of angina was probably influenced by the fact that nitroglycerin, a known antispasmodic agent, relieved angina. The spasm concept prevailed for a long time before studies by SCHLESINGER (1938) became accepted facts. Quantification of atherosclerotic coronary lesions by injection methods left little doubt that structural rather than functional narrowings of coronaries were the cause of angina and infarction. The spasm concept had a sizable following until the late 1950s and it influenced research and development of pharmaceutical laboratories. The duration of action of nitroglycerin was believed to be too short, and longer-acting coronary vasodilators, chemi-

cally unrelated to nitroglycerin, were developed. Dipyridamole (KADATZ 1969; BRETSCHNEIDER et al. 1959) was the first of these drugs, soon followed by chromonar (NITZ and PÖTSCH 1963), verapamil (FLECKENSTEIN 1983), lidoflazine (SCHAPER et al. 1966), nifedipine (VATER et al. 1972), and many others. The common feature of all of these drugs was their ability to increase coronary blood flow greatly without seriously increasing myocardial oxygen demand. Their mode of action varies widely, but nonetheless clinical efficacy was shown for all these drugs whether they inhibit transport of nucleosides (dipyridamole, lidoflazine, dilazep) or whether they block calcium channels (verapamil, nifedipine) or neither (chromonar) of these mechanisms of action.

During the era of constant supply versus variable demand, all coronary vasodilators became very unpopular in spite of their earlier proven clinical efficacy. Several of these drugs survived this period of "bad press" because they changed their label or name and/or proposed mechanism of action (verapamil, nifedipine, lidoflazine) or additional effects became more important like inhibition of platelet aggregation by dipyridamole. Greatly helped by cardiac Reaganomics (variable supply side by spastic component) these drugs and some newcomers again enjoy great popularity, especially after their introduction on the American market.

When the supply versus demand concept ruled, β-blocking agents were the drugs of choice because they helped to adjust demand to the constant supply by reducing myocardial oxygen demand and by blunting the cardiac response to physical activity (RAHN 1981). Needless to say, those who reject the supply and demand concept tend also to reject therapy with β-blockers, especially with propranolol, because these drugs might increase the spastic component by unmasking the α-tone (BUFFINGTON and FEIGL 1981).

II. Influence of a Coronary Stenosis on Myocardial Perfusion

As discussed in Sect. B.I, the influence of a coronary artery stenosis on coronary blood flow is felt only during the later stages of the disease because of the capacity of the peripheral coronary resistance vessels to dilate in compensation for the degree of stenosis. Milder narrowings, i.e., 50%–60% of the cross-sectional area, produce relative reductions in blood flow only at high levels of physical exertion. Very tight stenoses (80%–90% area reduction) produce angina pectoris at mild exertion and with the tachycardia of emotional disturbances. These figures are rough clinical estimates rather than exact measurements because, even with the most sophisticated X-ray equipment and modern contrast media, measurements of the tightness of a stenosis are plagued with large standard deviations (GOTTWIK 1982). But even if the measurements are more precise, the situation is hardly improved because we have no way to tell in the living human heart how much myocardium is supplied by the stenosed artery. A stenosis that produces symptoms may progress toward complete occlusion. The speed of narrowing is of great importance for the afflicted heart muscle: if the stenosing speed is low, usually a collateral circulation develops and upon complete occlusion collateral vessels supply the entire myocardium at risk. Myocardial infarction can be avoided altogether. If the stenosing speed is fast or sudden (thrombus formation), collaterals cannot

develop and infarction occurs. In some cases, the degree of stenosis remains stationary and clinicians define this state as "stable angina".

It is extremely difficult to estimate the amount of blood flow through a stenosis because blood flow in coronary arteries is pulsatile and viscous and inertial properties play an important role. For the description of dynamic flow models in arteries we need at least two dimensionless parameters, i.e., the Reynolds number ($\mathrm{Re} = Dv/\vartheta$) and the α parameter ($\alpha = \mathrm{Re}\sqrt{w/\vartheta}$), where D is the vascular diameter, v is a characteristic speed, ϑ is the kinematic viscosity, and w equals the rate of the pulsatile flow. Normal coronary arteries exhibit pulsatile but laminar flow at medium or high Reynolds numbers. Compared with other arterial regions and with the aorta, the coronary system is not very elastic and stenoses in particular can be envisaged as fairly rigid structures not exhibiting time- and pressure-dependent variations of diameter (LOGAN 1975).

Factors that influence blood flow through a stenosis are:
The minimal cross-sectional area in relation to that of the nonstenosed part of the same artery (tightness)
Angle of entry
Angle of exit
Length.

All these factors together cause a flow-related drop of pressure across the stenosis which has the same effect on myocardial perfusion as if the coronaries were perfused at a much lower perfusion pressure, i.e., effective perfusion pressure for the peripheral coronary bed is the poststenotic pressure. Among the listed factors influencing the pressure drop across a stenosis, the tightness is the most important and the length of the stenosis is of only minor importance. The angles of entry and exit are important because the steeper they are the more turbulent the flow becomes, which greatly contributes to the pressure drop.

Our own experiments with fixed stenoses (SCHAPER and SCHAPER 1981) produced by tissue-inert Teflon(polytetrafluoroethylene)rings have shown that the exit angle-related turbulence is of particular importance because the eddy currents and "deadwater" regions lead apparently to a demixing of the corpuscular components of blood which results in platelet aggregation and thrombus formation. We could show that in an animal model of chronic fixed-diameter stenosis (dog coronary artery), progression occurs until complete coronary artery occlusion owing to a steep exit angle of the stenosis. The whole process shows a constantly changing dynamic pattern of events because some coronary artery occlusions so produced became recanalized (Fig. 3). The most interesting phenomenon of this experiment is the observation that apparently fixed stenoses become progressive in the absence of classical risk factors. If the stenosis was relatively tight at the moment of implantation (the stenosis allowed only resting basal blood flow), all animals died within 3 days after implantation. If the stenosis was tightened only to the point that full coronary reserve was reduced to 50% (tested by reactive hyperemia), all arteries were found to be occluded 6 weeks after implantation, but infarctions were avoided owing to collateral development. These experiments point to the role of inhibitors of platelet aggregation in halting the progression of coronary lesions.

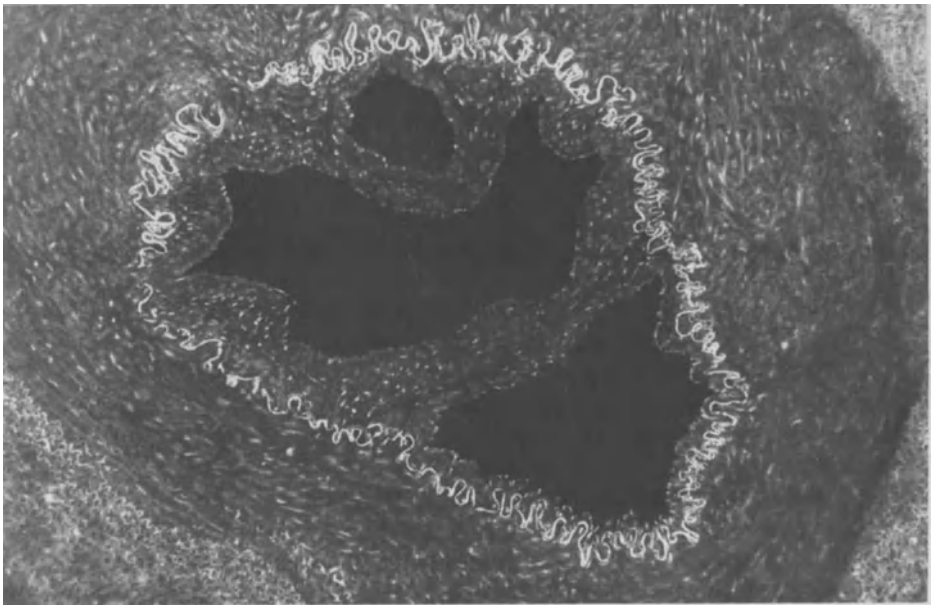

Fig. 3. A segment of dog coronary artery (*left circumflex*) that was taken distal from a fixed stenosis produced by a Teflon ring that had been completely occluded and was recanalized. The traversing "septa" contain tissue rich in nuclei, i.e., recanalization must have been a recent event

C. Influence of Underperfusion on the Myocardium

I. Influence on Substrate Metabolism

Under normoxic conditions, most mammalian hearts (DEJONG 1979) prefer fatty acids and lactate as substrates for oxidation. Special metabolic situations are handled by the heart with surprising ease: glucose, ketone bodies, and amino acids are also metabolized when these substrates are supplied in increased concentrations. Shortage or lack of oxygen changes the whole situation drastically and metabolism is shifted toward glycolysis, the most important source of ATP in anoxic states. Unlike skeletal muscle, the glycolytic capacity of heart muscle is limited and glycolysis is impeded by a number of factors. The large capacity of skeletal muscle for glycolysis must be viewed relative to its limited oxidative capacity, and it has to be borne in mind that, at times of lactate production, skeletal muscle enjoys high blood flows, whereas heart muscle in ischemia experiences a low blood flow which allows accumulation of lactate and other nonmetabolizable end products of metabolism.

During ischemia, the heart extracts much more glucose from what little residual blood flow there is, and it utilizes glycogen. Ischemia due to coronary artery occlusion or very severe coronary stenosis in patients is often associated with some residual perfusion, i.e., oxidative metabolism has not totally stopped. The

little oxygen that is delivered by residual flow is put to somewhat better use if glucose is oxidized instead of fatty acids, the difference being 13% (ATP:O ratio). It is therefore understandable that attempts were made to stimulate glucose oxidation as well as glycolysis by offering glucose (together with insulin) in patients suffering from acute coronary occlusion. The results of these trials have not been overwhelmingly convincing for a number of reasons:

End points of these studies are difficult to define because methods of measuring infarct size in living patients are very crude.

The rationale of these studies rested on not very solid assumptions: if there is perfusion (albeit lower than normal), glucose extraction, even at normal glucose blood levels, would suffice. If there is little or no perfusion (as in transmural infarction), the increase in blood glucose is pointless because of the transport problem. In this situation, the lack of oxygen overshadows all metabolic considerations. Restitution of blood flow is the only measure with a chance of success.

The glycogen reserves of heart muscle are limited and their mobilization in low flow ischemia is impeded by a number of factors:

The fall in pH inhibits phosphofructokinase (KÜBLER and SPIECKERMANN 1970; NEELY et al. 1975).

Lack of oxygen reduces the available NAD which is needed for proper functioning of glyceraldehyde-3-phosphate dehydrogenase. This is in part overcome by the fact that the conversion of pyruvate to lactate oxidizes NADH, which is the most important reason for lactate production in ischemia.

Lactate accumulates in low flow (or zeroflow) ischemia in the tissue and may contribute to tissue damage, although not via pH because the physical chemistry of lactate does not allow for a significant fall in pH (GEVERS 1977; PIPER 1979).

Lipolysis is activated in ischemia together with glycogenolysis in spite of the fact that there is no oxygen available for fatty acid oxidation.

A fraction of these fatty acids is resynthesized to triglycerides by "short-circuiting" of glycolysis at the level of glyceraldehyde-3-phosphate which furnishes at the same time energy (phosphate bond) and the glycerol backbone for triglyceride synthesis. This reaction may reduce the energy gain from glycolysis only to reduce the amount of fatty acids from activated lipolysis, a "nonsense" cycle which consumes energy in a nonproductive way and produces only glycerol, which cannot be metabolized by the heart because of the absence of the enzyme glycerate kinase (WIELAND and SYSTER 1957). A fraction of the newly synthetized triglycerides may also stem from fatty acids supplied by collateral flow. In any case, electron microscopic evidence exists for greatly increased triglyceride synthesis in surviving ischemic or ischemic reperfused myocardium (Fig. 4; SCHAPER 1979 b) and the energy can originate only from glycolysis. This observation (TRACH 1984) may lead to new therapeutic principles, i.e., blockade of endogenous lipolysis to optimize glycolysis.

There is another pathway which provides high energy bonds anaerobically through substrate level phosphorylation: the amino acid aspartate is used in a reaction where 2-oxoglutarate is transaminated to glutamate and aspartate transformed to oxaloacetate which in turn is transformed to malate (malate dehydro-

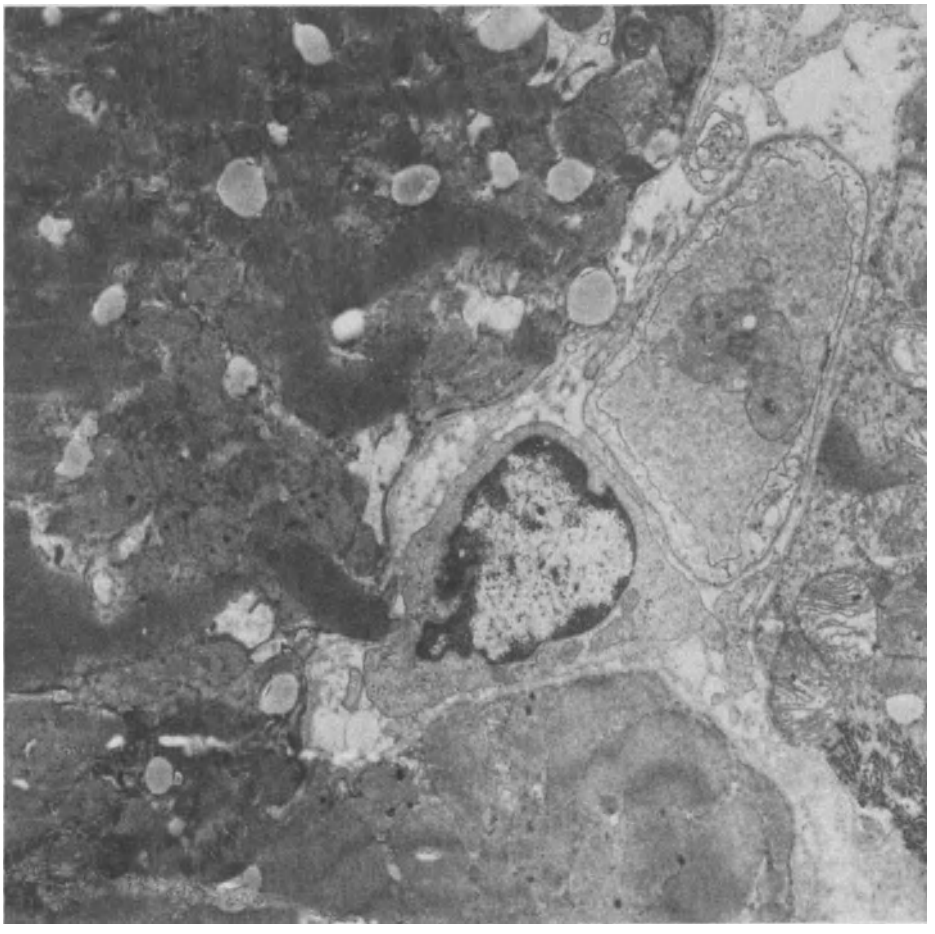

Fig. 4. Ischemic myocardial cells that contain numerous fat droplets. × 12,000

genase favors that reaction) and to fumarate which, when reduced to succinate, produces one molecule of ATP from ADP (Fig. 5; TAEGTMEYER 1978). In this sequence of reactions, the Krebs cycle "runs backward". In another sequence, which is coupled with the first glutamate (from the transamination reaction) and pyruvate are transformed to 2-oxoglutarate and alanine. The 2-oxoglutarate turns the Krebs cycle forward in the reaction to succinate, where GTP is produced from GDP. The end products of these reactions are succinate and alanine which have been detected in increased amounts in diving mammals (HOCHACHKA et al. 1975), in exhaustive exercise in humans (HOCHACHKA and DRESSENDORFER 1976), in coronary sinus blood of patients when angina pectoris was provoked (MUDGE et al. 1976), and in anoxic rabbit hearts (TAEGTMEYER 1978). The sequence is based on a steady supply of aspartate and produces about 16% of the amount of ATP produced by undisturbed glycolysis (TAEGTMEYER 1978).

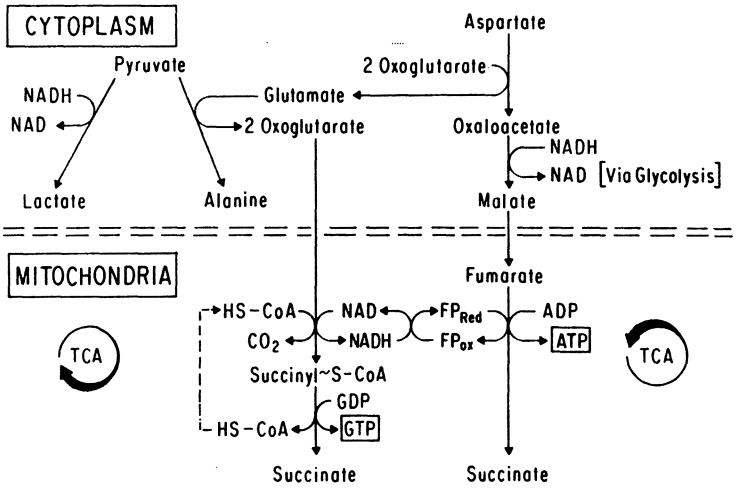

Fig. 5. Aspartate and pyruvate serve as substrates for substrate level phosphorylation whereby the Krebs cycle (tricarboxylic acids) runs partially backward. Modified from TAEGTMEYER (1978)

II. Influence on High Energy Phosphates

It has been known for a long time that cardiac tissue ATP concentrations decrease with time following the onset of ischemia (CHANG 1938; BURDETTE 1956; FURCHGOTT and DEGUBAREFF 1958; DANFORTH et al. 1960). GERLACH et al. (1963) described in heart muscle an important deviation from skeletal muscle of the breakdown pathway of AMP. In skeletal muscle, AMP is deaminated by the enzyme adenylate deaminase to IMP. In cardiac muscle, AMP is dephosphorylated to adenosine by the enzyme 5′-nucleotidase. The importance of this difference is the fact that adenosine diffuses (facilitated transport KÜBLER et al. 1970) across the cell membrane and, after some time, becomes unavailable for salvage pathways. Adenosine is also fairly rapidly deaminated intracellularly and is thereby also lost for the salvage pathway. In maximally stimulated skeletal muscle (the analog of ischemia) IMP does not leave the cell and is at the disposal of the salvage pathway upon restoration of the balance between mechanical energy output and rate of oxidation. From this analogy we may infer that skeletal muscle is well adapted to borderline situations because nucleotide breakdown as a rule ends with IMP and recovers rapidly after a short period of rest. Heart muscle in ischemia continues with the breakdown process and nucleosides and purine bases are lost through washout. The de novo synthesis of adenine nucleotides after normalization of blood flow is extremely slow in heart muscle (ZIMMER et al. 1973; ZIMMER 1980; MAUSER et al. 1984) and requires several days to a week for full restoration of the sum of nucleotides (REIMER et al. 1981) after a relatively short period of ischemia.

Since ATP is the key energy source for muscle contraction, transport across membranes, and biosynthesis pathways, significant losses of ATP during isch-

emia that are not quickly restored after reperfusion will probably interfere with these functions. Since most ATP, produced in the mitochondria, will be used for muscle contraction and since regional contractility is greatly reduced after a bout of ischemia followed by reperfusion in structurally intact and surviving myocardium, it was intuitively very attractive to assume a cause and effect relationship between reduced ATP concentrations and reduced contractility.

III. Regional Contractility and Nucleotides in Reperfused Myocardium

The introduction of mechanical and enzymatic methods to restore blood flow in an acutely thrombosed human coronary artery by RENTROP et al. (1981) has focused new interest on the particular problems of reperfused myocardium which eventually survives the ischemic damage. Postischemic reperfused myocardium is characterized by:

Reduction of adenine nucleotides which requires several days for normalization
Reduction of regional contractility which also requires several days for normalization
Reduction of pyridine nucleotides which is not restored directly upon reflow
Structural repair mechanisms which lead to normal mitochondrial ultrastructure, but activation of interstitial mesenchymal cells and phagocytosis of exocytotic material may be seen for several days.

As already stated, adenine nucleotides can be built up again by using salvage pathways for adenosine. Unfortunately, only short occlusions, not lasting longer than 3 min, produce a situation where adenosine is salvaged and readily transformed into AMP upon reflow. During longer occlusions, adenosine is removed from the myocyte by deamination and it is washed out by the subsequent reactive hyperemia of reperfusion. The de novo synthesis of ATP requires a long time and a lot of energy. ZIMMER et al. (1980) have shown that one of the rate-limiting steps of adenine nucleotide biosynthesis is the conversion of glucose-6-phosphate to ribose-5-phosphate in heart muscle. The very slow rate of action can be bypassed by the infusion of ribose (ZIMMER 1980) which accelerates ATP production by a factor of four. The activity of the enzyme involved varies from one species to the other. The activity in dog (MAUSER et al. 1984) and human myocardium is even lower than that in the rat, the most often used model in this field. Even if the immediate precursor of IMP, 5-aminoimidazole-4-carboxamide riboside (AICAR) is infused directly into a canine coronary artery, it takes up to 12 h before a fraction of the lost ATP is replenished (SABINA et al. 1982; SWAIN et al. 1982; MAUSER et al. 1984). This shows that several steps in the biosynthesis are of limited capacity in addition to the fact that other steps are feedback controlled. Our own research had focused on utilizing the salvage pathways of ribose, adenosine, and AICAR (MAUSER et al. 1984), but only adenosine is able to increase previously reduced ATP levels to near normal within 3 h of reperfusion. In the experiments with adenosine and AICAR, the respective tritiated compounds were used in trace amounts together with the unlabeled substrate. The enzymatic makeup of

mammalian hearts is such that inosine cannot be phosphorylated to IMP (DE-JONG 1979). It is first cleaved by purine nucleoside phosphorylase (PNP) to hypoxanthine and ribose-1-phosphate. Hypoxanthine combines with phosphoribosylpyrophosphate (PRPP) to IMP, but removes thereby the basis for de novo biosynthesis. Inosine and hypoxanthine are not effective substrates for the salvage pathway in postischemic reperfused dog myocardium. More optimistic results obtained in rats (ZIMMER 1980) may be due to species-dependent differences in enzyme activity or to the utilization of a mechanism other than salvage pathways. The fact that inosine inhibits 5′-nucleotidase (WORKU and NEWBY 1982) may have interfered with adenosine formation.

The adenosine salvage pathway is difficult to utilize in the clinical setting because adenosine is vasoactive and causes a fall in blood pressure. Because it is rapidly deaminated by blood, one has to infuse relatively high doses and the kidneys are loaded with fairly high amounts of poorly soluble uric acid. We have therefore tried ways to conserve adenosine inside the myocardial cell by inhibition of nucleoside transport and by inhibition of the enzyme adenosine deaminase. This is best done in combination since blockade of transport alone is of little use because deamination proceeds uninhibited. Neither does inhibition of deamination alone make much sense because reflow would wash out and greatly dilute the conserved adenosine. Inhibition of nucleoside transport is achieved by dipyridamole, the first fairly specific coronary vasodilator, by dilazep, lidoflazine, and by nitrobenzylthioinosine (NBMPR) and nitrobenzylguanosine (PATERSON et al. 1981). Inhibition of adenosine deaminase is achieved by erythro-9-(2-hydroxy-3-nonyl)-adenine (EHNA) (SCHAEFFER et al. 1974) (competitive) and deoxycoformycine (noncompetitive, irreversible). The hypothesis behind this concept of conservation of adenosine for the salvage pathway is based on the assumption that cardiac tissue concentrations of adenosine reflect those inside the myocyte and that the fall of ATP during ischemia also reflects ATP inside the cardiac myocyte. Since the rise in adenosine (deaminase blocked) equals the fall in ATP, the assumption appeared valid.

We tested several experimental situations where we combined nucleoside transport block (dipyridamole) with inhibition of deamination (EHNA) in hearts which had been made ischemic. In a first orientational experiment, the heart (dog) was removed and incubated at room temperature, and tissue samples were removed every 15 min for 3 h (Fig. 6). In this experiment, adenosine concentration rose rapidly, but not to very high levels, fell again to almost normal levels, while inosine (its breakdown product) rose. When nucleoside transport was blocked by dipyridamole, adenosine rose to much higher levels and stayed elevated. The rise in adenosine, inosine, and hypoxanthine paralleled the fall in nucleotides, i.e., the sum of nucleotides, nucleosides, and bases remained about constant. When dipyridamole and EHNA were given, adenosine was the only nucleoside formed, and the rise in adenosine concentration paralleled the fall in nucleotides. These experiments suggested that if ATP, ADP, and AMP are indeed present to a large extent (probably 96%) in cardiac myocytes, adenosine as a major breakdown product in untreated hearts will also be produced inside the cardiac myocyte. Part of it will be deaminated inside the cell, but some fraction will leave the myocyte by diffusion and transport and may be deaminated in another (nonmyocytic) cell

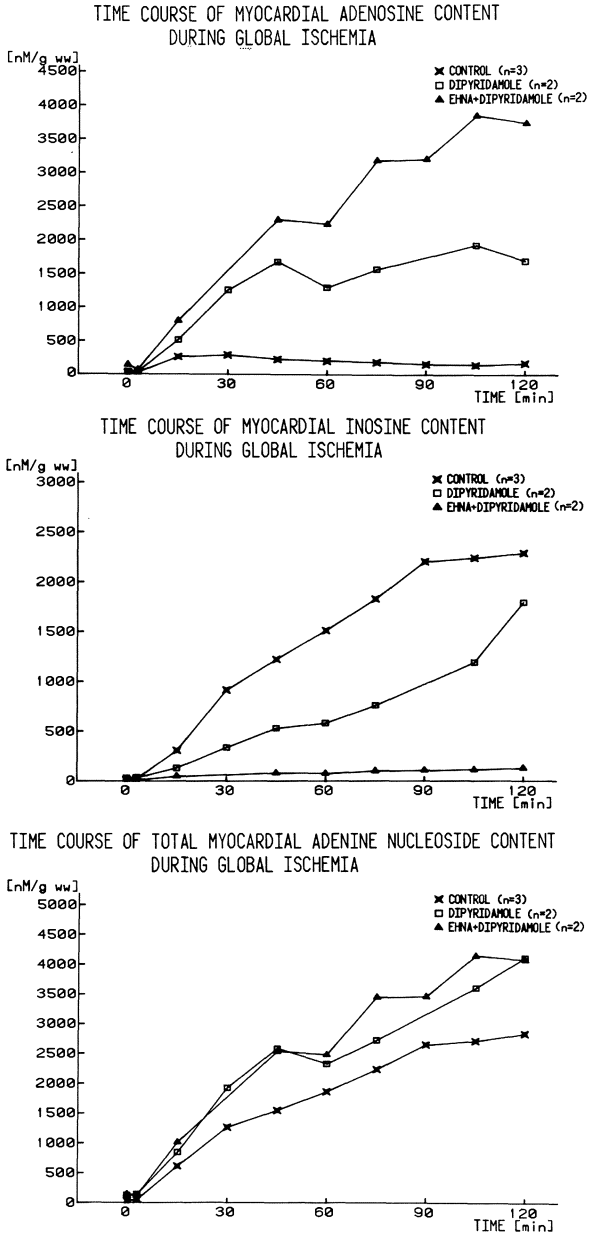

Fig. 6. Nucleosides accumulate during global ischemia in the heart. The accumulation can be drastically changed by inhibition of outward adenosine transport, by inhibition of the enzyme adenosine deaminase (EHNA), and by a combination of both. Inhibition of adenosine transport by dipyridamole leads to a drastic increase in tissue adenosine levels and to a similar reduction of inosine content. This is explained by assuming a very active adenosine deaminase outside the myocyte which cannot be reached when adenosine transport is inhibited. Inhibition of transport plus inhibition of deamination leads to very high adenosine levels, adenosine being the only product of nucleotide breakdown

in the interstitium. Reasons to believe this stem from experiments with dipyridamole: the much higher adenosine concentrations measured in these hearts are believed to reside within the cardiac myocyte because outward transport is inhibited. We must also conclude that there are two sites of adenosine deamination, one inside the myocyte and the other in some other cell, whereby the latter must be much more active than the former, otherwise the drastic rise in adenosine following total ischemia under the influence of dipyridamole is difficult to explain: the transport block prevents adenosine reaching its second site of deamination, its concentration rises almost as much as that of ATP falls. The blockade of deaminase by EHNA shows the activity of the intracellular and of the nonmyocyte deaminase: the additional rise over and above that of dipyridamole alone quantitatively parallels the fall in ATP.

Similar results were also obtained in other experimental situations in intact, in situ, beating hearts with coronary artery occlusion, and it was tempting to study whether the increased adenosine concentrations accumulated under the combined influence of dipyridamole, EHNA, and ischemia can be utilized during reperfusion in the salvage pathway leading to AMP and finally to ATP. The results of these experiments were not very convincing: there was some increase in ATP during a 3-h reperfusion period, but many experiments were needed to come to a convincing statistical significance (HENRICHS and SCHAPER, to be published), and exogenous infusions of adenosine were far more effective in restoring ATP levels at lower intracellular concentrations than the much higher concentrations under EHNA and dipyridamole. There are two explanations for these unexpected findings:

1. It is known that adenosine kinase, the enzyme that phosphorylates adenosine to AMP, is inhibited by its own substrate, and the high adenosine levels may have reached inhibitory concentrations.
2. Another experiment shed doubt on the whole basis of "intracellular" conservation and salvage of adenosine: in an in situ model (dog coronary artery occlusion for 45 min and reperfusion), adenosine accumulation was tested during ischemia under three conditions: without treatment, with dipyridamole, and with dipyridamole plus exogenously infused adenosine deaminase.

Under control conditions, the adenosine concentration rose only briefly because of rapid deamination to inosine. Under dipyridamole, adenosine rose steeply and stayed elevated as described. Under dipyridamole plus exogenous deaminase, the adenosine concentrations were very significantly less than with dipyridamole, a totally unexpected finding, because the infused deaminase is known to reside only in the extracellular space; if adenosine stems from intracellular ATP breakdown and if dipyridamole blocks transport out of the cell, the adenosine should not have reached the extracellular cell-free deaminase. Again two conclusions can be drawn from this experiment:

1. For as yet unexplained reasons the accumulated adenosine (Ischemia plus dipyridamole) does not reside inside the cardiac myocyte, but rather in the extracellular space. It accumulates because dipyridamole does not permit entry of adenosine *into* the cardiac myocyte. This would explain why the high adenosine

concentrations during ischemia plus EHNA plus dipyridamole are not readily used for the salvage pathway. But for the sake of logic, we have also to assume that the amount of ATP converted into adenosine is outside the cardiac myocyte, a very unlikely assumption.

2. Another, and probably more likely, explanation would be that the transport inhibition by dipyridamole was not perfect and that a certain amount of adenosine has diffused out of the cardiac myocyte. In the absence of cell-free extracellular deaminase, the extracellular adenosine (originating from the cardiac myocyte) cannot enter other cells (pericytes, etc.), because their cell membranes have become impermeable to adenosine owing to the action of dipyridamole. Cell-free deaminase in the extracellular space, however, has free access to extracellular adenosine and is hence transformed to inosine. This explanation would assume an asymmetric transport inhibition, i.e., the outward transport of adenosine is less well blocked than the inward transport. such a mechanism was proposed by BERNE (1980) some time ago.

All these different maneuvers, i.e., stimulation of de novo synthesis of adenine nucleotides by infusions of ribose and AICAR and the intracellular conservation of adenosine in ischemia and reperfusion by EHNA plus dipyridamole, were meant to aid the heart to resume regional function quickly following reperfusion.

It has been known since the studies by DE BOER et al. (1980) that even short coronary occlusions lasting only 15 min produce a regional dysfunction which lasts for many hours or even several days. The parallelism with the slow return to normal of tissue ATP concentrations suggested a cause and effect relationship. Our successful attempts to replenish tissue ATP concentrations with exogenous adenosine (MAUSER et al. 1984) appeared to be an interesting tool to test the hypothesis whether steady state tissue ATP concentrations are related to the contractile state. This hypothesis was tested using ultrasonomicrometer crystals implanted into a nonischemic and into a potentially ischemic region (dog hearts); regional contractility was compared (see Fig. 7) during ischemia, at reperfusion, and during adenosine infusion directly in one coronary artery. Although adenosine was indeed able to replenish ATP levels from 50% of normal (end of ischemia) to 75% of normal (end of a 3-h period of reperfusion), the regional contractility remained significantly depressed and showed no tendency to improve.

The question of a relationship between cardiac ATP concentrations and cardiac contractility remains controversial. Some authors find such a relationship (REIBEL and ROVETTO 1978; WATTS et al. 1980; OHARA et al. 1981; NISHIOKA and JARMAKAIN 1982), whereas others do not (GUDBJARNASON et al. 1970; VARY et al. 1979; NEELY et al. 1973). From a theoretical point of view, such a relationship is not expected because the ATP concentration at which the actomyosin complex is saturated is much lower than those concentrations that are usually found in cardiac tissue (KATZ 1977).

The slow return of regional contractile function after a relatively short period of ischemia is difficult to explain. As already stated, lack of ATP can be excluded from the list of probable causes. The analysis of waveforms obtained from ultrasonomicrometer crystals shows that shortening does indeed occur, but at a later time in sytole. It looks as if the reperfused segment is only somewhat weaker

than the normal muscle fibers exerting their force upon the reperfused muscle. When the force of the normal segment declines below the force developed by the reperfused segment, it results in measurable shortening. This would suggest that the difference in developed force between a normal and a reperfused segment is not as great as the measurement with ultrasonomicrometer crystals would suggest. This situation can be compared to a tug-of-war where the winning team need only be slightly stronger, i.e., the type of measurement may actually amplify small differences in the force developed. It is not easy to differentiate between a true and an apparent depression of regional contractility. One way to do this would be the measurement of regional myocardial oxygen consumption. If regional myocardial O_2 consumption does not differ markedly between the reperfused and normal myocardium, the ultrasonomicrometer crystals have indeed amplified small differences in developed force. Substantial differences in regional $M\dot{V}O_2$ would suggest that the observed differences in contractility are real. The measurement of regional $M\dot{V}O_2$ is not easy since local venous oxygen content is difficult to obtain because of the large-caliber venous anastomoses which carry the danger of contamination with blood from normal regions. Since blood flow to regions of depressed contractility during reperfusion is lower than normal (after $\leqq 30$ min of reactive hyperemia following release of the ligature), we may indeed assume a reduced regional $M\dot{V}O_2$. However, reduced flow may have other causes, i.e., regions of irreversible injury or edema formation.

Other indications that the observed differences of contractility are real stem from the fact that creatine phosphate (CP) concentrations in reperfused muscle are above normal values. This observation would suggest intact mitochondrial function, but impaired utilization of ATP at the sarcomere site. The model of the mitochondrial sarcomere energy shuttle, as described first by GUDBJARNASON et al. (1970) and later by JAKOBUS and INGWALL (1981), predicts that ATP does not leave the mitochondrion, but rather phosphorylates creatine at the outer mitochondrial membrane. CP is released into the cytosol where it transforms ADP to ATP at the sarcomere. The higher than normal CP levels in reversibly injured reperfused myocardium would suggest that there is a slower ATP turnover at the sarcomere which results in higher CP concentrations, both as a result of depressed contractility. Another indicator for significantly depressed contractility in reperfused myocardium is our observation (HOFFMEISTER et al. 1984) that repeated occlusions lead to a much slower fall of CP concentrations as compared with the first occlusion where fully contractile myocardium was suddenly deprived of blood and oxygen. Since all these arguments in favor of truly and significantly reduced contractility (rather than an apparent reduction) are either indirect or have been obtained with methods of limited accuracy, measurements of ATP turnover in reperfused myocardium employing the rate of incorporation of ^{32}P into ATP should be carried out.

IV. Effect of Regional Ischemia on Local Myocardial Function

It is a well-known fact that regional ischemia leads to a functional impairment of the affected myocardium. Clinical examples are the pump failure of the heart in an acute myocardial infarction or the regional dysfunction after an acute cor-

onary occlusion with a possible, at least partial, recovery of the previously ischemic segment after reperfusion. Dysfunction after coronary artery occlusion in an experimental model was described by TENNANT and WIGGERS (1935) and attracted many further investigators (BUGGE-ASPERHEIM et al. 1969; EDWARDS et al. 1981; FRANKLIN et al. 1973; GALLAGHER et al. 1982).

The degree of dysfunction depends on the extent of ischemia, i.e., on the size of the ischemic region and on the perfusion deficit. Therefore, one main factor influencing the dysfunction is the collateral supply in the myocardium. In the pig, with its lack of sufficient collaterals, a medium-size coronary artery occlusion rapidly causes a systolic outward bulging of the ventricular wall, whereas the same occlusion in a dog, with a good collateral supply, may only lead to a delayed and reduced contraction.

1. Measurement of Regional Function

The method most commonly used in experiments in intact hearts is pulsed sonomicrometry. Short ultrasound impulses are sent and received at a high frequency between two transducers. Since the speed of ultrasound in the myocardium is well known, it is possible to determine the actual distance between both transducers by measurement of the transit time. This method was described by RUSHMER et al. (1956) for the estimation of global myocardial function and was further developed by many other investigators for the analysis of regional dysfunction (BUGGE-ASPERHEIM et al. 1969; EDWARDS et al. 1981; HAGL et al. 1976; THEROUX et al. 1974). The implantation of the newer microtransducers causes only minimal myocardial lesions and thus allows determination of segment length in different layers of the myocardium as well as wall thickness measurements with a high resolution in time and space. The main advantage of this method is the fact that the transducers are not mechanically connected to each other. Other devices to monitor regional function, like the Walton–Brodie gauge, mercury-in-silastic gauges, and similar types, have the problem that mechanical connections lead to a loss of sensitivity and produce artifacts (BUGGE-ASPERHEIM et al. 1969; EDWARDS et al. 1981). SCHELBERT et al. (1971) pointed out that mechanical force gauges are well suited for measurement of isometric contraction without interference from neighboring tissue. On the other hand, measurements of ischemic contractile changes with ultrasonomicrometer crystals are always affected by the surrounding nonischemic myocardium and do not represent the function of the ischemic region only. We share this view, but still prefer the more dynamic sonomicrometry because it allows a measurement during the entire cardiac cycle. It records the differential of the power output between the ischemic segment and the nonischemic segments which exert a force of opposing vectors on the ischemic fibers. We call this a "tug-of-war" situation where even relatively small differences in power generation as well as a desynchronization of force development between these regions may become very obvious.

2. Effects of Hemodynamic Changes

The measured indices of regional function can be influenced by induced or spontaneous hemodynamic changes. Changes of the preload affect the segment length;

the end-diastolic length is particularly sensitive to loading changes. On the other hand, the segment shortening is dependent on the afterload of the ventricle. In the autonomic blocked conscious dog, a linear relationship between regional work and regional end-diastolic length was obtained by preload changes (GLOWER et al. 1983). One way to appreciate the influence of hemodynamic factors on the ischemic and postischemic regional segment length and shortening is the comparison between the ischemic/postischemic area and a control area (HOFFMEISTER et al. 1984). But then two assumptions are necessary: (a) the ischemic region is small enough not to influence the function of the rest of the left ventricle; (b) ischemic, postischemic, and nonischemic myocardium react similarly to changes of preload or afterload. Because of these problems, the measurement of the unstressed length (l_0) at zero transmural pressure recorded during transient vena caval occlusions was introduced as a more load-independent variable for the diastolic properties (RANKIN et al. 1980).

3. Role of Implantation Site

The extent of segment shortening is also dependent on the position of the microtransducers in the left ventricular wall. In the apex region, the ratio of shortening to segment length is markedly higher than near the base of the ventricle. Since ventricular geometry and fiber orientation influence the amount of segment shortening, the largest amplitude in the subendocardial layer is usually obtained along the short axis of the ventricle (HEIMISCH et al. 1981). The extent of shortening in the subendocardium was reported to be larger than in the epicardium (SABBAH et al. 1981). In a study on the role of myocardial fiber orientation for subepicardial segmental contraction during coronary stenosis, the importance of the implantation angle was shown under conditions of nonuniform transmural blood flow (GALLAGHER et al. 1982). Therefore, it is necessary to have a very standardized technique of ultrasound crystal implantation. Additionally, the correct position of the transducers in the layer under investigation should be controlled after every experiment by heart sections to avoid artifacts, the most common being a partial wall thickness determination combined with a segment length measurement.

4. Time Reference Points

To compare the influence of interventions it is necessasry to consider the different variables which can be derived from the segment length curve obtained for that region. A main problem is the definition of the time points of measurement. The end-diastolic length is easily derived from such a recording, but other authors prefer the onset of ejection as the beginning of shortening (GLOWER et al. 1983). Another nonstandardized point is the end of the systolic phase, especially with respect to the surrounding myocardium. If only the footpoint of the length curve is taken for end-systolic length, irrespective of time of occurrence, the measurement becomes very insensitive and delayed contraction (dyskinesia) will be missed; on the contrary, an "improved function" due to slight ischemia may even be obtained since the delayed contraction, lasting into the early ventricular diastole, may have an increased amplitude (HOFFMEISTER et al. 1984). The earlier one

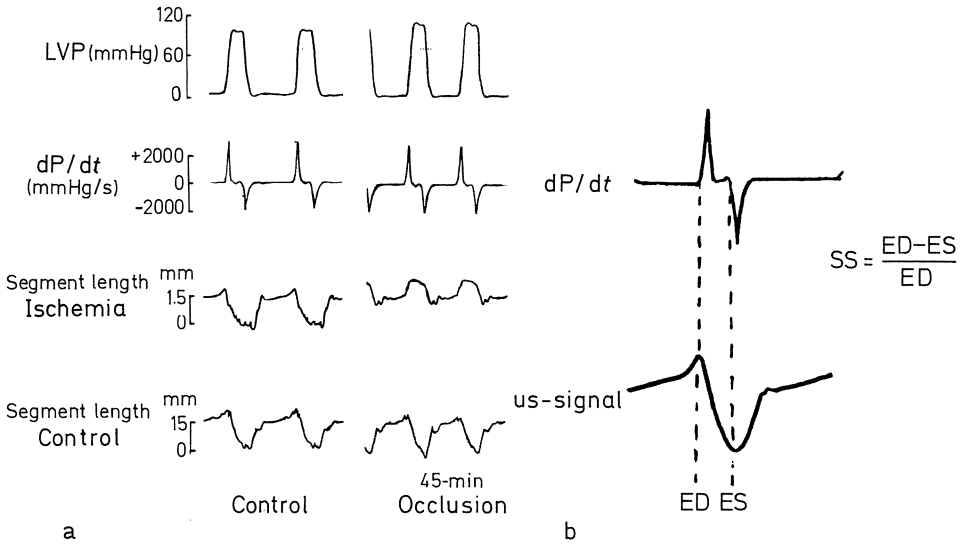

Fig. 7 a, b. Regional contractility measured by implantation of two pairs of ultrasonomicrometer crystals, one into a prospective ischemic region, the other into a control region **a** Ischemia causes a holosystolic bulge; **b** to ensure that the degree of shortening is always measured at the same moment within the cardiac cycle, the dp/dt signal is used as an internal standard

chooses the end point of shortening measurement toward the end of the ventricular ejection period, the more sensitive the measurement becomes to slight changes due to ischemia. But in any case, determinations during ejection are influenced by the afterload. For these reasons it is absolutely necessary to know which points were chosen by the respective authors to describe regional systolic function. Figure 7, showing a very obvious bulging, is a good example. Between end-diastole and end of ejection one gets a "negative contraction," but if one considers only the ejection period, no length change or even a slight contraction is observed, in spite of the obvious bulging.

Another derived variable from transit time sonomicrometry is dl/dt_{max}. As can be seen in Fig. 7 and 8, it declines during ischemia. A higher sensitivity of this derivative compared with segment shortening could not be observed (HEYNDRICKX et al. 1975). Some authors also calculated "segment work" (TYBERG et al. 1974). This variable is not exactly "work", but the area of the global ventricular pressure–segment length loop. It was shown that this index of regional function is not superior to segment length alone which is reasonable if the pressure during intervention does not vary. Dissociation of the time courses of segmental work, shortening, or velocity are more dependent on changes of hemodynamics or incorrect normalization than on ischemia (HOFFMEISTER et al. 1984). One always has to be cautions if preload or afterload of the heart are changing because these influence the end-diastolic length and systolic function.

Other approaches to regional functional monitoring use local myocardial wall thickness measurements either with small crystals (EDWARDS et al. 1981; HEYN-

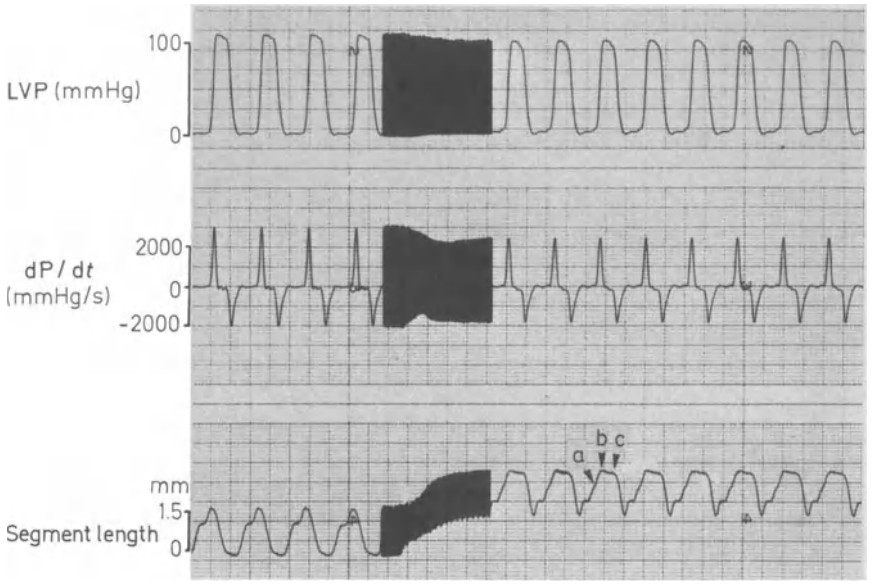

Fig. 8. This recording shows the typical length changes of a segment supplied by the LAD during a proximal LAD occlusion in an open-chest dog. During coronary artery occlusion left ventricular systolic pressure, dP/dt_{max}, and dP/dt_{min} decline and the ischemic segment length increases. The end-diastolic (*a*), onset of ejection (*b*), and end of ejection (*c*) time points are indicated and demonstrate the importance of the first measurement point for calculation of shortening. For details see text

DRICKX et al. 1978) or with external ultrasound transducers (PADIAN and KERBER 1982). For these methods, independence of fiber orientation is claimed, but a global wall thickness determination includes various layers of the myocardium which have a different flow, a different biochemical status, and which react differently to flow deprivation (SCHAPER 1979). It seems, therefore, not to be superior to the determination of the length changes in a single myocardial layer (LEWINTER et al. 1975) as obtained by subendocardial crystal implantation. Measurement of regional function with ultrasonic crystals was also performed in humans and the results were very similar to those from animal experiments (HAGL et al. 1978; HILL et al. 1978; TYSON et al. 1982).

5. Alterations Due to Ischemia

After an acute coronary artery occlusion, the most prominent sign is the loss of contraction. A representative recording of a left anterior descending artery (LAD) occlusion in an open-chest dog is shown in Fig. 8. It demonstrates an increase of end-diastolic length as well as of end-systolic length. This is typical for a severe acute ischemia, but since myocardial blood flow is different in different layers of the myocardium and much influenced by the collateral supply, an occlusion, e.g., of a LAD side branch, in many cases leads only to a reduction of regional contraction (HOFFMEISTER et al. 1983 a), not always totally abolishing a sys-

tolic shortening. Depending on the degree of the perfusion deficit, all grades of dysfunction from merely delayed contraction to holosystolic bulging can occur as VATNER (1980) indicated, showing a sensitive correlation between flow reduction and decrease of shortening.

After the onset of ischemia, the amount of shortening until the end of ejection and the velocity decline (HEYNDRICKX et al. 1975), and a further shortening may occur early in ventricular diastole when the stresses exerted by the surrounding normal myocardium decrease. A more severe sign of ischemia is an increase of segment length at the onset of systole during the isovolumic phase. This is usually combined with delayed contraction. With even more severe ischemia, the outward bulding, registered as an increase in segment length, becomes holosystolic with a decrease in length segment during early diastole. Beside these systolic alterations, diastolic changes due to regional ischemia are seen such as an increase of the end-diastolic length (SASAYAMA et al. 1980; THEROUX et al. 1976) and an elongation of the unstressed segment length (l_0) (EDWARDS et al. 1981). A rightward shift of the pressure–dimension curve occurs in ischemia (THEROUX et al. 1974), but using a normalization with respect to l_0 and taking viscoelastic properties into account, EDWARDS et al. (1981) calculated an increased myocardial stiffness due to ischemia.

6. Changes in the Nonischemic Part of the Ventricle During Regional Ischemia

Segment length and shortening in the nonischemic part of the ventricle in the presence of an ischemic region depend on the size of that region. Side branch occlusions in the dog with good collateral blood supply may have no effect on the rest of the heart, but high LAD occlusions lead to a "compensatory hyperfunction" of the nonischemic left ventricle (SASAYAMA et al. 1980).

This hyperfunction is registered as an increased segment length amplitude. A detailed analysis referring to the different phases of the heart cycle showed an increased shortening only during the isovolumic phase in the nonischemic part, but this needs further confirmation (LEW et al. 1983). Some authors reported a slightly decreased ejection shortening in the control region during a LAD occlusion (GLOWER et al. 1983), whereas other investigators described the very opposite site of the ventricular ring working at least normally (LIMA et al. 1982). These results make it very difficult to find a "control" region. KUMADA et al. (1979) explained the initial, but quickly recovering depression of dP/dt_{max} and dP/dt_{min} as the result of the synchronous behavior of the ischemic and nonischemic parts of the left ventricle. Thus, while there is no doubt about the hyperfunction in most reports, the reaction of the nonischemic myocardium during acute coronary artery occlusion needs further detailed investigation.

7. Regional Function During Reperfusion of Previously Ischemic Myocardium

The effect of reperfusion on regional function depends mainly on the reversibility and the amount of reversibly injured tissue in the myocardial segment investigated. After the onset of reflow following reversible ischemia, myocardial func-

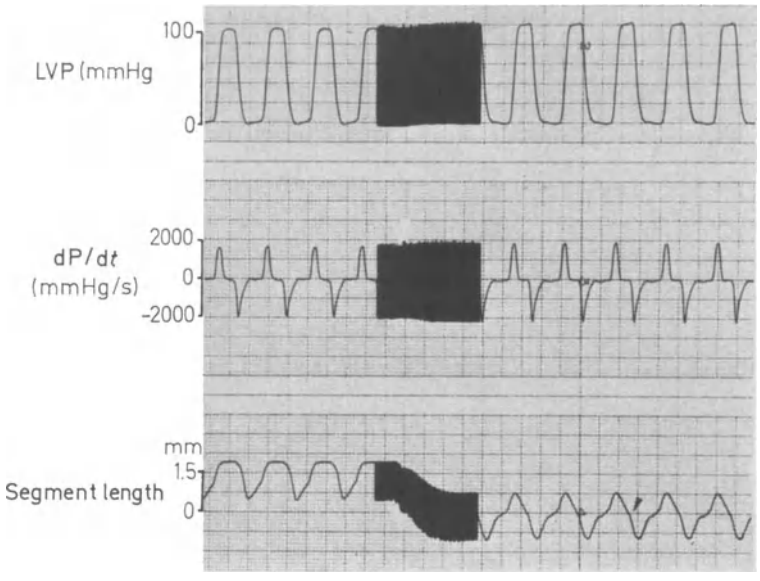

Fig. 9. The reperfusion of a proximal occluded LAD leads to an increase of the left ventricular systolic pressure, dP/dt_{max}, and dP/dt_{min} in the open-chest dog. The segment length decreases, but in spite of the reversible tissue injury, a dysfunction with slow and delayed contraction (*arrow*) remains

tion recovers quickly (Fig. 9), but not completely. This first improvement is followed by a very slow further recovery to normal values. KLONER et al. (1981) showed that even 4 days after 15 min of LAD occlusion, regional function was not yet normal although the injury was histologically reversible. HEYNDRICKX et al. (1975, 1978) also found a reduction of endocardial blood flow paralleling the long-lasting functional segment recovery after 15 min coronary occlusion in the conscious dog. A very similar time course of changes of diastolic properties (l_0) compared with the systolic dysfunction was seen by GLOWER et al. (1983). These changes were supposed to be associated with ultrastructural alterations influencing the cross-bridge overlap relative to the actin filaments. Also, very short, but repeated periods of ischemia lead to a dysfunction not only during ischemia, but also during reperfusion. In open-chest dogs, an effect on the postischemic systolic function as well as on the diastolic properties could be observed (HOFFMEISTER et al. 1983 b). The degree of rapid recovery and the time needed for complete normalization depend on the severity of the ischemic tissue injury which can be evaluated by electron microscopic and biochemical methods (SCHAPER 1979). Interestingly, the regional function during acute ischemia is not a reliable predictor of the possible improvement during reflow. The duration of the perfusion deficit also plays a considerable role. For example, if a high LAD occlusion leading to a holosystolic bulging is released after 3 min, function can recover almost completely (HOFFMEISTER et al. 1984). But a 45-min side branch occlusion without irreversible tissue damage producing only a decrease of shortening to 20% recovers to only about 50% during the early reperfusion and remains at that level for the

next few hours (HOFFMEISTER et al. 1983 a). Therefore, it is not the ischemic function (i.e., the actual intensity of ischemia), but the product of time and intensity of perfusion deficit which is the best predictor.

Because of the striking correlation between the time courses of decreased postischemic ATP levels and the reduced postischemic regional function – both show a very delayed recovery (KLONER et al. 1981) – an elevation of postischemic ATP levels was supposed to improve the regional function. This hypothesis could not be confirmed. Recently, the failure of accelerated ATP repletion during reflow to affect the depressed postischemic function was demonstrated (HOFFMEISTER et al. 1983 a). In another experiment with repeated 3-min coronary occlusions leading to a successive decrease of postischemic function and ATP levels, an attempt at pharmacologic preservation of ATP by inhibition of both adenosine transport and adenosine deamination had no influence on regional shortening, in spite of an approximately 1 μmol/g higher ATP concentration compared with the control group after 20 acclusions; for 20 further occlusions, no prospective beneficial effect of the relatively higher ATP-levels was seen (HOFFMEISTER et al. 1984). The cause of postischemic dysfunction is still an unresolved problem.

In conclusion, the regional dysfunction caused by coronary artery occlusion depends on the intensity of the ischemia. The main alterations are delayed and decreased or totally abolished segment contraction and a partial or holosystolic bulging. The diastolic properties also change and the end-diastolic length increases. If the ischemic injury is reversible, a quick, but only partial recovery occurs, depending on the degree of the tissue damage. Further recovery needs a long time and cannot be influenced by acceleration of the postischemic ATP repletion.

D. Myocardial Infarction

I. Mechanisms Leading to Cell Death

From an ultrastructural point of view, subcellular organelles of myocardial cells have been discussed in terms of bringing about the decisive event leading to cell death. This section will describe the different subcellular systems in the possible role of myocardial cells in the progression of ischemic injury until cell death occurs.

1. Mitochondria and Nuclei

In ischemia, the mitochondria lose their normal matrix granules, the electron density of the matrix, and finally the cristae. The nuclei show gradual dissolution preceded by extensive swelling or clearing and different degrees of clumping of chromatin. Most of these ultrastructural alterations of myocardial mitochondria and nuclei in ischemia have been described extensively during the last 20 years (JENNINGS 1969, 1976 a, b, 1979; JENNINGS and GANOTE 1972; JENNINGS and REIMER 1981; JENNINGS and SOMMER 1960; JENNINGS et al. 1964, 1965, 1969). In electron microscopy, a general agreement has been reached about the characteristic subcellular symptoms of reversibly versus irreversibly injured mitochondria and nuclei (SCHAPER 1979 b; JENNINGS 1969; TRUMP et al. 1976) in heart and different tissues.

Mitochondria, the central machinery of cellular metabolism, are the most sensitive organelles toward the effects of ischemia (SCHAPER 1979 b; OPIE 1980; JENNINGS 1976 b; SCHAPER et al. 1979 c). Structural changes of differing severity are correlated with the intensity of the ischemic insult. The disappearance of the small matrix granules as the earliest ultrastructural symptom of ischemia is comparable to the rapid loss of CP as the earliest metabolic symptom, and to the loss of contractile activity as the earliest functional defect. These changes coincide with regard to duration of ischemia; they occur after 0.5–5 min of coronary artery ligation in the canine heart. This finding is in agreement with JENNINGS' (1979) observations.

The consistency of normal matrix granules in mitochondria is still a matter of controversy in the literature, a fact most probably due to technical limits for the analysis of these small (250–500 Å) particles. Most authors, however, agree that these granules contain Ca^{2+} (DHALLA et al. 1977, 1978; HARRIS 1977; PEACHEY 1964; VIAL et al. 1978). Since mitochondria are known to contain high levels of Ca^{2+} (HARRIS 1977; SAETERSDAL et al. 1980, 1981) and to be able rapidly to accumulate or discharge Ca^{2+} under various conditions (CARAFOLI and ROMAN 1980; LEHNINGER 1982), intramitochondrial retention of Ca^{2+} seems to be an important factor in the regulation of cardiac function on the cellular level (SORDAHL 1979), either for its contractile (DHALLA et al. 1978) or metabolic performance (WOKOWICZ and MCMILLIN-WOOD 1981; COELHO and VERCESI 1980). The capacity of uptake and release of Ca^{2+} across the inner mitochondrial membrane is an energy-dependent process occurring as exchange processes with other ions such as Na^+ or H^+ (LEHNINGER 1982); this mitochondrial function is completely abolished in ischemia (DENTON et al. 1980). The disappearance of the small granules from mitochondria in early ischemia may be indicative of an altered membrane permeability, allowing massive amounts of Na^+ and other ions in exchange with Ca^{2+} to enter the inner mitochondrial space which results in functional disturbances (SORDAHL 1979).

There have been several technically different approaches to clarify the composition of "flocculent" (TRUMP et al. 1976) or "amorphous" (JENNINGS et al. 1965; JENNINGS 1969) densities, those dark intramitochondrial deposits that are generally considered to indicate the occurrence of irreversible injury. It is our opinion that these amorphous densities observed in cardiac mitochondria as a consequence of severe ischemic injury are composed of the various lipid and protein components from dissolved mitochondrial membranes as well as multienzyme complexes plus Ca^{2+} and perhaps other ions as well. These complexes are insoluble and very electron-dense; for both reasons they are easily detectable in the electron microscope. Their number and size vary greatly, depending mainly on the stage of progressing necrosis. Mitochondria in ischemia very often show an electron-lucent matrix space with no increase of size or volume (SCHAPER et al. 1982). Since ischemic mitochondria also exhibit a diminution of their cristal membranes, clearing of the mitochondrial content, as evidenced in the electron microscope, may reflect the fact that dissolution of the formerly highly organized mitochondrial components takes place during ischemia while the outer membrane of this organelle is still structurally (but not functionally) intact. Fragmentation and partial dissolution of cristae as well as remaining matrix proteins and lipids

may give rise to the appearance of intramitochondrial homogeneous gray material which then also gradually disappears at more progressed stages of ischemic injury.

Rupture of the outer mitochondrial membrane usually occurs at late (irreversible) stages of cardiac ischemia. Mitochondrial alterations as described by BUFFA and PASQUALI-RONCHETTI (1977) in chicken myoblasts treated with fluoroacetate resembled those observed in ischemia; it is not surprising, therefore, that these authors established a close correlation between the biochemical lesions of respiratory enzymes and configurational changes of mitochondria in vivo which is also in accordance with SJØSTRAND's (1979) view that the permeability of the outer mitochondrial membrane as determined by electron microscopy is closely related to the metabolic rate of these organelles. A close relationship between mitochondrial configuration and their metabolic capacity had been established for in vitro conditions by HACKENBROCK as early as 1968, and it has been confirmed by many studies since then (HACKENBROCK 1981).

In conclusion, mitochondrial and nuclear changes in ischemia can be differentiated gradually into several degrees, reflecting the severity of ischemia. Changes in these cellular organelles are the most sensitive and the most reliable ultrastructural symptoms and allow the differentiation between well-defined stages of reversible and irreversible myocardial ischemic injury.

2. Sarcolemma and Occurrence of Intracellular Edema

The sarcolemma shows increasing disruption in severe ischemic injury and it completely disappears in irreversible injury. The basement membrane is usually still recognizable, even when the cell membrane is completely absent; for this reason even extremely damaged myocytes still appear as a cellular unit with a very distinct borderline to the interstitial space. Morphological damage of the sarcolemmal membrane, however, is not necessarily correlated with the occurrence of intracellular edema, and cells with apparently intact membranes can be extremely edematous. In the current literature, the debate continues as to whether or not structural damage of the sarcolemma must be regarded as the prerequisite for the occurrence of fluid accumulation within cardiac cells. WILLERSON et al. (1977) proposed an abnormal fluid distribution from the extracellular to the intracellular space since edema frequently develops in the absence of an overall weight gain while the sarcolemma remains ultrastructurally intact. Intracellular edema was thought to occur prior to extensive irreversible cell injury, and according to WILLERSON et al. (1977) it may be due to a reduced Na^+, K^+-ATPase activity.

LEAF (1970) has postulated that in ischemia as a consequence of the inability of the Na^+, K^+-ATPase pump actively to extrude sodium from the interior of the cells, an intracellular movement of Na^+, Cl^-, and water results, thereby causing cellular edema. This classical "pump leak" hypothesis (TOSTESON and HOFMANN 1960) implies that water content is related to Na^+, K^+-ATPase pump activity and cell swelling to monovalent ions.

Metabolic blockade by immediate cold shock was shown to increase cell water and monovalent cation content reversibly, owing to inhibition of the Na^+, K^+-ATPase pump activity (PINE et al. 1979). However, PINE et al. (1979) also dem-

onstrated that there exists a dissociation of sodium–potassium exchange by pump activity and cell volume regulation. PINE et al. (1979) explained the loss of cell volume regulation in ischemic canine myocardium as observed by Jennings and his co-workers (GROCHOWSKI et al. 1976; GANOTE et al. 1976) as secondary to the loss of a mechanism of cell volume control other than the ouabain-sensitive Na^+, K^+-ATPase pump. PINE et al. (1979) drew attention to the fact that cell swelling may be the cause rather than the result of increase in sodium permeability and that the pump leak theory therefore will possibly have to be revised as an explanation of myocardial volume regulation.

On the other hand, Jennings and co-workers (GROCHOWSKI et al. 1976; GANOTE et al. 1976) believe that the loss of cell volume regulation in ischemic myocardium is one of the early events in ischemic injury, leading eventually to irreversibility of cellular alterations, i.e., to death of the cell (JENNINGS and GANOTE 1972). JENNINGS and REIMER (1981) not only observed heavy edematous swelling of ischemic heart tissue, but also showed the existence of plasmalemmal defects in swollen myocytes by electron microscopy. In these studies, the reduced selectivity of cell membrane permeability was claimed to be the cause of irreversible cell injury.

Our own ultrastructural results show that a slight to moderate degree of reversible ischemic injury is usually accompanied by the occurrence of intracellular myocardial edema (SCHAPER 1984). This, in fact, is in the early stage of ischemic injury at which cell permeability, when measured as the activity of the sarcolemmal Na^+, K^+-ATPase, has been shown to be intact (WINKLER et al. 1981). On the other hand, movements of mono- or divalent ions may already cause osmotic alterations and therefore the inward shift of fluid into the cells. In severe reversible and in irreversible ischemic injury, edema may be present to varying degres; it may also be completely absent, even when the sarcolemma is entirely destroyed.

In conclusion, intracellular water content alone is certainly not a good predictor of cell viability, and sarcolemmal functional defects in early ischemia may not correlate with its structural appearance, facts indicating that both these symptoms as seen in the electron microscope *do* have importance in the evaluation of the degree of ischemia when they are distinctly abnormal. Absence of intracellular edema and/or of membrane defects in ultrastructural investigations, however, should not be overestimated when other cell organelles are severely injured.

3. Myofilaments and Lysosomes

In more severe ischemia, the myofilaments show an irregular arrangement; the sarcomeres are either contracted or relaxed with wide I-bands exhibiting a fine N-line. In more progressed stages of ischemia, especially in irreversibly damaged cells, the Z-line is irregular or completely absent, actin filaments appear to dissolve and/or to clump together, and in advanced necrosis only myosin filaments are still present.

The mode of degradation of myofilaments is still a matter of discussion. It has been shown that lysosomal proteases are present in cardiac cells and that these enzymes, cathepsin B and D, are released from lysosomes and activated during the early phase of ischemia (BIRD et al. 1980; DECKER et al. 1977, 1979). Lyso-

somes have been shown to disappear with increasing severity of ischemia while releasing lytic enzymes, and they have been implicated in the occurrence of cell death. Furthermore, though mitochondrial as well as myofibrillar proteins undergo enzymatic degradation, it is still unclear whether or not lysosomal enzyme activity is the cause or the consequence of ischemic myocardial injury (WILDENTHAL 1978; WILDENTHAL et al. 1977). On the other hand, BIRD et al. (1980) in a recent review, described the existence of several proteinases of nonlysosomal origin, present either in myocardial cells or located in mast cells, which were all implicated in the early disruption of the sarcomeres, especially of Z-line material and α-actinin. The claimed selectivity of protein degrading enzymes would be in accordance with our own ultrastructural observations that Z- and I-band material disappears earlier in ischemic cells than do myosin filaments.

According to our experience (SCHAPER et al. 1979c), global ischemia of canine hearts produces relaxation of sarcomeres that is usually increased in severe ischemia, and relaxation is also evident in late stages of autolysis of the heart. In regional ischemia, however, the situation is more complex because of the mechanical stretch of contracting myocardium acting on ischemic tissue, and because the infarcted area is usually only partially ischemic, owing to collateral blood flow. Therefore, the existence of both relaxed and contracted myofibrils in the same cell and the concurrent incidence of contracture bands are not surprising.

In conclusion, in the electron microscope it is notable that:
An increased number of relaxed sarcomeres indicates a more severe ischemic injury.
The lysis of myofibrils begins at the Z-lines and within the I-bands, whereas the A-bands, i.e., myosin filaments, persist for a longer period of time.
Lysis of the myofibrils begins at early stages of ischemia, i.e., with moderate, still reversible, ischemic injury.

4. Other Cellular Components

Numerous other ultrastructural changes may be seen in cells finally undergoing cell death in ischemia. Accumulation of lipid droplets and proteinaceous material and disappearance of glycogen are indicative of severe disturbances in cellular metabolism. Dilatation and final dissolution of T-tubules and the sacroplasmic reticulum system may be a morphological symptom of the loss of excitation–contraction coupling. Morphological disturbances of the Golgi apparatus and the rough endoplasmic reticulum may indicate the inability of the injured cell to resynthesize cellular material needed for its survival.

5. Summary and Conclusion

From the foregoing text it becomes evident that an ischemic event finally leading to cell death involves all cellular components. This statement is mainly based on morphological observations, but it is firmly believed that these accurately reflect actual or possible functional alterations. It is further believed that hypotheses involving only one particular cellular component in the process of cell death depend mostly on the fact that in biochemical studies only purified fractions, e.g., sar-

colemma, mitochondria, or sarcoplasmic reticulum, are being studied. Ultrastructural studies, on the other hand, take into account the entire cell with its different constituents; i.e., electron microscopy, though investigating static situations, provides a more complete insight into cellular processes leading to cell death. On the basis of our own ultrastructural data, the theory is proposed that cell death is of multifactorial origin. Mitochondria, because of their unique role in providing cellular energy by metabolic processes and because of their well-established close link to the metabolic state of the cell, are certainly those cellular organelles that seem to be the prime candidates for bringing about cell death when their capacity is exhausted. On the other hand, mitochondrial membrane properties are closely connected with those of the sarcolemma, both membrane systems regulating the ion balance in each cell. Failure of the membrane pumps, i.e., of membrane enzymes, owing to ischemia, may contribute to cell death by allowing uncontrolled loss (potassium) and accumulation (calcium, sodium) of ions. Disturbances in the sarcoplasmic reticulum further add to the inability of the cell to maintain an ionic balance. On the other hand, even if mitochondria, sarcoplasmic reticulum, and the sarcolemma survive the ischemic insult, the ongoing destructive processes involving nuclei, Golgi apparatus, and rough endoplasmic reticulum would mean a loss of recuperative power through resynthesis of cellular components. The early occurrence of disturbances in and destruction of the contractile material would mean the loss of the specific functional capacity of the myocardial cell, even if the energy necessary for contraction could still be provided by the mitochondria.

In conclusion, ischemia finally leads to cell death by simultaneously involving all cellular organelles and therefore all cellular functions, i.e., energy provision, ion and fluid balance, contractile capacity, including excitation–contraction coupling, and the ability to resynthesize cellular components.

II. Reduction of Infarct Size as a Therapeutic Goal

To prevent the spread of necrosis from reaching its expected size some time after acute coronary artery occlusion was *the* theme of cardiac research in the 1970s. Initiated by BRAUNWALD and MAROKO (1979), the concept of "infarct size reduction" (a misnomer) was met with great enthusiasm by the cardiovascular research community worldwide. The problem was not particularly well phrased in the beginning; it was rather the dissatisfaction with the existing and mainly symptom-oriented therapy (treatment of pain, arrhythmias low blood pressure, etc.) that initiated a more direct approach toward protection of myocardium, especially since it had become an accepted fact that primary and secondary mortality were significantly influenced by the amount of muscle undergoing necrosis. The supply and demand concept dominated the whole spectrum of coronary heart disease and since the supply side was believed immovable, reduction of demand was thought to be a worthwhile therapeutic goal. This coincided with the availability of and the interest in β-adrenergic blocking agents that are potentially able to reduce myocardial oxygen demand. However, agents and compounds not reducing $M\dot{V}O_2$ were also tried in the hope of finding "inherent" protective activity.

Methods in the early phases of this endeavor were crude, like ECG surface mapping, or did not live up to expectations, like washout curves of creatine phosphokinase activity in plasma. Only after several years of industrial screening activity and hastily initiated clinical studies it became quite clear that the pathophysiologic basis of the new research activity was either not well enough known or available knowledge was ignored. It became quite obvious that when studying infarcts one has to measure them with quantitative morphological techniques and that a proper reference system is needed with which the size of an infarct must be compared. The proper basis of reference for the size of an infarct is the region of perfusion of the occluded artery. By definition, and in practice, an infarct can maximally reach 100% of the perfusion area of the artery. This concept was introduced by SCHAPER et al. (1969) and reintroduced by SCHAPER et al. (1979 a).

It also required several years before it was realized that the supply side (i.e., collateral blood flow) is an important part of the equation and that animal species lacking collateral blood vessels are unsuited for the purpose (SCHAPER 1979 a). Already existing knowledge about the course of tissue decay (SCHAPER et al. 1979 a) was often simply ignored or became accepted very slowly. The reliance on indirect indices of tissue damage and the lack of a proper reference system created an erroneous concept of tissue salvage: it was believed that irreversible tissue damage spreads from an ischemic centre in a "bulls-eye" fashion toward the periphery and the lateral spread was believed to be the target of intervention (COX et al. 1968). The "lateral border zone" concept became a hotly debated issue because it was almost immediately recognized by others (HIRZEL et al. 1977) that infarcts do not spread laterally, but rather spread like a wavefront (REIMER et al. 1977; SCHAPER et al. 1979 b) from the entire subendocardium toward the subepicardium.

1. Present Concepts

The general lack of a solid conceptual basis was often felt as a fundamental weakness of this research endeavor and the industrial screening activity for active compounds and the multitude of active compounds so discovered made the weakness of the central hypothesis rather more apparent. My own concept of salvage is based on the assumption that heart muscle dies in spite of the fact that the residual (collateral) blood flow provides enough energy for structural survival for at least 70% of the area at risk. The fact that (in the canine heart) over 70% of the risk region undergoes necrosis is seen as the result of "poisonous" influences amenable to corrective treatment. It is known from the studies of BRETSCHNEIDER (1964) that an oxygen supply of 0.7 ml/min per 100 g heart tissue is needed for the maintenance of structural integrity of the nonbeating heart at 37 °C. The activation of ionic pumps requires an additional 0.7 ml/min per 100 g (based on a rate of 60 beats/min and a duration of systole of 0.4 s), i.e., the activated but nonbeating heart requires 1.4 ml/min per 100 g. To deliver this amount of oxygen, about 9 ml/min arterial blood per 100 g tissue is needed. In the dog heart on the average 8 ml/min per 100 g is delivered via collaterals to the subendocardium (inner third of left ventricular wall) 12 ml/min per 100 g to the midmyocardial third, and 28 ml/min per 100 g to the subepicardial third. These values, obtained a few minutes after acute coronary occlusion (SCHAPER 1979 a), increase substantially beyond

the first 6 h after occlusion (with the exception of those for the subendocardium) and they almost double for the subepicardium after 24 h.

It is clear from these data that O_2 supply via collaterals is only slightly deficient for the subendocardium, but nevertheless more than two-thirds of the left ventricular wall undergoes necrosis. If we add to aerobic energy the ATP production from glycolysis and from substrate level phosphorylation of Krebs cycle intermediates obtained via transamination from aspartate and glutamate (TAEGTMEYER 1978), even the subendocardium should be more resistant to necrosis than it actually is.

The reasons for this "unnecessary" loss of tissue may be the result of the following influences:

Additional energy is spent in futile attempts to contract

Ischemia-related release of catecholamines "flogs" failing muscle and increases energy expenditure

Free fatty acids (FFAs) from endogenous lipolysis, and from collateral flow "short-circuit" glycolysis, inhibit energy transfer between mitochondria and sarcomeres, and exert detergent (i.e., damaging) actions

Calcium overload occurs

Calcium-activated phospholipases destroy membranes

Slightly damaged cell membranes attract leukocytes which intensify the damage to myocytes that may have survived – with or without reflow

Free radicals may be produced from the cleavage of purines and from the catabolism of catecholamines and they may lead to damaging peroxidation of vital structures.

Among these potentially detrimental influences, electrical activation of the ischemic myocardium, subsequent electromechanical coupling, and abortive attempts to contract are probably the most important ones because of their energy-wasting effects. If drugs were available that would inhibit electromechanical coupling only in ischemic myocardium, structural damage might be greatly delayed if not altogether prevented.

It is known that myocardial ischemia releases catecholamines and interferes with reuptake processes (HIRCHE et al. 1980). The release as well as the inhibition of reuptake stimulate adenylate cyclase and the tissue concentration of cyclic 3′-5′-monophosphate rises (WOLLENBERGER et al. 1969; PODZUWEIT et al. 1978). Although these actions of catecholamines can be blocked with β-blocking agents, several members of this class of compounds have been tested in the canine coronary occlusion model and have not been found effective as protective agents.

All other listed mechanisms that are potentially detrimentral to survival probably play only a minor role. FFAs are often increased in plasma of patients with acute myocardial infarction because of secondary adrenergic stimulation (OLIVER 1976). They enter ischemic myocardium via collateral flow and may disturb metabolism in several ways: by short-circuiting glycolysis at the level of glyceraldehyde-3-phosphate because FFAs are reesterified to triglycerides, fat droplets can be visualized with the electron microscope. They may, in the form of long-chain acylcoenzyme A, inhibit the adenine nucleotide translocase of mitochondria (SHUG et al. 1975), thereby interrupting the supply of ATP from the mitochondria to the cytoplasm and they may damage membranes because of their detergent ac-

tion. Excessive concentrations of FFAs are associated with the occurrence of arrhythmias (OLIVER 1975). There is evidence that the activation of glycolysis (and of glycogenolysis) is always associated with lipolysis (HULSMAN and STAM 1979) although fatty acids cannot be oxidized in ischemia. Endogenous lipolysis in ischemia may even be of greater damaging importance. Drugs that inhibit lipolysis have been shown to reduce indirect indices of ischemia; conclusive evidence about the protective action of these drugs is missing.

Calcium overload was postulated as a pathogenetic mechanism of cell death in some animal models that are only remotely related to coronary-induced ischemia, i.e., acute poisoning of rats with excessive doses of isoproterenol (RONA et al. 1975). Necrotic cells have a high affinity for calcium and cause and effect relationships are thus difficult to establish. However, compounds known to inhibit calcium channels of the cell membrane prevent necrosis in these models (FLECKENSTEIN 1983) and it was therefore concluded that calcium overload is a cause rather than a consequence of catecholamine-induced necrosis. In a coronary occlusion model, the situation is by no means very clear: surviving but heavily damaged ischemic and reperfused myocardium does not show a net uptake of calcium, only irreversibly damaged (i.e., infarcted) tissue does (R. B. JENNINGS 1984, personal communication). No conclusions can be drawn from these experiments pertaining to intracellular redistribution of calcium. The activation of phospholipases during ischemia and its quantitative role (probably small) is difficult to estimate at present.

The production and the damaging effects of free radicals is particularly well known in the lung, but interesting new observations also suggest a role in ischemia, mainly during reperfusion (MCCORD 1983). Free radicals of oxygen are formed in enzymatic reactions involving oxidases where electrons are directly transferred to oxygen. The conversion of hypoxanthine to xanthine and from xanthine to urate is catalyzed by xanthine oxidase, and part of the catabolism of catecholamines involves monoamine oxidase. Xanthine oxidase is an interesting enzyme, because in some tissues (intestines) it is transformed during ischemia from xanthine dehydrogenase, an enzyme not producing free radicals.

Since adenine nucleotides are broken down during ischemia to urate (and allantoin in the dog), the production of free radicals is a very real possibility, and if they are produced, it is almost certain that they produce tissue damage. Although this new hypothesis is very attractive, a few observations tend to limit the significance of free radicals in ischemic tissue damage:

Since oxygen is in very short supply during ischemia, the oxidase reaction may be limited by the availability of oxygen. It appears that more favorable conditions for free radical production exist during reoxygenation. This leads immediately to the question of reperfusion damage which probably does not exist (SCHAPER and SCHAPER 1983).

Xanthine oxidase is not present in all human hearts nor in all mammalian hearts. If xanthine oxidase is present, its activity is low. Our own experiments with nucleoside transport blockers have shown (HENRICHS et al. 1984 b) that xanthine oxidase probably does not reside within the cardiac myocyte, but rather in pericytes and in endothelium.

Experiments employing allopurinol, a xanthine oxidase inhibitor, have produced controversial results: no myocardial protective action was reported by K. REIMER (1983, personal communication), whereas a significantly protective effect was reported by AKIZUKI et al. (1984).

Premature "autoaggression" by leukocytes is another concept which tries to explain premature cell death. The casis for this hypothesis are the following observations:
Smaller infarts were reported after coronary ligation in the dog heart when the animals were previously made leukocytopenic either by antisera or nitrogen mustard (J. CAULFIELD 1983, personal communication)
Smaller infarcts were reported after coronary ligation in the dog heart with steroidal and nonsteroidal anti-inflammatory agents
Very soon after coronary occlusion (i.e., 30–40 min) leukocytes can be found in the extravascular–extracellular space (SCHAPER 1979)

Autoaggression of potentially viable cells, that are only reversibly damaged by ischemia, is probably not a viable hypothesis, because ultrastructural studies from my group (SCHAPER 1979b) have shown that early leukocyte invasion is found only in the vicinity of irreversibly damaged myocardial cells. Since the diagnosis of cell death rests on ultrastructural criteria that are not influenced by the presence of leukocytes (appearance of mitochondria), we believe that irreversible damage of myocytes is the primary event, and invasion of leukocytes is a consequence rather than the cause. Early studies with leukocytopenia could have been misled by the light microscopic appearance of irreversible ischemic injury. Areas of no flow at all, i.e., posterior papillary muscle after proximal left circumflex occlusion in poorly collateralized canine hearts, do look well preserved under the light microscope, but they are, in fact, "mummified" because vital reactions to cell death come late, because of the total absence of blood flow. If studied with the electron microscope, these mummified cells have all the classical signs of cell death.

The earlier mentioned NIH-sponsored study, where four laboratories in the United States tested coded solutions in their animal models, produced only negative results with the nonsteroidal anti-inflammatory agent ibuprofen (NIH 1984). Our own studies with the ibuprofen derivative flurbiprofen in the anesthetized, open-chest, two-vessel occlusion model (MATSUOKA and SCHAPER 1984) was also negative. In spite of reported positive results with cortisol and its derivatives, this principle of treatment was soon abandoned because it interfered with scar formation, and the incidence of ventricular aneurysms was increased.

2. Diagnosis of Experimental Infarcts and Measurement of Infarct Size

As already pointed out, the measurement of infarcts must rely on morphological criteria. Infarct size so determined must be compared with the perfusion area of the occluded coronary artery. This comparison is necessary because otherwise infarct size depends mainly on the size of the occluded coronary artery: occlusion of small arteries produces small infarcts and vice versa. Before the introduction of the concept of the perfusion area (or risk region), infarcts were often compared

with the surface area of a left ventricular ring, which produced enormous variation because the perfusion areas of arteries vary so much. For the diagnosis of infarcts and for the measurement of infarct size, light microscopic histology is the "gold standard". Light microscopic diagnosis depends on the visualization of cell lysis, on vital reactions to myocardial cell death (leukocyte invasion, macrophages, activated mesenchymal cells), and on altered staining properties of dead tissue. All these signs become positive discriminative criteria only after 12 h, i.e., when it is too late for intervention. For a correct infarct size measurement, infarcts as well as reperfused infarcts must have been present for at least 24 h or, preferably, 2 days. This makes histology a very time-consuming method, not to mention the technical difficulties in producing and processing histologic sections from the entire left ventricle of a large mammalian heart (dogs, pigs).

We showed (SCHAPER et al. 1969; KLEIN et al. 1981 a) that incubation with either triphenyltetrazoliumchloride (TTC) or with *para*-nitroblue-tetrazolium (*p*-NBT) produced results identical to those of histology (SCHAPER et al. 1979) with the added advantage that the diagnosis of infarcts and the measurement of infarct size is possible after relatively short occlusion times (longer than 3 h) or after very short occlusion times (20–40 min) if the myocardium is reperfused. Tetrazolium salts are electron acceptors, and the transition from a colorless incubation medium containing tetrazolium to a dye precipitate over noninfarcted muscle of a ring of left ventricular tissue requires the activity of dehydrogenases. Since enzyme activity declines in infarcted myocardium, partially because enzymes "leak" out of damaged cells and are washed out of the infarcted area by collateral flow, and partially because of denaturation, the absence of staining over infarcted tissue was always explained by the absence of dehydrogenase activity. In experimental myocardial ischemia followed by reperfusion, this mechanism is not operative, although a discriminative staining takes place. We were able to show (KLEIN et al. 1981 b) that occlusions lasting up to 24 h have sufficient dehydrogenase activity for the reaction to proceed. With short occlusions (20–40 min) followed by reperfusion, dehydrogenase activity is perfectly normal in clearly infarcted tissue. We discovered (KLEIN et al. 1981 a, b) that the mechanism of differential staining (normal tissue stained, infarcted tissue not stained) is not the absence of dehydrogenase activity, but rather the absence of NAD, i.e., the coenzyme for most dehydrogenase reactions:

If a tissue slice with an experimental infarct is incubated in *p*-NBT, the nonstained infarcted tissue turns purple immediately upon addition of NAD.

If a similar tissue slice is incubated in *p*-NBT (or TTC) and succinate is added as a substrate, the previously nonstained infarct turns purple immediately: succinate dehydrogenase does not require NAD as a cofactor.

If NAD is actually measured in a *p*-NBT-negative (infarcted) tissue sample, the tissue concentration of the sum of NAD plus NADH is extremely low (KLEIN et al. 1981 a, b) and does not recover upon reflow. Reflow usually decreases NAD further.

The reason for the disappearance of NAD/NADH is the activation of a cell membrane-bound enzyme (glycohydrolase) by ischemia, probably via damage of

the sarcolemmal membrane. NAD is cleaved by glycohydrolase and thereby irreversibly lost. This process coincides with (and is probably causally related to) the "point of no return", i.e., the moment when reversible injury becomes irreversible. Although the correlation between ultrastructure and NAD tissue concentration is excellent (KLEIN et al. 1981 a, b), we have reason to believe that irreversible injury begins before cleavage of NAD: a myocardial infarct cannot be diagnosed with tetrazolium salts before about 3 h of coronary occlusion – unless the tissue is reperfused. If, for example, a coronary occlusion has lasted for 2 h and the tissue is not reperfused, the tissue will stain uniformly, i.e., the NAD concentration is sufficient for electron transport. If the tissue is reperfused, the NAD content suddenly drops in infarcted tissue and the tissue does not stain. I interpret this observation by a "labilization" of NAD which had already left its natural compartment, but which was still available for the staining reaction. With reperfusion, this labile NAD is rapidly washed out and staining becomes discriminative.

The differences between TTC and *p*-NBT are minor, but they may become significant under special conditions: TTC is diffusible, whereas *p*-NBT is not, TTC crosses cell membranes and can be infused intravenously for the staining of normal tissue. Since tissue respiration is bypassed, the injection is usually lethal. The easy diffusibility of TTC causes a somewhat fuzzy border between normal and infarcted tissue, whereas the *p*-NBT border is very sharp: the reaction takes place only on the cut surface of a cell and the reaction product is completely insoluble, whereas formazan (the dye precipitate) from TTC is slightly soluble in water. If TTC- and *p*-NBT-treated tissue are stored in formaldehyde, the traces of methanol, usually present in formalin, will rapidly dissolve formazan from TTC, but not that from *p*-NBT.

Infarcts visualized with tetrazolium salts are usually measured by planimetry and expressed as a fraction of the region at risk. There are several methods to measure risk regions. The first and one of the most reliable methods was introduced by Kalbfleisch and Hort (KALBFLEISCH 1975) who measured risk regions of the human heart using barium–gelatin injections of the coronary arteries at autopsy. The vascular territories were identified on the basis of stereoangiograms of the whole heart and on the basis of angiograms of heart slices. The angle of penetration of the arteries and the density of filling of small arteries are reliable estimates of the risk region. Anatomic risk regions based on the area of perfusion of the occluded artery are also obtained by postmortem perfusion of the occluded artery with TTC and of the remaining normal myocardium with a blue dye (Monastral blue, methylene blue, etc.). Under the condition that both perfusions occur simultaneously and under identical perfusion pressures, three color zones are obtained: nonischemic normal tissue is blue, ischemic surviving tissue is red, and infarcted tissue is (almost) white. The latter is also caused by the washout of myoglobin.

An essentially different method of measuring the risk region is the systemic or intracoronary injection of radioactive tracer microspheres (AKIZUKI et al. 1984). Since delivery of these microspheres is by coronary and collateral blood flow, this risk region may be somewhat smaller than the anatomic risk region. Infarct sizes based on a microsphere flow risk region are usually somewhat larger than those that are compared with anatomic risk regions.

3. Determinants of Infarct Sice

The speed of necrosis and the final size of an infarct relative to the perfusion area of the occluded artery is determined by three factors:

Time after occlusion
Collateral blood flow
Myocardial oxygen consumption.

Time after occlusion is a very obvious determinant of speed and extent of necrosis: myocardium does not die immediately after cessation of blood flow. If a heart is made globally ischemic, as in the early days of cardiac surgery, by clamping venous return as well as the aorta, the heart, after ischemic arrest, could be successfully resuscitated after about 15–20 min at 37 °C. Replacing ischemic arrest by cardioplegic arrest (procainamide or high potassium concentrations) increased the reversible ischemic interval, and cooling of the heart to reduce oxygen requirements increased survival to about 2 h and longer, depending on temperature and type of cardioplegia. With these experiments, certain principles were established (delay of necrosis by reduction of O_2 demand), but these principles are difficult to translate into the clinical management of acute coronary occlusion. The acute coronary occlusion in humans is comparable to ischemic arrest at 37 °C with two modifications:

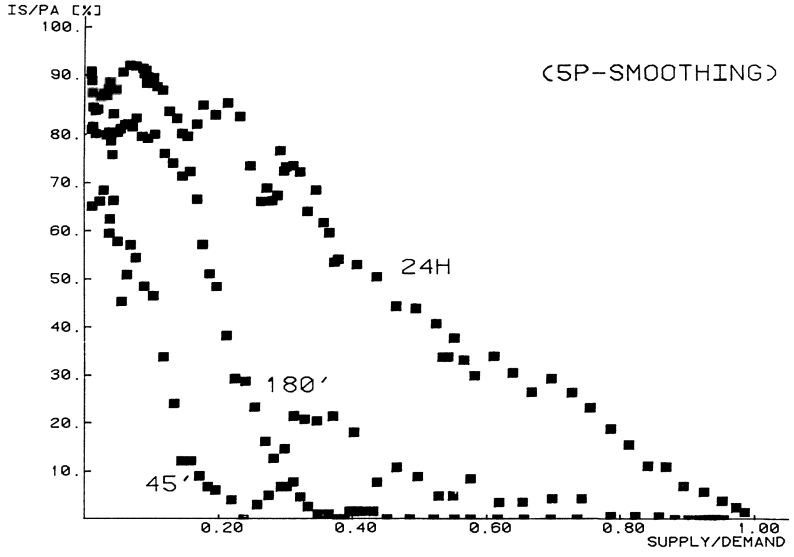

Fig. 10. Infact size (IS) is expressed as a fraction of the perfusion area (PA) of the occluded artery. This fraction is contrasted with the perfusion deficit which is expressed as the ratio of supply (collateral flow) to demand (flow to nonischemic left ventricular regions). The graph shows that short occlusion times (45 min) are tolerated even in the presence of low supply : demand ratios. Infarct size increases with time and with the perfusion deficit. Data from about 200 hearts were subjected to a five-point smoothing procedure which leaves some uncertainties near the 100% infarction mark; a supply : demand ratio of 0 with a 24-h occlusion should give a 100% infarct. Extrapolation of the 24-h curve would have intersected at the 100% mark

Unlike elective ischemic arrest in cardiac surgery, there is an unknown amount of collateral blood flow (a positive modifier)
Unlike ischemic arrest, normally perfused myocardium exerts strong physical forces upon the noncontracting of weakly contracting ischemic myocardium (a negative modifier)

The outcome of the struggle between these opposing factors is difficult to predict, but depends crucially on the presence of collateral blood flow: if there is no collateral flow, time would remain the only determinant of infarct size, and any modification of cardiac metabolism in vivo would have only a small influence on the speed of necrosis and all tissue within the risk region is doomed. The existence and amount of collateral blood flow markedly changes the speed and extent of the necrotizing process and modifications of cardiac metabolism (reduction of O_2 demand) influence the speed of infarction only in the presence of collateral flow. Let us assume a situation of acute coronary occlusion in a heart with good collateral blood flow (about 30 ml/min per 100 g): the change from a high normal blood flow of 100 ml/min per 100 g to 30 ml/min per 100 g is quite feasible by reduction of heart rate to about 50 beats/min. These 30 ml transport O_2 6 ml/min per 100 g to the tissue of which at least 4.5–5 ml/min can be extracted. This amount of oxygen allows mechanical function at a low heart rate and prevents ischemia and infarction. At a high O_2 demand, infarction is inevitable. The relationships between O_2 demand and collateral blood flow are shown in Fig. 10. The

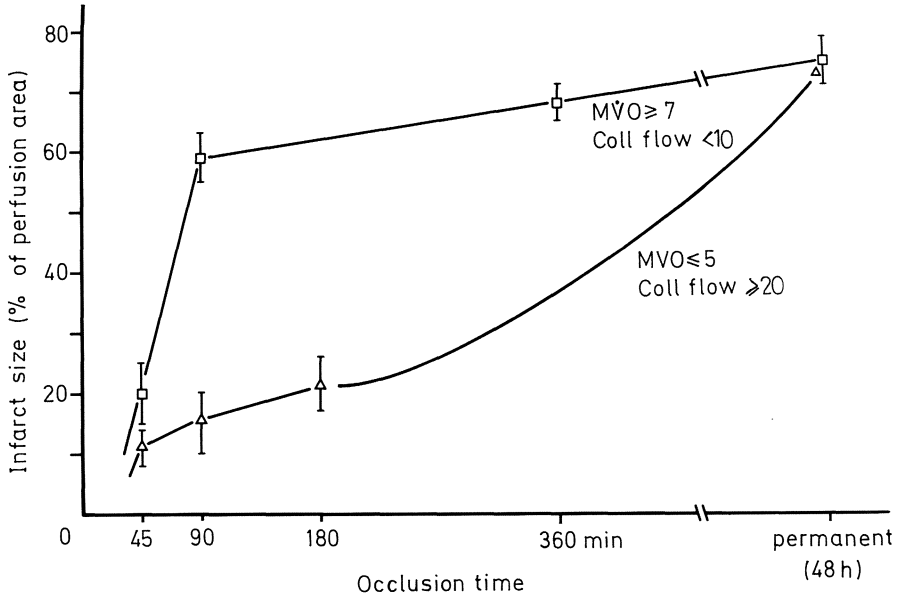

Fig. 11. Infarcts size expressed as a fraction of the perfusion area is plotted versus occlusion time. All values (with the exception of 48 h) show reperfused myocardium. Infarct diagnosis was made with *p*-NBT. The graph shows the influence of $M\dot{V}O_2$ and collateral blood flow. Salvage of ischemic myocardium by low $M\dot{V}O_2$ and relatively high collateral blood flow is possible up to 6 h after occlusion, but at 48 h identical infarct sizes have been reached

ratio of collateral flow to flow in nonischemic muscle reflects the relationship between supply and demand. Demand is met by sufficient flow in the normal region. True supply to the ischemic region is the collateral flow. When this ratio is 1, no flow deficit exists; with no collateral flow, the ratio is zero, the tissue is maximally ischemic, and will die soon. If the perfusion deficit is 0.5, i.e., collateral flow is 50% of normal flow, no infarction will occur up to 3 h of occlusion, but about 50% of the risk region will infarct if the occlusion is maintained for 24 h.

A simpler way to demonstrate the relationship between time, collateral blood flow, and O_2 demand is the "characteristic curve" of tissue decay (Fig. 11) which plots infarct size (relative to risk region) as a function of time with O_2 demand and collateral flow as parameters on the curve. Figure 11 shows that interventions aimed at reduction of O_2 demand do indeed delay tissue necrosis, but they cannot prevent it: final infarct size is virtually the same. The delay of the necrotizing process has already been shown in Fig. 10, it assumes special significance in clinical reperfusion, i.e., streptokinase treatment or acute coronary artery bypass operations.

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CHAPTER 3

Pharmacodynamic Principles of Action of Antianginal Drugs

O. KRAUPP

A. Introduction

Actions of substances on biological systems are termed pharmacodynamic when they are considered to counteract a particular disease of the underlying pathological disorder. It follows that throughout the ages the pharmacodynamic principles of action have been directly dependent on the prevailing concepts of pathology and developed in close conjunction with advances in this field. The clinical pharmacological testing of preparations on patients on the basis of these considerations frequently failed to result in any clinical efficacy, not least because the pathological concept of the disease in question proved to be incorrect. The mutual interdependence of pharmacodynamic principles of action and fundamental pathophysiological concepts of the causes and nature of specific disturbances has been manifest in coronary disease with greater clarity than in any other disease.

The concept expressed by BRUNTON (1897) of the antianginal action of amyl nitrite was the elimination of the pressure load of the heart during an anginal attack by means of the peripheral vasodilating action of the substance. Advances in the pathophysiological basis of coronary disease corrected this concept by bringing "the disparity between the myocardial demand for oxygen and the supply brought by the coronary circulation" (LEWIS 1931; HAMMAN 1935) into the foreground in explaining the mechanism of cardiac pain. The logical consequence of the new concept was to ascribe the clinically proven antianginal action of the organic nitrates and nitrites to coronary dilating components of action, as shown to occur in vitro (ESSEX et al. 1940; KATZ et al. 1938). The pharmacodynamic guiding principle of coronary artery dilatation led, consequently, to the development of a series of specific coronary vasodilators, whose effect on the total coronary circulation in the intact animal by far outstripped the action of nitrates, both with regard to intensity and duration (BRETSCHNEIDER et al. 1959; KRAUPP et al. 1964; NITZ and POETZSCH 1963; SCHAPER et al. 1966).

The clinical failure of coronary dilators of the dipyridamole type to cut short attacks of angina pectoris (KINSELLA et al. 1962; DEGRAFF and LYON 1963; FOULDS and MACKINNON 1960; HUNSCHA et al. 1966; SBAR and SCHLANT 1967) led to new concepts of the site of action of vasodilating substances on the coronary circulation and their influence on the blood flow to, and metabolism of, ischaemic tissue. This applies, in particular, to the effect on collateral blood flow (SCHAPER 1979b) and to the blood distribution between endo- and epicardium (BECKER et al. 1971; MOIR 1972; BERDEAUX et al. 1976; WINBURY 1971; MOIR and DEBRA 1967) and also between ischaemic and normal myocardium (FAM and

MACGREGOR 1964; BECKER et al. 1971; SAITO 1976; PIT and GRAVEN 1970; THUILLEZ et al. 1983; TOMIOKE et al. 1978; NUMORA et al. 1980). A further result was the discovery of the unfavourable redistribution of blood from ischaemic to normal myocardium (coronary steal phenomenon) under the influence of such vasodilators (BECKER 1978; COHEN 1982; COHEN et al. 1976; GROSS et al. 1978; MANTERO and CONTI 1969; MEYER et al. 1974; SCHAPER et al. 1973; WICHMANN et al. 1978 a, b; WILCKEN et al. 1971).

B. The Principles of "Unloading" the Heart

Because of the dominant role of autoregulation of metabolic processes in the control of the vasal components of coronary resistance, neurogenic and cardiodynamic influences receded temporarily into the background, not only as factors responsible for physiological regulation, but also as causes of circulatory disturbances. However, the development of modern methods to measure and record blood flow and pressure in intact animals and humans drew attention to the significance of extravascular factors in circulatory regulation under physiological conditions, as well as to their role in the pathological mechanism of circulatory disturbances (BRAUNWALD and MAROKO 1979; BRAUNWALD et al. 1958; FEIGL 1983; KIRK and HONIG 1964; MEESMANN 1973; MÜLLER and RORVIK 1958; PARKER et al. 1966; RAFF et al. 1972). The following feedback mechanisms were recognized as being of causal significance with respect to the course of acute myocardial ischaemia: decrease in blood flow due to intravasal processes; peripheral initiation of anaerobic metabolism; lowering of contractility with increase in left ventricular diastolic pressure; increase in left ventricular volume and wall stress; increase in the intrinsic components of coronary resistance; and, finally, augmentation of the hypoxia in the poststenotic peripheral areas. In parallel to this there are: decrease in contractility; increase in preload; decrease in stroke volume, cardiac output, and systolic blood pressure; activation of the sympathetic nervous system, and, thus, a rise in heart rate and in the peripheral vascular resistance, as well as in the contractility of the as yet adequately perfused myocardial areas; and increase in oxygen consumption with a consequent further increase in hypoxia of the already ischaemic myocardium.

These events lead to the concept of angina on effort, with the assumption of a primary rigid stenosis at typical sites on the epicardial coronary artery branches and the secondary development of these cyclic pathological processes on effort and on exceeding the coronary reserve. On the basis of this concept it is possible to derive several pharmacodynamic principles of action which largely aim at the abolition of feedback effects of disturbances of cardiac dynamics on the circulatory and metabolic state of the ischaemic myocardium. In this connection it is necessary to distinguish between pharmacodynamic measures to reduce the oxygen requirements of the heart and those aiming to reduce the extravasal component of coronary resistance.

The oxygen consumption of the heart largely depends on the contractility, heart rate and total force generation in the ejection phase (afterload) (BRETSCHNEIDER 1972; SONNENBLICK et al. 1968; BRAUNWALD 1971; WEBER and JANICKI 1979). Hence, feasible and purposeful individual pharmacodynamic effects to re-

duce myocardial oxygen consumption are: (1) a decrease in preload; (2) a decrease in contractility; (3) a diminution of heart rate; and (4) a decrease in afterload: (a) through a decrease in arterial impedance; and (b) through a reduction in left ventricular volume.

Pharmacodynamic effects aimed at reducing the extravasal components of the coronary resistance are: (1) a fall in left ventricular diastolic pressure (reduction of preload); (2) a prolongation of the relative duration of diastole; and (3) a reduction in systolic tension development. The individual functions influenced by these effects are closely interrelated within the regulatory mechanisms of cardiac activity. Hence, the pharmacodynamic action components are also subject to mutual interference and are, moreover, affected by the activity and state of the individual biological function.

An important aspect is the differentiation between effects on the heart with normal output and effects on the decompensated heart. One example to illustrate this point is as follows: a negative inotropic effect usually leads to a decrease in oxygen consumption in the heart with a normal stroke volume. On the other hand, a negative inotropic effect on the decompensated heart with raised diastolic pressure values and reduced ejection fraction results in a further increase in preload and in a reflex activation of the sympathetic nervous system, whereby the increase in heart rate and contractility may antagonize, or even reverse, the original effect on cardiac oxygen consumption. This accounts for the fact that a positive inotropic effect on the decompensated heart may lead to a lowering of the raised myocardial oxygen consumption via a diminution of reflex activation of the sympathetic nervous system (COVELL et al. 1966; WEBER and JANICKI 1979).

C. Groups of "Unloading Substances"

The substances selected according these principles of action and introduced into the armamentarium of clinical management of coronary disease all display several components with respect to their spectrum of action. Three groups of coronary drugs of this type can be distinguished according to their clinically and experimentally proven principal mode of action:

1. Drugs whose main effect is to achieve a diminution of a raised preload by means of lowering the venous return: organic nitrates (reviewed by LICHTLEN et al. 1981; NEEDLEMAN 1975), molsidomine (reviewed by BASSENGE and SCHMUTZLER 1982; LOCHNER and BENDER 1979). These are vasodilators with a segmental preference for the smooth muscles of the postcapillary capacity vessels (PARKER et al. 1967; WILLIAMS et al. 1965; MARCHETTI et al. 1964; MASON and BRAUNWALD 1965; HONIG et al. 1960; FERRER et al. 1966; HOLTZ et al. 1978; WILKINS et al. 1937) and a specific mechanism of action utilizing activation of cytoplasmic guanylate cyclase via the intermediary formation of *S*-nitrosothiols (IGNARRO et al. 1981). Direct consequences of this principal action are: (a) a reduction of the extrinsic component of coronary resistance (VATNER and HEYNDRICKX 1975); (b) a diminution of ventricular size (WILLIAMS et al. 1965; FRICK et al. 1968; VATNER et al. 1972; O'ROURKE et al. 1971); (c) a reduction of diastolic and systolic wall tension (WILLIAMS et al. 1965; FRICK et al. 1968; KIRK and HONIG 1964; COHEN

et al. 1973); and (d) a decline in myocardial oxygen consumption (MARCHETTI et al. 1964; GANZ and FRONEK 1961; BERNSTEIN et al. 1966; PARKER et al. 1971; HOESCHEN et al. 1966). Further components of action are a weak vasodilating effect on the large epicardial arterial branches (FAM and MACGREGOR 1968; WINBURY et al. 1969; HARDER et al. 1979; SCHNAAR and SPARKS 1972; FORMAN and KIRK 1980; COHEN and KIRK 1973; FELDMAN et al. 1981) and, moreover, a dilatory effect on the peripheral circulation, with a decrease in peripheral resistance and an increase in aortic compliance (WILLE et al. 1980; BERNSTEIN et al. 1966; SAUER et al. 1981) and, consequently, an additional lowering effect on afterload (WILLE et al. 1980; VATNER et al. 1972). The diminution of the extrinsic component leads, in addition to a dilating action on the epicardial arterial circulation, to an improvement in the blood flow to the subendocardial myocardium (BECKER et al. 1971; MOIR 1972; MATHES and RIVAL 1971; WINBURY 1971; MOIR and DEBRA 1967), and to an increase in collateral blood flow to ischaemic myocardial segments (FAM and MACGREGOR 1964; MATHES and RIVAL 1971; GOLDSTEIN et al. 1973, 1974; WINBURY et al. 1969; HOROWITZ et al. 1971; LINDER and SEEMAN 1967).

2. Drugs whose main effect consists of a lowering of the arterial impedance, and, thereby, of a reduction in the afterload of the heart (calcium channel blocking agents). These are vasodilators with a preferential site of action on smooth muscles of the arterial vessels and a specific mechanism of action through blockade of the slow influx of calcium ions across the membrane (reviewed by FLECKENSTEIN and ROSKAMM 1980; FLECKENSTEIN 1983). Regarding the antianginal action, the inhibition of calcium entry is associated with at least four beneficial effects: (a) unloading of the left ventricle owing to a decrease in peripheral arterial impedance (SELWYN et al. 1979; ROSS and JORGENSEN 1967; GROSS et al. 1979; WARLTIER et al. 1983; SATO et al. 1971; EKELUND 1978; VERDOUW et al. 1980; ROSKAMM et al. 1966; KALTENBACH et al. 1972, 1979; KURITA 1975); (b) coronary vasodilation (NAYLER et al. 1968; NAGAO et al. 1972; GRÜN and FLECKENSTEIN 1972; HIMORE et al. 1975 b; ANGUS et al. 1976; RUDOLPH et al. 1971) with an increase in collateral blood flow to ischaemic segments (WARLTIER et al. 1983; ZYVOLOSKI et al. 1982; HENRY et al. 1978; SELWYN et al. 1979; WEINTRAUB et al. 1981; NAGAO et al. 1975; JOLLY and GROSS 1980); (c) redistribution of blood flow from epicardial to endocardial parts of the myocardium (BERDEAUX et al. 1976; WARLTIER et al. 1981; MILLARD 1980); and (d) reduction of myocardial contractility (SELWYN et al. 1979; NOMURA et al. 1980; HIMORI et al. 1975 a; NAYLER and SZETO 1972; ANGUS et al. 1976).

3. Drugs whose main effect is a lowering of the sympathetically induced increase in heart rate, contractility, and myocardial metabolism (β-adrenoceptor blocking agents: PARRATT 1980; PRICHARD 1981; BRAUNWALD et al. 1983). These substances act as competitive inhibitors of the agonistic action of norepinephrine released from sympathetic nerve endings or catecholamines released from the adrenal medulla on the β_1-receptors of the heart (LEDSOME et al. 1974; MINNEMAN et al. 1979; SAAMELI 1972). The most important consequence of the principal action is an economization of cardiac performance under conditions of stress (JORGENSEN et al. 1973; WOLFSON and GORLIN 1969), owing to a diminution of the rise in heart rate (HILLIS et al. 1979; MUELLER and AYRES 1977; ROSKAMM 1972) and

contractility (ROSKAMM 1972; SONNENBLICK et al. 1965; WOLFSON and GORLIN 1969), in conjunction with a compensatory increase in stroke volume (BATTLER et al. 1979; ROSKAMM 1972). There is a simultaneous diminution of a stress-linked increase in myocardial metabolism (ARMSTRONG et al. 1977; GOODLETT et al. 1980; PIEPER et al. 1980) and oxygen consumption (ARMSTRONG et al. 1977; MAROKO et al. 1973; MUELLER and AYRES 1977). Further components of action consist of: (a) a redistribution of blood from the subepicardial to the subendocardial myocardial layers, owing to a depression of vasodilating β-adrenergic influence and, hence, a predominance of α-adrenergic tone in the larger epicardial arteries (BECKER et al. 1971; BERDEAUX et al. 1978; GROSS and WINBURY 1973; PARRATT and GRAYSON 1966; STEIN et al. 1967) as well as an improvement of collateral blood flow to ischaemic segments (BARCIA et al. 1976; KLONER et al. 1971; PIT and GRAVEN 1970; TOMOIKE et al. 1978; VATNER et al. 1977); and (b) a shift in myocardial metabolism from free fatty acid oxidation to the relatively oxygen sparing aerobic metabolism of carbohydrates (MARCHETTI et al. 1968; MUELLER et al. 1974; OPIE and THOMAS 1976).

D. The Vasospastic Concept

Over the past decade concepts of the nature of the pathophysiological mechanisms of disturbances of myocardial blood flow have undergone certain changes (SPANN 1983). The observations of PRINZMETAL et al. (1959) and, especially, the work of MASERI et al. (1975, 1976, 1978) gave the impetus for reconsideration of the vasospastic genesis of, or at least a vasospastic contribution towards, disturbances of the cardiac circulation (HILLIS and BRAUNWALD 1978). A series of clinically proven and well-documented cases of vasospastic angina (CHENG et al. 1973; MACALPIN et al. 1973; OLIVA et al. 1973; OLIVA and BRECKENRIDGE 1977) provoked experimental studies on conscious dogs with reinvestigation of the influence of the α-adrenergic nervous system on the resistance and blood flow parameters in the coronary circulation. The long-standing theory of the exclusive dominance of metabolic autoregulatory influences on the coronary vessels was no longer tenable (FEIGL 1983, pp 107ff) on the basis of the results obtained.

An increase in coronary resistance, which was preventable by α-blockade, was elicited by direct and indirect reflex stimulation of efferent sympathetic nerve fibres (PITT et al. 1967; SZENTIVANYI and JUHASZ-NAGY 1963) and by intracoronary injection of norepinephrine (VATNER et al. 1974). It is now certain that α-receptors at the larger coronary artery branches play a role in the pathogenesis of certain forms of disturbances of coronary circulation. In particular, there appears to be a tendency towards release of lumen-narrowing constrictor substances in areas affected by partial occlusion (FREEDMAN et al. 1982; HARKER and RITCHIE 1980; HENRY and YOKOYAMA 1980; MASERI et al. 1980). The concept held over decades that angina on effort is caused by rigid stenosis and that acute myocardial infarction is due only to occlusive degenerative changes in the vessel wall was modified by the assumption of simultaneously occurring vasospastic processes (MASERI et al. 1980). This augmented view of the pathophysiological nature of cardiac circulatory disturbances goes hand in hand with a change in the concepts of pharmacodynamic action. The therapeutic principle of coronary vasodilation, which had

been virtually deserted on discovery of the coronary steal phenomenon following the intravenous administration of coronary drugs of the dipyridamole type has been reintroduced in a modified version. Drugs with a specific vasodilating point of attack on the smooth muscles of the larger arterial branches (calcium channel blocking agents, nitrates) with a positive effect on the collateral blood flow to ischaemic myocardial segments are now used as the drugs of choice in the management of suspected coronary angiospastic processes (BRAUNWALD 1981; DISTANTE et al. 1979; FLECKENSTEIN 1983, pp 297–306).

E. Concepts Underlying Inhibition of Platelet Aggregation

A concept of simultaneously occurring anatomical (obstructive) and functional (constrictive) processes has become manifest also with respect to the pathogenesis of acute lumen-narrowing processes on the basis of atherosclerotic changes of the intima. The concept of rigid stenosis determining coronary reserve has been replaced by a more dynamic model (MASERI et al. 1980). The central effect consists of platelet aggregation at the site of intimal lesions (HARKER and RITCHIE 1980; MASERI et al. 1980; MUSTARD 1976) or of unfavourable flow conditions (COLMAN 1978; DOCK 1946), triggered off by the action of additional factors: platelet activators such as ADP (BORN 1979; BORN and KRATZER 1981; JORGENSEN et al. 1967), or norepinephrine (HAFT et al. 1972). Platelet aggregation can produce a temporary narrowing, which either resolves spontaneously or, alternatively, leads to permanent occlusion (HARKER and RITCHIE 1980). In a secondary phase, vasoconstrictoring substances such as thromboxane A_2 and serotonin are released (HAMBERG et al. 1975; HENRY and YOKOYAMA 1980; MULLER-SCHWEINITZER 1980; SVENSSON et al. 1976), a procedure which is considered to initiate vasospastic reactions (HARKER and RITCHIE 1980; HENRY and YOKOYAMA 1980; HIRSH et al. 1981 b; MASERI et al. 1980; NEEDLEMAN et al. 1977; SVENSSON et al. 1976).

Current views of the initial processes of platelet aggregation achieve special importance on consideration of preventive or curative pharmacodynamic concepts. Two major concepts are being followed up at present and subjected to mutual assessment.

1. The assumption of a primary causal role of an intravasal ADP increase, whereby the erythrocytes provide the ADP source as a result of chemical or mechanical damage (BORN 1979; BORN and KRATZER 1981; BORN et al. 1976; GAARDER et al. 1961).

2. Changes in the dynamic equilibrium between aggregation-inhibiting prostanoids in the vessel wall (prostacyclin) (AIKEN et al. 1981; GRYGLEWSKY et al. 1976; MONCADA et al. 1976 a, 1977) and aggregation-triggering prostanoids in the platelets (thromboxane A_2) (DEMBINSKA-KIEC et al. 1977; ELLIS et al. 1977; GRYGLEWSKY et al. 1976; Hirsh et al. 1981 a; MONCADA and VANE 1970).

Pharmacodynamic concepts emanate from both views (BRAUNWALD 1978). Pharmacodynamic effects leading to an inhibition of ADP release are in accordance with the basic concepts of the ADP theory (BORN 1976, 1979; BORN and WEHMEIER 1979; BORN et al. 1976). Stabilizing effects on the erythrocyte membrane also fall into this category (chlorpromazine) (BORN 1976; BORN and WEH-

MEIER 1979; BORN et al. 1976), since a fleeting incident of haemolysis at a point of vessel wall change, followed by ADP release, is considered to play a fundamental role in the initial phase of platelet aggregation (BORN and KRATZER 1981; BORN et al. 1976; GAARDER et al. 1961). Pharmacodynamic concepts on the basis of prostaglandin metabolism aimed for the first at a general blockade of synthesis at the cyclooxygenase step (FOLTS et al. 1976; HIRSH et al. 1981 a; LEWY et al. 1979; PICK et al. 1979). Clinical trials of various cyclooxygenase blocking agents showed no influence on the incidence of attacks in patients with variant angina (MIWA et al. 1981; ROBERTSON et al. 1981). The reason for this failure of response is though to be due to a simultaneous decrease both in prostacyclin content of the vessel wall and in thromboxane A_2 content of the platelets, owing to blockade of synthesis of the common precursors of both substances (CHIERCHIA et al. 1980; DUSTING 1983; MIWA et al. 1981; ROBERTSON et al. 1981). A further development is the attempt at differential inhibition of the synthesis of both prostanoids:

1. On the basis of the different sensitivity of prostacyclin synthetase and thromboxane A_2 synthetase to specific inhibitors (BAENZINGER et al. 1977; BASISTA et al. 1978; BURCH et al. 1978; ELLIS et al. 1980; MASOTTI et al. 1980), a concept which has proved true in the successful clinical evaluation of low doses of acetylsalicylic acid, resulting in a specific decline in thromboxane A_2 content of platelets (BAENZINGER et al. 1977; ELLIS et al. 1980; ELWOOD and WILLIAMS 1979; ELWOOD et al. 1974).
2. On the basis of specific synthetase blocking agents (GORMAN 1980). Specific inhibitors of thromboxane A_2 synthetase were developed for this purpose and tested in vivo (ALLAN et al. 1980; GRYGLEWSKI et al. 1977; GORMAN et al. 1977; MONCADA et al. 1976 b; MYERS et al. 1981; SCHROR et al. 1980; SMITH et al. 1980; TYLER et al. 1981). The synthetase blockers caused not only a decrease in thromboxane A_2 content of the platelets, but also an increase in prostacyclin content of the vessel wall, in conjunction with simultaneous sensitization of the platelets to prostacyclin (AIKEN et al. 1981). It is, thereby, possible to guide specific blockade of the synthesis of prostanoids from common endoperoxide precursors in a certain direction (AIKEN et al. 1981; DUSTING 1983).

F. Conclusion

In conclusion, a short synopsis of essential pharmacodynamic effects on disturbances of myocardial blood flow is given, whereby the guiding principle is the abolition of, or improvement in the disproportion between oxygen demand and oxygen supply in ischaemic myocardial tissues.

I. The Augmentation of Oxygen and Substrate Supply to the Heart

1. Diminution of coronary vascular resistance
1.1. Effects on the vasal component
1.1.1. Vasodilating effects on the smooth muscles of larger arterial segments (calcium channel blockers, organic nitrates, molsidomine): antianginal effects: (a) increase in perfusion pressure at the prearteriolar collateral vessels (BECKER et al.

1971; FAM and MACGREGOR 1964; MATHES and RIVAL 1971; NOMURA et al. 1980; THUILLEZ et al. 1983); and (b) antagonism to coronary vasospasm (BRAUNWALD 1978, 1981; HILLIS and BRAUNWALD 1978)

1.1.2. Vasodilating effects on the smooth muscle of arteriolar (precapillary) vessels (dipyridamole, chromonar, hexobendine, dilazep): effects with the same site of action as the mediator substances of autoregulation (BERNE 1964; FEIGL 1983), with possible effects on the formation of collateral vessels in chronic myocardial ischaemia (FAM and MACGREGOR 1964; VINEBERG et al. 1962) and with the risk of redistribution from ischaemic to normal myocardium (coronary steal) (COHEN 1982; MEYER et al. 1974; SCHAPER et al. 1973; WILCKEN et al. 1971), especially after intravenous administration

1.2. Effects on the extravasal component of coronary vascular resistance

1.2.1. Diminution of the left ventricular diastolic pressure (nitrates, molsidomine). Antianginal effect: increase in diastolic blood flow to the endocardial segments of myocardium (VATNER and HEYNDRICKX 1975)

1.3. Redistribution of blood flow from epicardial to endocardial segments of normal and ischaemic myocardium (β-adrenoceptor blocking agents) caused by bradycardia and dominance of α-adrenergic constricting influences on the larger epicardial vessels and, consequently, an increase in the endocardial : epicardial flow ratio (BECKER et al. 1971; GROSS and WINBURY 1973; KLONER et al. 1971; PARRATT and GRAYSON 1966; PIT and GRAVEN 1970; STEIN et al. 1967; VATNER et al. 1977).

1.4. Antagonistic effects to lumen-narrowing processes

1.4.1. Inhibition of platelet aggregation

1.4.1.1. Inhibition of platelet thrombus formation by preferential inhibition of thromboxane A_2 formation (low doses of acetylsalicylic acid, selective inhibitors of thromboxane synthetase) (ALLAN et al. 1980; CHIERCHIA et al. 1980; DUSTING 1983; ELLIS et al. 1980; GRYGLEWSKI et al. 1977; MASOTTI et al. 1980; MONCADA et al. 1976 b)

1.4.1.2. Inhibition of platelet thrombus formation by augmentation of platelet 3,5-cAMP content (dipyridamole) (BEST et al. 1979; GAARDER et al. 1961; MONCADA and KORBUTT 1978; MILLS and SMITH 1971)

1.4.1.3. Inhibition of platelet thrombus formation by prevention of ADP release and stabilization of erythrocyte membrane (dipyridamole, sulfinpyrazone, chlorpromazine) (BORN 1979; BORN and KRATZER 1981; BORN and WEHMEIER 1979; BORN et al. 1976)

1.4.2. Inhibition of blood coagulation (heparin, oral anticoagulants) (CHALMERS et al. 1977; SELZER 1978; STEELE et al. 1978; WESSLER and GILEL 1979)

1.4.3. Recanalization by fibrinolytic agents (streptokinase, urokinase) (GANZ et al. 1980, 1981; GOLD and LEINBACH 1980; HIRSH et al. 1981 a; MATHEY et al. 1981; RENTROP et al. 1981; RUTSCH et al. 1980)

II. Reduction of Myocardial Oxygen Demand: Improvement in the Economy of Cardiac Performance

Principles of action: diminution of arterial pressures with concomitant increase in cardiac output; depression of heart rate with simultaneous increase in stroke

volume; diminution of left ventricular end-diastolic volume and diameter and wall stress; changeover from lipid to carbohydrate metabolism

1. Partial blockade of myocardial β-adrenoceptors

Antianginal effect: reduction of myocardial oxygen consumption by prevention of sympathogenic increases in heart rate and contractility (ARMSTRONG et al. 1977; GOODLETT et al. 1980; HILLIS et al. 1979; JORGENSEN et al. 1973; LEDSOME et al. 1974; ROSKAMM 1972)

2. Diminution of preload by reduction of the venous return (nitrates, molsidomine)

Antianginal effects: diminution of left ventricular end-diastolic pressure and volume, decline in wall stress (BERNSTEIN et al. 1966; FRICK et al. 1968; HOLTZ et al. 1978; HONIG et al. 1960; O'ROURKE et al. 1971; PARKER et al. 1971; WILKINS et al. 1937; WILLIAMS et al. 1965)

3. Decline in afterload by diminution of arterial impedance and of the ventricular volume (calcium channel blockers, nitrates, molsidomine); antianginal effect: decrease in myocardial oxygen consumption by diminution of afterload (EKELUND 1978; GROSS et al. 1979; HASHIMOTO et al. 1975; KALTENBACH et al. 1972, 1979; KURITA 1975; ROSKAMM et al. 1966; RUDOLPH et al. 1971; SELWYN et al. 1979)

4. Direct and indirect effects on myocardial contractility (calcium channel blocking agents, β-adrenoceptor blocking agents, cardiac glycosides); antianginal action: decrease in myocardial oxygen consumption by diminution of the velocity of fibre shortening (ANGUS et al. 1976; HIMORI et al. 1975a; NAYLER and SZETO 1972; NOMURA et al. 1980; ROSKAMM 1972; WOLFSON and GORLIN 1969); on the decompensated heart: decrease in myocardial oxygen consumption by increase in contractility, and, consequently, a diminution of preload and afterload and, moreover, a decrease in heart rate by reflex attenuation of the sympathetic nervous system (cardiac glycosides) (COVELL et al. 1966; WEBER and JANICKI 1979).

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Test Methods

CHAPTER 4

Experimental Testing of Antianginal Drugs in Animals

G. RABERGER

A. General Considerations

One of the major problems in finding relevant experimental methods to assess substances of potential therapeutic value is the fact that it is very difficult to mimic human disease in animal experiments. Human disease is, in most instances, a multifactorial event, which runs an individual course in each patient, with a variable outcome. The aim of an experimental model of a disease should, therefore, be to include the main pathogenetic factors for this disease. Animal models used for drug testing are mostly artificially induced diseases or disturbances of normal physiologic function and are very seldom naturally occurring diseases in animals displaying symptoms similar to human disease. The natural occurrence of cardiac insufficiency in dogs, for example, is not sufficiently frequent to allow the complete testing of potentially useful drugs in a relevant setup. The Syrian golden hamster, on the other hand, would fulfill some criteria for drug testing, but has the big disadvantage of being too small to allow complete hemodynamic assessment of the dysfunction or of drug effects. Another great problem is the availability of the experimental animals and the legal restrictions which further limit the species available for use in establishing the therapeutic efficacy of a drug.

Aside from these problems one crucial point in drug testing is to choose a model which fulfills the criteria of clinical relevance. Although these very essential reflections will be discussed in detail later on, it should be stated here that clinically relevant investigations can be done only in conscious animals in order to obtain basic criteria comparable to conditions in humans. It is not meaningful to use animals with a high sympathetic tone since humans are mostly geared to a low sympathetic output and use increased sympathetic tone to meet increased hemodynamic or metabolic demands. Furthermore, intact reflexes are very important, since true drug action is a summation of primary drug-induced alterations and secondary reflex adaptations which, in turn, markedly influence the primary drug action. Impairment of reflex activity, as has been shown to occur with all intravenous and inhalational anesthetics, leads to experimental results which are of only limited value in the assessment of the clinical relevance of a drug. It must moreover be taken into account that underlying disease can markedly alter primary drug action and reflex activity. In view of these considerations, drug testing should be limited to conscious animals which are anatomically, physiologically, and pathologically comparable to humans.

The scope of this chapter covers the description and appraisal of the methods used for the assessment of cardiovascular function and those used to induce

pathologic situations comparable to human angina pectoris in experimental animals. The reader is referred also to other books dealing with this subject in more detail (SCHAPER 1971, 1979; WILKERSON 1981).

B. Measurement of Relevant Parameters

I. Myocardial Blood Flow

Attempts to measure myocardial blood flow are hampered by many obstacles. Access to the coronary arteries necessitates thoracotomy and, hence, disturbance of the physiologic time course of intrathoracic pressure. Even free access after thoracotomy leaves the investigator with a further problem, namely the fact that three major branches supply the heart and that the amount of myocardium supplied by each of these branches can vary considerably. Thus, total myocardial blood flow can be determined only by measuring all three arterial blood flows. Another mode of measuring the myocardial blood flow is to measure the venous efflux from the heart. Here, too, the difficulty is encountered that not all of the venous blood leaves the heart via one vessel. The major venous efflux from the heart occurs through the coronary sinus, but the percentage of blood leaving the heart by this route varies from individual to individual and consists of blood from the right and the left ventricle. This leads to another problem of coronary blood flow measurement. Because of the difference in the prevailing pressures, blood flow to the right and left ventricle are different, and hence an overall blood flow measurement is not applicable to left ventricular blood flow, which is of major interest since it supplies the part of the heart which performs the main work. Apart from the differences in right and left ventricular blood flow, one has to take into consideration differences in regional distribution of blood flow within the left ventricle. These differences can be due both to narrowing of individual branches and/or local variations of blood flow to subendocardial and subepicardial layers. Blood flow distribution between different layers of the ventricle is of particular interest since the ratio can vary considerably, especially under pathologic conditions.

Many methods have been used to assess myocardial blood flow, but none of them has met all the requirements of an ideal method, which should combine the following prerequisites. Blood flow should be assessed continuously and with high temporal resolution in conscious animals, allowing a differentiation of regional flow distribution to different areas of the heart and simultaneously giving data on the distribution of blood flow to subendocardial and subepicardial layers of the left ventricle. As will be discussed in detail later on, even a combination of several methods can only approximately fulfill these ideal criteria. Since modern cardiovascular research is mainly carried out in intact animals, experimental setups for isolated organs will not be discussed in great detail.

The first measurement of myocardial blood flow was carried out by LANGENDORFF in 1895 in isolated perfused hearts of different species. The modifications of the original Langendorff heart preparation are given later on in Sect. C.

1. Venous Effluent

MORAWITZ and ZAHN (1912) were the first to measure venous effluent from the coronary sinus by direct volumetric methods. A specially designed cannula was inserted into the coronary sinus through the right atrium, thereby allowing quantification of myocardial blood flow with the heart in situ. The limitations which apply to this method hold true for all methods which use coronary venous effluent as a measure of total myocardial or left ventricular blood flow. In some species such as the rabbit, rat, and mouse, a persisting vena cava cranialis sinistra empties into the coronary sinus, thus allowing access to coronary venous blood via the jugular vein or measurement of coronary venous effluent via a specially designed cannula (BUSCH 1960).

Attempts to measure coronary sinus blood flow have also been made using indirect methods of blood flow measurement. FRONEK and GANZ (1960) described a specially designed catheter for insertion into the coronary sinus via the jugular vein, thus circumventing thoracotomy. These authors used the thermodilution technique for quantification of blood flow. An upstream injection of cold saline or glucose solution is used in combination with a downstream thermocouple which measures the change in temperature with time. Blood flow can be derived from the inverse correlation which exists between changes in temperature and blood flow. The limitations of this method arise from the discontinuous mode of measurement of blood flow, although measurements can be repeated at short intervals. The time limit for one continuous infusion of cold indicator solution into the coronary sinus is 20 s, in order to minimize the effects of recirculation. This method was further developed for simultaneous measurement of blood flow in the great cardiac vein and the coronary sinus (GANZ et al. 1971). Another method of blood flow measurement in the coronary sinus was described by LOCHNER and OSWALD (1964), who used an electromagnetic flow sensor at the tip of a coronary sinus catheter which allowed free passage of the blood into the right atrium through an electromagnetic field. This method enables continuous measurement of blood flow in combination with high temporal resolution. The same holds true for coronary sinus blood flow measurement using a Pitot–Rohr catheter (HENSEL and BRETSCHNEIDER 1970). According to Bernoulli's law, the difference between the pressure measured against the bloodstream and the pressure measured at an angle of 90° to the bloodstream is proportional to the square of the velocity, which, in turn, in this situation with a fixed diameter is proportional to the blood flow. Thus, the pressure difference which is determined through the catheter in the coronary sinus has to be amplified and the square root of this difference represents blood flow. The limited value of coronary blood flow measurement in the prediction of left ventricular flow has been established in many publications. For references see HEISS et al. (1973), who found a constant contribution of left ventricular flow at various flow ranges within the same animal, but variations from 63% to 83% between different individuals.

2. Arterial Inflow

Another approach toward quantifying myocardial blood flow is to measure arterial coronary inflow. GRÜGG et al. (1943) cannulated either the right coronary artery distally to ligation of the artery near the aorta or the left coronary artery us-

ing a specially designed cannula which was advanced from the subclavian artery into the lumen of the left coronary artery. Blood flow measurements were performed using a rotameter (GREGG et al. 1942) which has, per se, little influence on flow. These rotameters with stainless steel or aluminum "floats" allow mean blood flow measurements only. Measurements of coronary arterial inflow without thoracotomy can be obtained by modification of the coronary cannula to a flow-through cannula similar to the one used to quantify flow in the coronary sinus. PIEPER (1964) designed a flow sensor using the principles of electromagnetic blood flow measurement, which can be advanced into the coronary artery via the carotid artery and aorta. The same approach was used by SMITH et al. (1974), who adapted the principles of ultrasonic blood flow measurement to coronary artery flow through a cannula. An extracorporeal shunt with an electromagnetic flow probe was used by YEAGER et al. (1977) for coronary blood flow measurement in closed-chest dogs.

These techniques for blood flow measurement all have the limitation that they cannot be used chronically since intravascular blood flow measurement necessitates anticoagulation and poses a lot of difficulties for chronic exteritorization in the intrascapular area, which is believed to be the safest place for the outlet of chronic devices. At present, two methods are used for acute and chronic coronary arterial blood flow measurement in anesthetized and conscious dogs: electromagnetic and ultrasonic blood flow meters with adequate noncannulating flow sensors.

The first with electromagnetic flow meters were described by KOLIN (1936) and WETTERER (1937). Flow probes applicable to the coronary arteries were introduced by KHOURI and GREGG in 1963. Electromagnetic measurement of blood flow is based on Faraday's low of induction. Ionized liquid which passes through an electromagnetic field at an angle of 90° induces a voltage which is proportional to the magnetic field, the diameter of the lumen, and the velocity of the liquid. The magnetic field is produced either by a sine wave or square wave excitation, which is pulsed (interrupted) for the production of a stable electronic zero without interruption of the blood flow. Special filtering and adequate excitation voltages are needed to keep the noise: signal ratio to a minimum. Interference from other sources (e.g. electrocautery) must be excluded for a reliable flow signal. If more than one flow probe is used in the same animal, synchronization of the flow meters is necessary to ensure simultaneous excitation of all flow meters by one oscillator. The flow probes consist of an electromagnet and two sensing electrodes placed in a precisely oppposite position which is at an angle of 90° to the electromagnet. The flow probes should fit tightly in order to receive a waveform free of artifacts. With chronic implantation, the diameter of the flow probes must exceed the true vessel diameter to prevent narrowing of the vessel by reparative processes after the implant surgery. The advantages of electromagnetic blood flow measurement lie in the continuous registration of pulsatile flow profiles over unlimited time and the discrimination between forward and backward flow. Disadvantages are the need of an occlusive device for true zero flow and the high power requirements which limit telemetry of flow to very short periods in the range of 15–30 min. A special technique for the implantation of coronary flow probes was described by ALEXANDER et al. (1969).

The method using ultrasound backscattering for blood flow measurement was first described by FRANKLIN et al. in 1961. This method was also used in combination with telemetry as described by FRANKLIN et al. in 1964. Using this setup, VAN CITTERS and FRANKLIN (1969) investigated the effects of sled running on blood flow in various arteries in sled dogs. The principle used is the Doppler frequency shift of backscattered ultrasound. In stationary blood, the frequency of the scattered ultrasound equals the emitted frequency, but is altered depending on the blood flow velocity. For these measurements, the probes consist of two crystals which are oriented toward the center of the vessel. One crystal is used for transmission, the other as a receiver. Since the change in frequency depends only on the velocity of the bloodstream, this flow meter cannot distinguish between forward and backward flow, which might be limiting in establishing blood flow in coronary arteries near the origin from the aorta, where backflow is frequently observed. The same problem applies to aortic blood flow in the ascending part where backflow occurs immediately after the closure of the aortic valves. Advantages are the absolute zero stability and the possibility of obtaining and transmitting this signal via telemetry over prolonged periods of time, since power requirements are much smaller than needed for electromagnetic blood flow measurement. Zero flow can be established without occlusion (VATNER et al. 1970).

3. Extravascular Indicators

The use of thermal conductivity for blood flow measurement was described by GRAYSON in 1952. This method was adapted by GRAYSON and MENDEL (1961) for blood flow measurement in rabbit heart and by PARRATT (1969) for monkeys and baboons. The main limitations of this method are that the blood flow obtained represents an average value over a period of more than 1 min and that blood flow is measured only in the immediate vicinity of the thermocouple.

Other methods used for the measurement of local blood flow are based on the analysis of the washout of locally administered radioactive substances. KETY (1949) was the first to show that washout of radioactive ^{24}NaCl from skeletal muscle was mainly a function of blood flow. This method was adapted for myocardial blood flow measurement using Na^{131}I by HOLLANDER et al. in 1963. BRANDI et al. (1968) injected ^{133}Xe- and ^{131}I-labeled antipyrine dissolved in saline solution locally into the myocardium and determined washout of the activity by a crystal scintillation counter. The limitations of these methods are the difficulties in transforming washout curves to real blood flow values and the disturbances which may occur locally in response to the injection of 0.2 or 0.5 ml saline into the myocardium. Since the washout occurs over a period of some minutes, this method allows only average blood flow values to be established, and these values may be obscured by the initiation of cardiac arrhythmias. Furthermore, comparative measurements performed by reinjecting the indicator at the same location might not be reproducible.

4. Intravascular Indicators

a) Diffusible Indicators

The use of diffusible indicators dates back to investigations by ECKENHOFF et al. in 1948, who used nitrous oxide for blood flow measurements. Arterial and cor-

onary sinus concentrations were determined after a 10-min equilibration period with constant inspiration of a mixture of 15% N_2O, 21% O_2, and 64% N_2. Since the arteriovenous difference is dependent on blood flow and myocardial uptake kinetics, a steady state period of approximately 10 min is necessary for this method of blood flow measurement. This of course, limits the use of this method and stimulated investigations of other indicators.

Both the intracardiac concentration and the washout curve of indicators which are extracted from the blood may be used for determination of blood flow. Highly diffusible indicators like ^{131}I- and, ^{14}C-labeled antipyrine, and tritiated water, are rapidly extracted by the heart, but undergo very rapid washout and recirculation in intact animals (SAPIRSTEIN 1958; YIPINTSOI and BASSINGTHWAIGHTE 1970). Although the kinetic behavior is clearly different from other indicators such as radioactive potassium, for instance, or rubidium, the relative distribution, if measured by determination of myocardial content, is comparable for these indicators (YIPINTSOI et al. 1973).

Inert gases like xenon, krypton, or argon can also be used for blood flow measurements in the heart. The argon method, described by BRETSCHNEIDER et al. (1966), depends on determination of the content of this gas in the arterial and venous blood. Blood flow determinations with xenon and krypton are carried out by establishing washout curves of the radioactive isotopes ^{133}Xe and ^{85}Kr using scintillation detectors. A comparative study done by BASSINGTHWAIGHTE et al. in 1968 revealed that the washout curves for ^{125}I antipyrine and ^{133}Xe differed slightly in shape owing to different distributions and lipid solubility. Estimation of blood flow from the steepest part of the curves overestimated actual blood flow by 10%, whilst calculation from the slope at 30% of maximal activity led to an underestimation of the same magnitude with both indicators in the isolated dog heart. The partition coefficient for ^{133}Xe between myocardial muscle and blood which is 0.72 at normal hematocrit values, can be increased to values of 0.95 by marked reduction of the erythrocyte count (MURRAY and RAPAPORT 1972). ^{85}Kr was injected intracoronarily by HERD et al. (1962) in unanesthetized dogs and the radioactivity was monitored by a precordial scintillation detector. The washout curve could be described by a monoexponential equation for the first 2 min after the injection. The slope of this part of the curve was used to obtain a good estimate of mean coronary blood flow. Both inert gases were used in a comparative study with cannulation of the coronary artery and direct blood flow measurement. Thus, it was observed that single monoexponential washout curves were obtained only when the gas solution was injected intracoronarily. Recirculation of inert gases is minimal since 95% enter the alveolar space and are expired at one lung passage (CHIDSEY et al. 1959). For chronic use in conscious dogs, KHOURI et al. (1977) developed an implantable β-radiation detector which measures blood flow in a small part of the myocardium underlying the detector. The use of this system is limited because the radioactive gas mixture has to be injected into the coronary artery. ^{81}Kr^{m}, a short-lived radionuclide, was used for blood flow measurements by SELWYN et al. (1978). The advantage lies in the half-life of only 13 s, but this necessitates continuous infusion of the indicator, which has to be eluted from a bedside generator.

b) Monovalent Cations

Since rubidium has biologic effects similar to potassium, and since rubidium is taken up into tissues like potassium, LOVE and BURCH (1957) introduced ^{85}Rb as a radionuclide for blood flow measurement. The calculated initial rate of myocardial rubidium uptake during intravenous infusion of ^{85}Rb over a 30-min period was found to be a good predictor of myocardial blood flow, which, moreover, allowed the measurement of pharmacogenic alterations in myocardial blood flow. After a single intravenous injection, both, ^{42}KCl and ^{85}RbCl are progressively taken up by the heart for the first 10 s after the injection and the myocardial content of each indicator remains virtually constant over a period of 1 min (SAPIRSTEIN 1958), although recirculation starts as early as 10 s after the injection. Further investigations with simultaneous pulsed injections of ^{86}Rb, ^{22}Na, sucrose ^{14}C, and ^{125}I albumin led to the conclusion that Rb exchange at the capillary wall was flow dependent, but uptake into the cell correlated poorly with myocardial blood flow (ZIEGLER and GORENSKY 1971). Hence, myocardial blood flow may be underestimated at high flow rates, but also at ischemic flow rates (MOIR 1960).

Although a direct supply from the cavities to the innermost part of the left ventricle was demonstrated by MYERS and HONIG (1966) using ^{86}Rb and MOIR (1969) using ^{131}I albumin, the significance of the contribution to overall and also endocardial blood supply is controversial. Comparisons of the kinetic behavior of ^{42}K and ^{131}Cs revealed marked differences in the respective half-lives after intra-arterial and intravenous administration. Cesium, which is extracted at a low rate and cleared from the myocardium with a half-life of up to 43 h, can be used only for comparative measurements of stable differences in myocardial regional blood flow (POE 1972). Using ^{84}Rb and a double-coincidence counting system, which allows the simultaneous quantification of myocardial and background activity, the sensitivity of the rubidium method was markedly increased (BING et al. 1964) and a method for quantitative determination of blood flow was described by the same authors (COHEN et al. 1965).

Another monovalent ion which has been used extensively in clinical medicine is ^{201}Tl. In order to eliminate the influence of background activity on myocardial blood flow measurement, either myocardial biopsies were obtained (POHOST et al. 1981) or the myocardial content was determined in postmortem samples. JACOBS et al. (1982) described a detector which enables the myocardial activity to be continuously determined. By insertion of the detector into the left ventricular cavity, the activity of the overlying myocardium is measured without interference by activity from the intraventricular blood. The cadmium telluride crystal, which is used as detector, can also be used in conjunction with other indicators possessing energies between 60 and 250 keV. ^{111}In, ^{67}Ga, and ^{99}Tc^{m} have been tested so far.

c) Microspheres

Radioactively labeled microspheres are widely used for assessment of myocardial blood flow in animal experiments. Microspheres are extracted during one passage of blood from the circulation and were used for the determination of blood flow distribution in the canine heart (MACLEAN et al. 1961) and measurement of cardiac output and its distribution into various organs (KAIHARA et al. 1968). Com-

plete extraction during one passage necessitates injection of the particles into the arterial part of the circulation, at a site where complete mixture occurs before blood enters the organs. The preferred site is the left atrium, especially if the coronary circulation is of primary interest. Distribution of cardiac output to other organs can also be measured on injection of the microspheres into the left ventricle. For assessment of blood flow to the heart, microspheres are injected into the left atrium and arterial sampling from the aorta lasts for 90 s, starting 5 s before the microsphere injection. The counts in the arterial sample divided by the flow volume represent the "phantom organ flow" which is used for calculation of blood flow to different sites of the heart (DOMENENCH et al. 1969).

KAIHARA et al. (1968) suggested the use of microspheres of at least 50 μm in size for the determination of cardiac output and organ blood flow, because mixing was found to be best with the bigger size of microspheres. DOMENECH et al. (1969), using microspheres of either 14 or 50–60 μm, also found a good correlation between blood flow assessed with big microspheres and directly determined myocardial blood flow using a right heart bypass. Differences were found in the distribution of blood flow within the heart for the microspheres of different size. the ratio between endocardial and epicardial blood flow was in the range of 2.3–2.7 : 1 for the 50-μm spheres, but only 1.3 : 1 for the spheres with a medium diameter of 14 μm. Similar results were obtained by FORTUIN et al. (1971), who obtained an endocardial : epicardial ratio of 1.17 : 1 using 15 ± 5-μm microspheres. The distribution of blood flow to the left and right ventricle was constant, irrespective of whether big or small microspheres were used. The same authors also found out that injection of 4×10^6 microspheres had no influence on myocardial reactive hyperemia, even if it was repeated three times. BUCKBERG et al. (1971) obtained an endocardial : epicardial blood flow ratio of unity using 8-μm diameter microspheres. The same authors stressed the importance of a minimum number of 400 microspheres in the tissue sample which is used for counting, in order to obtain reliable results. Since microspheres tend to aggregate in solution, Tween 80 is added to prevent clumping. MILLARD et al. (1977) found out that Tween concentrations above 0.01% clearly influence hemodynamics and should, therefore, be avoided.

Since blood flow measurements are mainly used to compare the distribution of blood flow before and after interventions, the multiple use of microspheres is necessary. At present the use of six microsphere injections with different labels seem to be the maximum number which can be dealt with. It is of major importance to select the microspheres in order to get maximum separation of the emitted energy which allows counting without marked overlapping. Nonetheless, an appropriate program has to be established to allow for the overlapping counts and to get true blood flow values (HALES 1974; HALES et al. 1979). The microsphere method was compared with other indicator methods both as regards total and regional blood flow measurement. Although good correlations were found for total blood flow, regional blood flow determinations differ. Using different size microspheres and antipyrine, UTLEY et al. (1974) found an overestimation of blood flow to the endocardium during ischemia with antipyrine in comparison with microspheres. The results were interpreted on the basis of either a direct diffusion of the indicator from the left ventricular cavity or a dissociation of plasma

and particle flow to this area. Similar results of an overestimation of ischemic blood flow in comparison with microsphere-assessed blood flow were found for ^{133}Xe by SCIACCA et al. (1979) and ^{86}Rb by BECKER et al. (1974). Underestimation in comparison with microsphere-assessed blood flow was observed in high flow regions with both ^{86}Rb (BECKER et al. 1974) and ^{43}K (PROKOP et al. 1974). The microsphere method was also performed in the isolated supported dog heart (WARLTIER et al. 1975). No shunting was observed using 15-μm diameter microspheres and blood flow to the endocardium exceeded epicardial blood flow.

Other problems with microspheres include shunting. At resting hemodynamics MARSHALL et al. (1976) observed a shunting of 15-μm microspheres up to 5% through the heart and shunting up to 10% using 9-μm microspheres. Shunting increased to 7.5% and 13.5% for 9- and 15-μm microspheres, respectively, during ATP infusion. These data of shunting were derived from the arterial – coronary sinus count rates and differ markedly from data using total myocardial – coronary sinus counts rates which give shunting rates in the range of 1%–2% (FORTUIN et al. 1971; MARSHALL et al. 1976). The use of microspheres for chronic experiments is limited by the loss of microspheres from the heart. CAPURRO et al. (1979), using 15-μm radioactive microspheres, reported a loss of microspheres from the endocardium if occlusion was sustained for at least 24 h and from the epicardium after 48 h of coronary occlusion. This loss was constant over longer periods of coronary occlusion, but was not predictable. CONSIGNY et al. (1982) confirmed previous studies which showed a higher shunting of 9-μm microspheres through the heart in comparison with 15-μm microspheres. During a 5-week interval, maximal microsphere losses amounted to 40% and 11%, respectively, for 10- and 15-μm microspheres. Mean microsphere losses were $13.8\% \pm 10.6\%$ for 9-μm and $3.3\% \pm 4.6\%$ for 15-μm microspheres. It seems to be of importance to use microspheres with a diameter distribution close to 15 μm since 98% of the microspheres found in the lung, i.e., shunted microspheres, had diameters less than 10.3 μm. Although no increased loss of microspheres was observed from infarcted myocardium, the question remains unsettled at the present time.

In summary, the microsphere method allows very precise determination of myocardial blood flow, with a high spatial resolution, but requires ex vivo measurements of tissue samples in a γ-radiation counter. Continuous or phasic determination of blood flow is not possible. If 15-μm diameter microspheres are used, interference due to acute or chronic microsphere loss can be minimized and measured endocardial : epicardial blood flow ratios seem to represent physiologic values.

II. Myocardial Metabolism

The heart needs a continuous supply of oxygen and substrates in order to maintain contractile performance. A quantification of myocardial metabolism can be performed either by direct determination of myocardial substrate and high energy phosphate levels and myocardial PO_2, PCO_2, and pH values, or by measuring myocardial balances of substrates, nucleosides, oxygen, carbon dioxide, and hydrogen ions. For the assessment of cardiac arteriovenous differences, the coronary sinus has to be catheterized under X-ray control. In some species such as the

rabbit, rat, and mouse (also in sheep and, sometimes, dogs), a persisting v. cava cranialis sinistra, discharging into the coronary sinus, may be found (BUSCH 1960; RABERGER personal observation). In calves, the hemiazygos vein empties into the coronary sinus, thus allowing catheterization without occlusion of coronary veins (WEBER et al. 1972).

Under resting conditions, the heart utilizes glucose, fatty acids, and lactate for aerobic metabolism (BING 1965). The distribution of glycogen content and lactate reveals higher levels in the endocardial layers than in the epicardial layers. Pyruvate is distributed evenly (GRIGGS et al. 1972; ALLISON and HOLSINGER 1977). This distribution pattern is not changed by increases in heart rate if arterial inflow is not limited. Reduction of arterial inflow or coronary constriction leads to marked increases in endocardial, but only moderate increases in epicardial lactate levels. The importance of myocardial contractility in accounting for this difference in lactate accumulation is seen from the equal increase in lactate content in epicardial and endocardial layers following coronary occlusion during ventricular fibrillation (DUNN and GRIGGS 1975). This ischemia-induced accumulation of lactate is also seen on reduction or even inversion of the arteriocoronary sinus lactate difference. Since blood from both the constricted (or occluded) and the intact branch of the coronary artery are mixed in the coronary sinus, changes are less accentuated in coronary sinus blood than those in the local venous blood draining the underperfused area (OWEN et al. 1970; RABERGER et al. 1978). Hence, a lactate uptake inversion to lactate release in the underperfused area may be underestimated, or even missed, if arteriovenous differences between aorta and coronary sinus are considered.

The uptake of fatty acids, which is also markedly reduced with myocardial underperfusion, is not used as an indicator of myocardial hypoxia since fatty acid determination is very time consuming. Changes in glucose uptake are very difficult to assess, since myocardial extraction is very low and the arteriovenous differences at rest are of similar magnitude to the accuracy of determination. Thus, myocardial lactate balance is a very sensitive indicator of myocardial underperfusion and one which can be measured in intact animals over any period of time. It is a superior parameter to direct determination of myocardial lactate content by myocardial puncture, which can be performed only a limited number of times in one animal, or indeed only once if the heart is instantly frozen and dissected for regional analysis.

Marked coronary dilating activity of adenosine was first described by DRURY and SZENT-GYÖRGYI in 1929. Release of nucleosides from the heart during hypoxia was described by BERNE (1963) and GERLACH and DEUTIKE (1963) for cat and rat heart, and led to the adenosine hypothesis of coronary blood flow regulation. Analysis of the distribution of high energy phosphates in the intact dog heart revealed an endocardial–epicardial gradient for creatine phosphate (CP) with higher concentrations in the epicardium, but an even distribution of ATP (BOERTH et al. 1969; GRIGGS et al. 1972; DUNN and GRIGGS 1975). Stress due to increased left ventricular volume and heart rate, as well as a reduction in resting myocardial blood flow lead to a reduction in endocardial ATP content. Coronary artery occlusion for 15–30 s induces a marked reduction in myocardial CP content in all layers, but no significant changes in ATP content. It is worth mentioning

that, at the time when the ATP content was unaltered, the myocardial lactate content was increased in both the endocardial and epicardial layers (DUNN and GRIGGS 1975). This fact has no bearing on the sensitivity of lactate and nucleoside balances as indicators of myocardial underperfusion or hypoxia. DE JONG et al. (1977) found a high correlation between reduction in blood flow and accompanying release of lactate and inosine from the pig heart. Lactate and inosine, which were both extracted by the heart under resting conditions, were released if the flow in the anterior descending branch of the left coronary artery was reduced by 74%. The sensitivity of nucleoside release to coronary occlusion over 45 s was investigated in dogs by FOX et al. (1979), by measuring myocardial balances for adenosine, inosine, and hypoxanthine. After myocardial ischemia of 15–30 s, 45 s, or 5 min, the additional release of inosine amounted to 24, 96, or 9384 nmol, respectively. The release of adenosine and hypoxanthine was also time dependent. Lactate, inosine, and hypoxanthine balances were measured in conscious dogs by VROBEL et al. (1982). Release of nucleosides was found to be the more sensitive parameter for myocardial ischemia induced by exercise and coronary inflow reduction.

Since myocardial function is mainly dependent on oxidative metabolism, attempts have been made to determine myocardial oxygen consumption or myocardial oxygen tension. Local measurements of myocardial oxygen tension are limited by the fact that wide variations in oxygen tension are encountered throughout the heart. Only multiple measurements and the construction of an oxygen tension histogram would provide representative values (SCHUBERT et al. 1978). Intramyocardial mass spectrometric probes which have been used for oxygen and carbon dioxide tension measurements have the additional disadvantages of tissue disruption and a slow response amounting to several minutes (YOKAYAMA et al. 1978).

Many investigators used the volumetric method of VAN SLYKE and NEILL (1924) for the determination of the blood oxygen and carbon dioxide content, in conjunction with coronary blood flow measurement, to calculate myocardial oxygen consumption. Commercially available oxymeters, which make oxygen content determinations less time consuming, mostly determine the bound oxygen, but exhibit high correlation coefficients if compared with the classical method of Van Slyke and Neill (VENNEBUSCH et al. 1978). Regional oxygen balances of the heart would be of special interest since here, too, the coronary sinus blood represents average values for the whole heart. A new approach to measure local myocardial oxygen delivery and consumption was followed up by WEISS et al. (1978) by measuring the oxygen content in arteries and veins of 20–200 μm diameter by a microspectrometer method in tissue sections. The relevant regional blood flow was assessed with microspheres. Total myocardial oxygen consumption (per 100 g tissue) in the left ventricle was found to be 10 ml/min, with lower values of 9.5 ml/min in the epicardium and higher values of 12.1 ml/min in the endocardium.

Many attempts have been made to derive myocardial oxygen demand from hemodynamic parameters. Two very close approximations are those of SARNOFF et al. (1958) and BRETSCHNEIDER (1971). Resting oxygen extraction is in the range of 75% in the left ventricle, but can be further increased during exercise (KHOURI et al. 1965; VON RESTORFF et al. 1977). This increased extraction could meet an

increase of approximately 10% in myocardial oxygen demand. Increases in oxygen demand beyond this limit are met by increases in blood flow. In conscious dogs, marked differences have been found between trained and untrained dogs. Trained dogs respond to exercise with higher oxygen extraction ratios and decreased oxygen consumption in comparison with untrained dogs, but the correlation between heart rate and myocardial oxygen consumption is identical for both groups (STONE 1980). Regional myocardial measurements of pH using a fiber optic probe are subject to the same pitfalls as already discussed in the case of oxygen probes (TAIT et al. 1982).

The main obstacle encountered with myocardial metabolic studies is the limited access to regional venous blood in conscious animals. Insertion of small polyethylene tubes into local veins is limited by the short duration of patency, in the range of a few days. At present it is not possible to analyze local myocardial metabolism in intact animals, but nuclear magnetic resonance spectra could be the next step toward regional metabolic analyses without invasive techniques.

III. Myocardial Function

Myocardial force–velocity diagrams can easily be established in isolated papillary muscle (SONNENBLICK 1962). Positive inotropic interventions increase the maximal velocity of shortening. In intact hearts, left ventricular pressure P and the first derivative, dP/dt are used for the assessment of myocardial contractility (dP/Pdt) (NEJAD et al. 1971). A curve similar to the force–velocity diagram can be derived from a diagram of left ventricular pressure (x-axis) and left ventricular dP/Pdt (y-axis). Extrapolation to the y-axis is a good measure of left ventricular inotropy (MASON et al. 1970). This maximal velocity of shortening provides an overall estimate of left ventricular function, since it is derived from left ventricular dP/dt. Regional ventricular dysfunction may, thus, be obscured by a compensatory increase in contractility in the remaining intact ventricular myocardium (WATERS et al. 1977).

Hence, attempts have been made to assess ventricular function by suturing strain gauges directly on to selected regions of the heart (DE V. COTTON and BAY 1956). Miniaturization of the gauges allowed simultaneous measurements to be made in different regions and variation of the suture depth or pin length enabled a comparison of epicardial and endocardial function (SONNENBLICK and KIRK 1971/72; MEERBAUM et al. 1976).

Another approach to the assessment of regional function was followed up by TYBERG et al. (1974), who measured segment length changes using a mercury-in-silastic length gauge. Pressure–length curves with intraventricular pressure on the y-axis and segment length on the x-axis were found to be very sensitive parameters of regional ventricular function. The area which is circumscribed by this curve is representative for regional stroke work. Since these length gauges might prevent free movement of the myocardium, a new method for segment length measurement was introduced by BRUGGE-ASPERHEIM et al. (1969) and FRANKLIN et al. (1973). Two ultrasonic crystals are implanted into the myocardium at regions of interest and allow continuous measurement of segment length. The myocardial shortening is in the range of 15%–20% of the resting length and can also

be used for the analysis of pressure–length loops (HAGL et al. 1975). One difficulty encountered with the use of regional shortening as an index of function is the fact that regional shortening is not a synchronous event throughout the whole ventricle (BRUGGE-ASPERHEIM et al. 1969). Systolic shortening is a more sensitive parameter than total shortening, which may occur also during diastole, especially in the ischemic myocardium (STOWE et al. 1978).

Using ultrasonic length measurements, regional wall thickness can also be taken as a parameter of regional myocardial function. Wall thickness exhibits cyclic changes comparable to segment length changes, but occurs reciprocally. Changes in wall thickness were analyzed in anesthetized pigs (SCHAMHARDT et al. 1979) and conscious dogs (TOMOIKE et al. 1978 a) as a parameter of regional function. The possibility of using this method for chronic experiments on conscious animals makes it a valuable tool in the assessment of the effects of underperfusion since myocardial function is a sensitive parameter of decreases in blood flow (DANIELL 1973; DOWNEY 1976; VATNER 1980). The importance of measuring regional function rather than regional perfusion is stressed by recent investigations of COX and VATNER (1982), who found a marked dissociation between blood flow and function in the border zones of infarcted myocardium.

IV. Electrocardiogram

It is well established that prolonged myocardial ischemia or infarction is accompanied by typical changes in the electrocardiogram (ECG). Hence, alterations in the electrical activity of the heart were taken as indicators of ischemia and regression of ischemia. SCHEUER and BRACHFELD (1966) using limb leads for ECG recording, reported that myocardial metabolic, and hemodynamic changes always occurred earlier than changes in the ECG. The use of epicardial electrodes and epicardial ECG mapping was found to be a more sensitive parameter of ischemia than limb lead ECG (MAROKO et al. 1971). Although both increased myocardial lactate levels and epicardial ST elevation were observed 17 min after coronary occlusion, no correlation was detected between these changes (KARLSSON et al. 1973). Using the epicardial mapping method, DANIELL (1979) introduced ST elevation as an indicator of myocardial viability, showing that ST elevation above 10 mV was always associated with transmural necrosis which was not found when the elevation was less than 8 mV.

With intramyocardial ECG recording, LEKVEN et al. (1975) classified ECG changes as a very insensitive parameter which responded only if local blood flow was reduced to 50% of its resting value. MILLER et al. (1976) confirmed these data and pointed out that simultaneously measured regional function was a more sensitive parameter, responding to flow reductions as low as 20%–30%. A close correlation between reduction in resting blood flow and changes in regional function and regional lactate balance was reported by WATERS et al. (1977) in the absence of any elevation of epicardial ST segments. Observations of blood flow and ECG changes after occlusion of the left anterior descending coronary artery over 2 h revealed poor correlations between blood flow and ECG changes in the infarcted myocardium and the border zone (SMITH et al. 1975). Investigations in conscious dogs confirmed these data, showing that epicardial and intramyocardial ECG

changes occurred with a temporal lag following the changes in regional function after brief coronary occlusion (HEYNDRICKX et al. 1975), and were not observed at all on reduction of coronary blood flow sufficient to impair regional myocardial function, as measured by regional wall thickening using ultrasonic crystals (BATTLER et al. 1980).

V. Signal Transmission

No problems arise in anesthetized animals with the transmission and registration of biologic signals. Difficulties are encountered with conscious animals who have to be restricted for on-line wire signal transmission. Telemetry would be the optimal way of signal transmission to obtain measurements in conscious animals, since the animal can move freely and even perform work such as sled running (FRANKLIN et al. 1964; VAN CITTERS and FRANKLIN 1969). No problems are encountered if signals of temperature or ECG are transmitted since energy requirements are low. Signals from transducers which have high energy requirements like electromagnetic blood flow are limited by the size of the power pack. Blood pressure and ultrasonic blood flow signals can easily be measured and transmitted over periods amounting to some hours. (For further details see VATNER et al. 1972; FRYER et al. 1975; TOMOIKE et al. 1978 a; MEINDL 1980).

C. Experimental Models

I. Isolated Perfused Hearts

Using the isolated perfused hearts of rabbits, cats, and dogs, LANGENDORFF (1895) described the influence of arresting coronary blood flow to the heart. He made no attempt to reduce coronary inflow, but performed only complete occlusion. In discussing the advantages and disadvantages of his preparation, Langendorff thought that the complete vascular and nervous isolation of the heart was of major importance for the assessment of the effects of various maneuvers and toxins on the heart.

Judging from present day experience, the isolated heart allows a lot of relevant investigations on the regulation of coronary blood flow and metabolism, since it can be perfused either at constant pressure or at constant flow. The first setup is mainly used for the investigation of changes in blood flow, the latter for the investigation of metabolism, since constant flow perfusion simplifies the calculation of arteriovenous differences by keeping the inflow and arterial substrate concentrations constant. When using isolated hearts, it must be kept in mind that the effect of drugs, in particular, can be completely different if the whole body circulation is intact and reflex phenomena which profoundly modify direct cardiac effects may occur. This integrated activity must be assumed to be the only clinically relevant action of a drug. Thus, the isolated heart allows a multitude of experimental modifications which are not feasible in the intact animal, but all results obtained under these conditions are far from being of clinical significance. Therefore, experiments with isolated hearts should represent only a first attempt at characterizing a potentially antianginal drug.

Interest in the application of refined technical methods to the Langendorff heart preparation persisted and research workers used whatever species was on hand. VICK and HERMAN (1971) performed experiments with blood-perfused monkey and dog hearts, VOGEL and LUCCESI (1980) with blood-perfused cat hearts, and SAITO (1976) with pig hearts. Various interventions were shown to prolong the normal performance period of isolated hearts. HABAL et al. (1976) stressed the importance of pulsatile perfusion of fibrillating hearts for left ventricular viability as judged from diastolic compliance, myocardial oxygen and lactate extraction, myocardial blood flow, and histology. A reappraisal of the Langendorff heart preparation as a research and teaching model was made by BROADLEY (1978). Perfusion with blood poses some problems such as oxygenation of the blood, changing substrate concentrations with time if the blood is recycled and, of course, the need for anticoagulation. Hence, the use of saline perfusion media like Locke's or Ringer's solution was promoted and various substrates were added. Thus, BÜNGER et al. (1979), using a guinea pig heart preparation, found an improvement in heart function, as measured by the pressure and volume work, if they added pyruvate to the perfusion medium. Addition of albumin to the perfusion fluid reduces edema formation and allows the addition of free fatty acids to the perfusion, thereby enabling investigations to be carried out on the effect of free fatty acids on oxygen consumption and arrhythmogenic potency. Since prostaglandins are nowadays known to manifest hemodynamic and also thrombogenic or thrombolytic activities, KÖHLER and SCHRÖR (1981) described a platelet-perfused isolated heart for studying the role of endogenous prostaglandins and prostaglandin metabolites in the heart. A modification of the Langendorff perfusion model, which allows the simultaneous measurement of pressure and volume work, was derived by using an isolated circuit for cardiac output measurement with two valves and an intraventricular balloon (BARDENHEUER and SCHRADER 1983). In summary, it can be stated that the isolated perfused heart is a valuable tool for basic scientific work, whereby the influence of changes in a single parameter can be studied without interference from central nervous or reflex activity. However, the effect of drugs established in this preparation will differ markedly from findings obtained in corresponding studies in intact and conscious animals or in humans.

II. Myocardial Underperfusion and Angina Pectoris

1. Heart In Situ

LANGENDORFF (1895) considered the heart–lung preparation in situ as a disadvantage to studies on the effect of drugs on the heart. Nonetheless, many investigators proceeded to modify in situ preparations in order to investigate the effects of drugs or flow reduction on the heart with intact reflex activity. The left coronary artery was cannulated and perfused using a roller pump (WYATT et al. 1975) or the systemic arterial pressure in the femoral (CSIK et al. 1976) or carotid artery (YAEGER et al. 1977) as driving force. Coronary inflow can, thus, be diminished by reducing flow through the bypass circuit. Although delay of the arterial pressure head entering the coronary arteries is not very marked with carotid perfu-

sion, it may be of significance if a long perfusion circuit via aorta, femoral artery, and retrograde catheter to the coronary artery is used. The aim was, thus, to reduce coronary inflow by directly narrowing one coronary branch in the heart in situ. In these studies, one major branch of the left coronary artery was dissected and freed of connecting tissue at two places without a coronary branch in between. The proximal site was used for blood flow measurement and the distal site for the partial or complete occlusion of the coronary branch. Complete occlusion and assessment of collateral flow and infarct size are described later. Occlusive devices used for these models are stainless steel clamps which can be adjusted by a thumbscrew (SHAVER and SHAVER 1974), snares which are applied directly to the artery (GOULD et al. 1974), snares which are fastened over pieces of plastic tubing which surround the coronary artery (FELDMAN et al. 1978), or hydraulic cuff occluders (KHOURI and GREGG 1967; DALLMER et al. 1979).

It was possible by these means to investigate basic pathologic responses to coronary artery narrowing. Up to this time, it had been held that an increase in coronary blood flow was beneficial for the underperfused myocardium and drugs were screened in anesthetized animals with intact coronary arteries for their coronary vasodilating potency (LENKE 1970). However, investigations on the dependence of flow reserve on the coronary artery diameter showed that coronary reactive hyperemia following an intracoronary injection of an X-ray contrast medium, or on occlusion of the coronary artery for 10 s was markedly reduced with coronary narrowing amounting to 30%–40% of the diameter, although narrowing to this degree has no apparent influence on resting coronary blood flow. A reduction in resting blood flow was not observed until there was stenosis of 85%. GOULD et al. (1974) also showed that the blood flow distribution, which had been normal during coronary constriction at rest, was markedly disturbed by the intracoronary injection of contrast medium, indicating a redistribution of flow to the normally perfused myocardium. GRIGGS et al. (1971), using an autoperfusion cannula in anesthetized dogs, reported an equal increase in lactate content in freely perfused endocardium and epicardium during β-adrenergic stimulation with isoproterenol. If, however, coronary inflow was reduced and the same dose of isoproterenol was administered, a marked differential increase in lactate content was observed in the endocardial layers. Under the former conditions of isoproterenol administration with free flow, lactate extraction amounted to 30%, but was inverted to a release of lactate when isoproterenol was given during coronary constriction. Similar results were obtained by LEKVEN et al. (1974) on cardiac stimulation with isoproterenol under control conditions and then following reduction of coronary flow amounting to 30%, 50%, and over 60%. Very sensitive parameters for the detection of effects of isoproterenol during graded constriction were the metabolic parameters such as oxygen and lactate extraction, as well as regional myocardial function assessed by ultrasonic crystals. Thus, stenoses which are not of obvious detriment during resting conditions may prove to be of relevance during cardiac stimulation (SEITELBERGER et al. 1984).

Using a mass spectrometric method for measurement of coronary PO_2 and PCO_2, O'RIORDAN et al. (1977) reported on decreases in oxygen tension and increases in carbon dioxide tension with direct coronary narrowing to give a critical coronary stenosis (i.e., no influence on blood flow during rest, but complete in-

hibition of reactive hyperemia following release of coronary occlusion). If atrial pacing was further added to the critical stenosis, very low PO_2 values and markedly increased PCO_2 values were found in the mid-myocardium. The effects of direct coronary narrowing on regional metabolism were compared in the intact and underperfused myocardium by RABERGER et al. (1978). In these experiments, blood flow is measured electromagnetically in both branches of the left coronary artery in anesthetized dogs. Two local veins, one draining blood from the area supplied by the circumflex and one from the area supplied by the descending coronary branch, were directly punctured with small catheters, allowing selective sampling from both areas. These local balances with respect to glucose, lactate, and free fatty acids were compared with the corresponding combined overall balances. Constriction of the circumflex branch, which had no significant influence on overall balance, markedly influenced regional balance in the constricted circumflex area. Thus, it would be desirable to assess metabolism locally in the underperfused area to detect the actual effects of drugs in the relevant area of the myocardium.

The influence of various drugs on stenosis resistance and coronary blood flow was investigated using coronary constrictors. Resistance of coronary stenoses was found to be increased with vasodilators such as isoproterenol or nitroglycerin, whereas it was decreased with vasoconstrictive drugs like methoxamine and vasopressin (SANTAMORE and WALINSKY 1980). Similarly, since coronary blood flow in critically narrowed arteries is mainly pressure dependent, nitroprusside leads to a decrease, whereas methoxamine induces an increase in coronary blood flow to the constricted artery (NAGATA et al. 1982). Ouabain, which is known to cause vasoconstriction in intact vessels, slightly reduces blood flow to intact areas of the heart, but has no influence on blood flow to underperfused areas. Calculation of the respective coronary flow/beat values stresses this divergent behavior of normal and underperfused areas of the heart (RABERGER et al. 1976).

Most experiments on coronary hemodynamics and metabolism have been performed in dogs. One attempt to use the anesthetized rat as an experimental animal for testing antianginal drugs was made by SAKAI et al. 1981. SAKAI (1981) reported marked vasoconstriction in isolated perfused hearts of rhesus monkey, pig, and dog on administration of cholinomimetic drugs. Either metacholine or acetylcholine given together with physiostigmine intra-aortically provoked marked increases in perfusion pressure in the isolated perfused heart, but a marked reduction in arterial blood pressure in the intact rat. This marked reduction in blood pressure was associated with a marked ST elevation, which is reversible and reproducible. This model might be of interest not merely for the testing of potentially antianginal drugs, but also for drugs effective in vasopastic angina. The coronary circulation of intact dogs, in contrast to monkeys and rats, seems to be rather insensitive to cholinomimetic drugs (SATOH et al. 1982).

2. Conscious Animals

A marked attenuation of baroreceptor reflex activity was found to exist in anesthetized, as compared with conscious dogs (COX and BAGSHAW 1979; VATNER and BRAUNWALD 1975; ZIMPFER et al. 1982). Chemoreceptor reflex activity was mark-

edly attenuated in comparison with the conscious state in dogs with α-chloralose and pentobarbital anesthesia (ZIMPFER et al. 1981) and completely abolished by inhalational anesthetics over the range of concentrations used for experiments or during operations in humans (BECK et al. 1982). Hence, the effect of potential antianginal drugs should be tested in conscious animals with intact reflexes. It is also known from studies performed by MILLARD et al. (1972) and HIGGINS et al. (1972a, b) in conscious dogs with experimental heart failure that reflex activity can also be markedly altered by underlying myocardial disease. The release of renin and the increase in plasma volume observed with vasodilators are also markedly reduced with heart failure (ENGELER et al. 1982). Judging from these differences between anesthetized and conscious animals, as well as the effect of the presence or absence of heart failure in the conscious animal, it appears desirable to investigate potential antianginal drugs in a model of angina pectoris in conscious dogs.

Coronary insufficiency was produced by the induction of coronary artery sclerosis. WATERS (1948) and CONRAD et al. (1956) used intrapericardial or intravenous injections of allylamine to produce coronary sclerosis. This method was also used by SAITO (1976), who investigated the coronary artery response to potentially useful coronary vasodilators and found a reduced vasodilating response during allylamine-induced vascular damage in comparison with control experiments. Drastic procedures, such as reported by SABISTON et al. (1961), consisting of aortic narrowing, thyroidectomy, and a high cholesterol diet also resulted in coronary sclerosis, but are probably very complex interventions which will not prove practical for experiments on a large scale. BUCKBERG et al. (1972) induced subendocardial ischemia in dogs with normal coronary arteries by combining arteriovenous fistulas with aortic constriction.

One main obstacle was the production of myocardial underperfusion in conscious dogs. BERMAN et al. (1956) used ameroid as a constrictive device. Ameroid, which is a hygroscopic casein, slowly takes up water. Thus, the diameter of a lumen within an Ameroid cylinder, which is applied to the coronary artery, will slowly decrease. In order to prevent the cylinder from expanding away from the coronary artery, a metal ring is used to keep a constant external diameter while the inner diameter decreases. The time necessary for complete swelling of this ameroid constrictor to give the final lumen reduction can be markedly prolonged if the ameroid constrictors are preincubated and coated with glycerin or petrolatum (LITVAK et al. 1957; VINEBERG et al. 1960). Ameroid constrictors with an inner diameter of 3 mm will reduce the lumen to 1.6 mm within 26 days in saline if not coated, but to only 1.8 mm within 54 days if coated with petrolatum. Ameroid constrictors were used both for lumen reduction and for complete obstruction, depending on the size of the inner diameter. Hydraulic cuff occluders were also used for coronary constriction, but mainly for acute reduction of blood flow to a predetermined value below the resting flow for producing critical coronary stenosis or for reduction of reactive hyperemia to a certain value (BALL and BACHE 1976; BACHE et al. 1977). Abrupt narrowing to 60% of the resting blood flow leads to a reduction of the simultaneously microsphere-assessed endocardial : epicardial blood flow ratio, which deteriorates further within 30 s of observation, indicating infavorable redistribution. During coronary constriction of this

magnitude, the perfusion in the constricted branch remains unaltered during systole, whereas diastolic blood flow is markedly reduced.

Experiments with marked reduction in resting blood flow do not mimic the clinical features of angina pectoris, which are characterized by normal resting hemodynamics, but marked dysfunction and pain during the acute attack. Models using a mild reduction of resting blood flow which are not sufficient to cause deterioration of the endocardial : epicardial perfusion ratio at rest seem to be very promising. NEILL et al. (1975) succeeded in narrowing the left circumflex coronary artery in conscious dogs to a value which led neither to hemodynamic nor to metabolic changes as assessed by the endocardial : epicardial ratio using radioactive microspheres and the lactate balance between arterial and coronary sinus blood. An increase in heart rate of 100 beats/min produced by arterial pacing or intravenous atropine at constant stenosis resulted in a marked redistribution of blood from the endocardial to the epicardial layers and a marked reduction of myocardial lactate extraction. The failure to observe any lactate release was probably due to the nonselective sampling of coronary venous blood. Up to now, there have been no reports of successful prolonged regional blood sampling in the conscious dog.

Studies on regional function during coronary stenosis and cardiac pacing were performed by TOMOIKE et al. (1978 a). A reduction in coronary resting flow to 75% resulted in no alteration of regional myocardial shortening as measured in the subendocardium with ultrasonic crystals. Although the coronary blood flow remained constant and the end-diastolic segment length did not change markedly, the ischemic segment responded to tachycardia with bulging, a systolic lengthening. At the same time, the normal segment increased its systolic shortening. This dysfunction was reversible within 5 min, indicating a transient deterioration of function which is consistent with subendocardial underperfusion during coronary artery stenosis and an increase in heart rate. This redistribution of coronary blood flow was also observed in conscious dogs following coronary inflow constriction of a markedly lesser extent, limiting exercise-induced blood flow increase to 66% of the maximum control value (BALL and BACHE 1976). These results show that distribution of blood flow is dependent on coronary vessel patency and flow reserve on the one hand and heart rate on the other hand.

Exercise is probably the best procedure to mimic stress which, in turn, leads to anginal attack. A selective increase in heart rate, as observed with atrial stimulation, speeds up the heart without increasing the venous return and is, thus, self-limiting. These assumptions can be derived from experiments on sled dogs, which respond to severe exercise with maximal heart rate values of 330 beats/min without signs of myocardial or coronary dysfunction (VAN CITTERS and FRANKLIN 1969). In dogs with a coronary stenosis which is not effective during resting conditions, regional dysfunction can be pharmacologically induced by isoproterenol infusions (GALLAGHER et al. 1982). This study in conscious dogs revealed the close correlation of decreased endocardial blood flow and reduction of endocardial segment shortening or regional wall thickening in the narrowed area. The experimental setups using microsphere-assessed blood flow and regional function clearly demonstrate that further testing of antianginal drugs has to be performed in conscious animals with coronary stenosis which limits reactive blood flow in-

crease either partially or completely. The restriction of inflow and the stimulus for increased cardiac performance or, at least, increase in heart rate, must be chosen in such a way as to result in a reversible dysfunction due to underperfusion in this area during free running, treadmill exercise, or pacing. Another approach is to limit coronary inflow to values which lead to regional dysfunction at rest and, then, test the influence of drugs on the animals with permanent dysfunction due to marked coronary inflow reduction (TOMOIKE et al. 1978 b).

The same experimental setup can, of course, be used in other species, although the size of the heart and coronary arteries sets a lower limit. Pigs were, therefore, used for studies in the anesthetized (SHAMHARDT et al. 1979) and also in the conscious state (GERWITZ and MOST 1981; GERWITZ et al. 1982; WALTERBUSCH et al. 1982). The advantage of using the pig as experimental animal is the closer resemblance of the coronary circulation to humans (LUMB and SINGLETARY 1962), especially concerning the intercoronary collaterals (SCHAPER et al. 1967; GEARY et al. 1981). However, it seems worth mentioning that the existence of collaterals can vary widely in the dog, with marked differences between inbred beagles and mongrel dogs (WÜSTEN et al. 1974).

III. Myocardial Infarction

Myocardial infarction models were first established in order to investigate arrhythmias and the influence of drugs thereon (HARRIS 1950). It was soon noted, however, that coronary collaterals had some influence on infarct size and, thus, infarct models were used to establish the appearance and functional significance of collateral vessels in the heart, and, of course, to test their pharmacologic response. Many drugs which had been used in the treatment of angina pectoris were, thus, reevaluated in view of their beneficial effects as regards infarct size reduction or, simply, survival. It is, of course, evident that the mortality rate depends on the site of coronary ligation (ALLEN and LAADT 1950), but many other aspects such as sympatheticotonia and the oxygen demand: supply ratio have been found to be of great relevance. The model of coronary artery ligation which was set up for dogs has also been described for rats (CLARK et al. 1980) and cats (RITCHIE et al. 1979). Infarcts in rats were also produced by cautery of the left anterior descending branch of the left coronary artery (STAAB et al. 1977). Hydraulic occluders which have already been mentioned with respect to coronary constriction or flow limitation are also used for the production of infarcts in dogs (KHOURI et al. 1968) or pigs (SAVAGE et al. 1981).

Other attempts were made to produce myocardial infarcts without thoracotomy by obstructing the coronary artery from the inside of the lumen. AGRESS et al. (1952) injected microspheres with diameters of 190, 325, or 450 μm and obtained the best results with the medium-sized spheres. An attempt to standardize this procedure was made by JAKOBEY et al. (1962) by injecting different amounts and correlating the microsphere dose to the mortality rate. WEBER et al. (1972) produced infarcts by infusing 7.5-μm diameter microspheres over a period of 4–6 h into the coronary artery of calves. Infarcts produced by just one plastic sphere of appropriate size were described by CHAGRASULIS and DOWNEY (1977) for closed-chest dogs. Other methods to make infarcts were to inject 0.2 ml mercury

(LLUCH et al. 1969) or two deposit helically bent copper wires (KORDENAT et al. 1972) or Teflon (polytetrafluoroethylene) cylinders (COHEN and ELDH 1973) into the artery. A method which was mostly used in anesthetized dogs was intracoronary occlusion using a Swan–Ganz catheter (CORDAY et al. 1974). This method also allows measurement of postocclusional pressure or the selective administration of drugs to the occluded area. The catheters used for coronary angioplasty (GRUENTZIG 1968) fulfill the same purpose, but have the advantage of easier guidance into the coronary arteries.

Another approach to the production of myocardial infarcts consists of induction of coronary thrombosis. SALAZAR (1961) inserted a shileded electrode selectively into one branch of the left coronary artery and induced thrombosis by constantly increasing the current until ECG changes occurred. ROMSON et al. (1980) modified this method by introducing a Teflon-coated silver wire into the artery via thoracotomy, simultaneously applying an electromagnetic flow probe to this artery. In the conscious state, an anode current of 50 μA from a 9-V battery over 24 h was sufficient to produce complete obstruction of the left circumflex branch in the dog. The use of an intracoronary injection of thrombin together with temporal occlusion of this branch (GIRAUD and MACCANNEL 1980) seems to be a rather inaccurate method.

One of the major problems in studying the influence of drugs on infarct size or blood flow is the great species and individual variability in the coronary vasculature. To circumvent this problem, SCHAPER et al. (1979 a, b) developed an experimental model comprising two infarcts within the same animal. This method allows a comparison to be made between untreated and pretreated or treated myocardial infarction, since the infarct size is kept small enough to avoid any overall hemodynamic changes. The limitations of this model are the acute nature of these experiments and the absence of hemodynamic changes which are typical of clinical observed infarcts of appropriate size.

In order to verify the influence of drugs on infarct development, it was necessary to get accurate measures for infarct size. The most commonly used methods which can be performed in vivo are assessment of the time course of plasma creatine phosphokinase (CPK) levels (SHELL et al. 1973), precordial ST mapping (MAROKO et al. 1972), and injection of infarct imaging agents (DAVIS and HOLMAN 1975). These methods give, of course, only a rough estimate of real infarction. Hence, other methods such as analysis of CPK depletion of the myocardium (SHELL et al. 1971), measurement of myocardial ATP, lactate, and CPK at multiple puncture sites in the heart (HEARSE et al. 1977), or injection and perfusion of the heart with various markers (SCHAPER et al. 1969, 1979 a, b), have been used in experimental medicine. The use of markers of infarct size, together with measurement of the perfusion area and the area at risk (GOTTWICK et al. 1981) are the best methods of quantification so far. For more detailed description see SCHAPER (1979).

IV. Collateral Circulation

Aside from measurement of infarct size, interest was also aroused in the amount of blood reaching the infarcted area via collateral vessels. Attempts to measure

collateral blood flow are very similar to the dilution methods used for coronary blood flow measurement. Thus, rubidium (LEVY et al. 1961) and microspheres (BISHOP et al. 1976; RIVAS et al. 1976; HIRZEL et al. 1976) have been used. One variation similar to coronary blood flow measurement by washout from a myocardial depot is the injection of the indicator into the occluded artery and the monitoring of the washout curve (REES and REDDING 1967). Retrograde coronary artery pressure and blood flow values, measured via catheters implanted into the occluded artery, were also used to quantify collateral blood flow, but seem to give different values in the hands of different investigators (KHOURI et al. 1971; PASYK et al. 1971; BLOOR and WHITE 1972).

Collateral blood flow is also of interest in situations of restricted inflow into one coronary artery. Experiments on intact dogs with permanent 50% restriction of reactive hyperemic blood flow, but no restriction of resting coronary blood flow, confirm the concept of the appearance of collaterals in response to need. Exercise increased resting collateral flow markedly and resulted in better performance during coronary artery occlusion in comparison with untrained dogs (COHEN et al. 1982). As stated previously, microsphere-assessed blood flow values certainly represent perfusion, but not necessarily myocardial function. Hence, experiments using regional function as a parameter of collateral efficacy seem to provide the best answer. TOMOIKE et al. (1981) using this method found that gradual reduction of the lumen of the circumflex coronary artery with an Ameroid constrictor led to the formation of a collateral supply sufficient to result in no resting contractile dysfunction. Exercise testing revealed the stenosis and insufficient collateral function in this situation. The collateral function is of interest, especially with respect to drug testing and the assessment of coronary steal (SCHAPER et al. 1973; COHEN et al. 1976; COHEN 1982; GROSS et al. 1982).

V. Reperfusion and Retroperfusion

Aside from collateral development, reperfusion and retroperfusion of the infarcted myocardium seem to be of clinical interest (LANG et al. 1974; HEYNDRICKX et al. 1975; MEERBAUM et al. 1976). Reperfusion is the restoration of blood flow after temporal occlusion from the arterial side of the circulation as would occur after bypass surgery, intracoronary lysis, or angioplasty. In retroperfusion experiments, an improvement in the supply: demand ratio is sought retrogradely from the venous side either by infusing arterial blood into the coronary sinus or by occluding the coronary sinus for a predetermined time (see MOHL et al. 1984).

Although myocardial blood flow to the occluded area may be completely reestablished by reperfusion, myocardial function is the critical parameter for such experiments (RAMANATHAN et al. 1978). DARSEE et al. (1981), using occlusion periods of 1–120 min, found out that complete restoration of myocardial function within 6 h occurred only after coronary occlusion periods of 1–5 min. A 15-min occlusion was followed by a progressive restoration of function of up to 50% of starting values within 6 h. KLONER et al. (1981), using the same experimental setup, reported impaired regional myocardial function after 3 days of reperfusion after a coronary occlusion of 15 min. Myocardial ATP content was also still markedly reduced in the reperfused area. MURPHY et al. (1982), performing simi-

lar experiments in anesthetized pigs, found myocardial damage after occlusion periods of up to 30 min. Occlusion periods of 15 min or less were followed by complete restoration of myocardial function. Thus, time seems to be the critical factor for reperfusion and retroperfusion experiments.

D. Summary

Testing of antianginal drugs represents a very difficult task, necessitating the utilization of modern measuring devices and models of disease in conscious animals. The most frequently used methods, aside from conventional pressure and flow measurement, are the assessment of regional myocardial flow and function using radioactively labeled microspheres and ultrasonic crystals. These hemodynamic data should be supplemented by biochemical analyses of myocardial contents of energy-rich phosphates or myocardial balances of sensitive indicators of underperfusion such as lactate of inosine and hypoxanthine. Resting blood flow or reactive blood flow increase can be limited acutely or chronically. The chronic reduction of reactive blood flow increase is probably of greatest clinical significance. In order to simulate an anginal attack, reactive or resting blood flow can be limited acutely or chronically, which probably is of greater clinical relevance. In order to simulate an anginal attack, stress such as free run, treadmill exercise, or pharmacogenic stimulation must be applied in addition to limited coronary blood flow increase. These models of coronary exercise or resting insufficiency in conscious animals are probably the best predictors of the clinical significance of drug actions.

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CHAPTER 5

Noninvasive Methods: Systolic Time Intervals and Echocardiography

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A. Introduction

The two most commonly used noninvasive techniques for the evaluation of drug action are systolic time intervals and echocardiography. These techniques will be described separately and their relative merits and applications discussed where appropriate.

B. Systolic Time Intervals

Measurement of systolic time intervals is a method of assessing left ventricular function in terms of the timing of well-defined events in the cardiac cycle. It is entirely noninvasive and therefore normal subjects can be studied in addition to patients. It also has the advantage that repeated measurements can be made either in the basal state of after interventions. It is these features which make the measurement of systolic time intervals attractive for the study of drugs with an action on the cardiovascular system. The technique has been in use for a number of years and has been used extensively to investigate clinical left ventricular disease. It has been the subject of several reviews (WEISSLER et al. 1969; HARRIS et al. 1974; LEWIS et al. 1977). The ability to express left ventricular function in terms of single numbers has advantages when the effects of drugs or other interventions are being compared, but it must be stressed that this simplicity is only apparent and may conceal complex underlying changes in the circulatory state. Furthermore, although left ventricular disease and drug administration have similar effects on the systolic time intervals, there is much evidence to suggest that the mechanisms responsible are widely different and not comparable in these simple terms.

I. Measurement of Systolic Time Intervals

Three systolic time intervals are commonly measured (WIGGERS et al. 1921):

1. Left ventricular ejection time (LVET), the time interval over which blood is ejected into the aorta.
2. Electromechanical systole (QA2), the time from the onset of electrical activation of the left ventricle until the start of relaxation.
3. The preejection period (PEP), or the interval between the onset of electromechanical systole and that of ejection time.

These time intervals are based on the following measurements (Fig. 1):

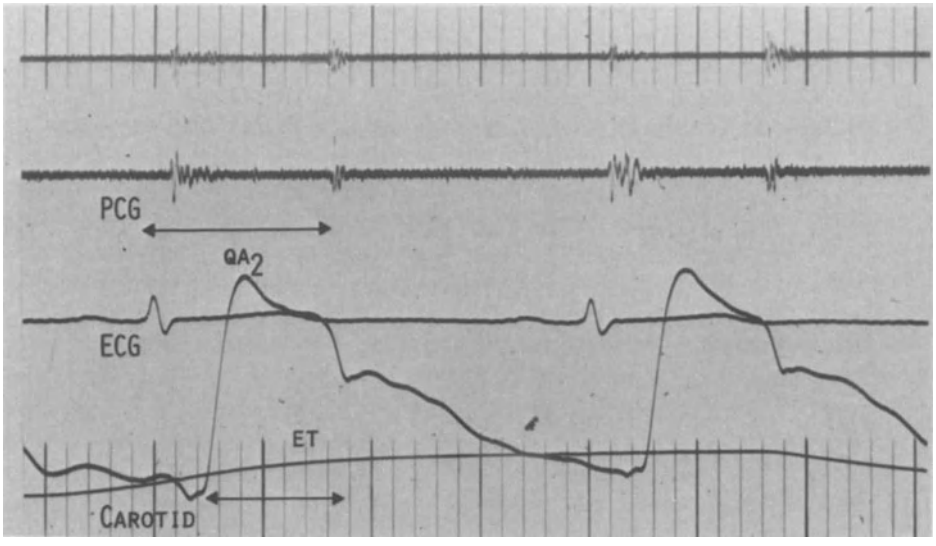

Fig. 1. Measurements of systolic time intervals

1. The ECG which is used to determine the time of onset of electrical activation of the left ventricle. This is normally the start of the Q wave in leads II or V_6, but this is not the case in patients with left bundle branch block, during right ventricular pacing, or in the presence of the Wolff–Parkinson–White syndrome where there is a delta wave on the upstroke of the ECG trace. In all these conditions the start of left ventricular activation is delayed with respect to the onset of the QRS complex by an unknown amount.

2. The phonocardiogram, in order to determine the timing of aortic valve closure from the aortic component of the second heart sound (A2). Phonocardiograms should be recorded from the region of the precordium where splitting of the second heart sound is most obvious clinically, usually in the second left interspace. Normally, A2 is the first component of the second sound, but this is not the case in patients with left bundle branch block, left ventricular disease or severe hypertension, where splitting may be reversed. In severe aortic valve disease it may be absent altogether. Recordings should be taken with a high frequency filter (greater than 100 Hz). Measurement of the timing of heart sounds is taken, by convention, as that of the onset of the first high frequency component.

3. The indirect carotid pulse. This is to measure LVET. Recordings are taken from the right carotid artery. The onset of left ventricular ejection corresponds with the start of the rapid upstroke of the carotid pulse; this is frequently preceded by a small upward displacement occurring during isovolumic contraction so that ideally the record should show both events. The end of ejection corresponds to the dicrotic notch or incisura, whose nadir in the central aortic trace is synchronous with A2. Transmission of the pulse to the carotid artery takes approximately 20 ms, but during this inverval there is no significant change in the waveform it-

self (LEWIS et al. 1977). This is not the case for indirect pulses recorded from more peripheral arteries, which are not therefore suitable for measuring the systolic time intervals. The characteristics of the transducer itself are important and should ideally be quoted in publication. If the time constant is less than 2.5 s, then partial differentiation of the record may occur, causing significant errors in timing.

II. General Points

Records should be made photographically at a paper speed of 100 mm/s. In order to allow for the effects of respiration, measurements should be made over at least ten successive beats and the results averaged.

III. Determinants of the Systolic Time Intervals

1. Heart Rate

Heart rate was recognised as a determinant of the ejection time as long ago as 1874 by GARROD. Exact relations between heart rate and the different systolic time intervals have not been defined physically so that empirical regression equations must be used if these variables are to be allowed for (Table 1). The most commonly employed were proposed by WEISSLER et al. (1968).

These regression equations have been made the basis of a "correction" procedure, which consists of expressing values of those predicted to occur at zero heart rate. Thus in humans, ejection time index (LVETI) is defined as:

$$\text{LVETI} = \text{LVET} + 1.7 \times \text{heart rate}$$

with a normal value of 413 ± 14 ms (WEISSLER et al. 1963). It can be seen from Table 1 that PEP is significantly less dependent on heart rate than either ejection

Table 1. Calculation of ST index values from resting regression equation

Sex	Equation	Normal index	Standard deviation
M	$QS_2I = 2.1\,HR + QS_2$	546	14
F	$QS_2I = 2.0\,HR + QS_2$	549	14
M	$LVETI = 1.7\,HR + LVET$	413	10
F	$LVETI = 1.6\,HR + LVET$	418	11
M	$PEPI = 0.4\,HR + PEP$	131	10
F	$PEPI = 0.4\,HR + PEP$	133	10

I index; HR heart rate; M male; F female

time or QA2 interval. Further minor differences exist in children (HARRIS et al. 1964) and patients over 65 years old (WILLEMS et al. 1970). These regression equations represent the largest population of normal subjects that have been studied, and are therefore the ones most commonly employed. They are based on spontaneous variation in heart rate in normal subjects, studied fasting and between 0800 and 1000 hours. Other workers (JONES and FOSTER 1964) have also established regression equations using exercise to vary heart rate; the slope of their regression line differed from that of WEISSLER et al. (1968). HARLEY et al. (1969) studied patients with complete heart block in whom the heart rate could be varied using a ventricular pacemaker. These workers found yet another relation with ejection time. If therefore follows that any correction for heart rate is arbitrary and strictly speaking limited to the conditions from which the original regression equation was derived. This is of less significance of spontaneous changes of heart rate are to be allowed for, than when variation is due to drug administration. A spontaneous increase in heart rate is brought about by a combination of parasympathetic withdrawal and sympathetic stimulation (ROBINSON et al. 1966), of which the latter might be expected to have a separate effect on left ventricular contraction independent of any change resulting from the increase in heart rate. If a similar change in heart rate was brought about by parasympathetic withdrawal alone the effects on left ventricular contraction need not necessarily be identical to those predicted by the standard regression equation. This possibility must be clearly borne in mind when interpreting the results of any study when drug-induced changes in heart rate occur.

A number of workers have avoided the application of population regression equations by correcting for heart rate in individual subjects. This has been done by either pretesting individuals with graded exercise tests and atrial pacing (KELMAN et al. 1980; MERTENS et al. 1981) or by use of increasing doses of atropine (KELMAN and SUMNER 1981). Interestingly in this latter study, the regression relationships showed little intrasubject variability, but a larger degree of intersubject variability.

2. Left Ventricular Filling

Head-up tilt or the application of venous tourniquets prolong PEP and LVETI (STAFFORD et al. 1970). It is difficult to determine the mechanism of such changes since a number of alterations in central haemodynamics occur. These include a reduction in venous return and of stroke volume as well as in left ventricular end-diastolic pressure and volume. These changes are interrelated, although in no predictable way. Thus a reduction in end-diastolic pressure is associated with a corresponding drop in volume, the exact relation depending on the range of pressures involved and the nonlinear left ventricular pressure–volume curve of the individual patient. A reduction in end-diastolic volume may be associated with a reduction in the force of left ventricular contraction, owing to Starling's law while a reduction in end-diastolic pressure is, per se, associated with an increased pressure gradient across the aortic valve, and thus with prolongation of PEP (AGRESS et al. 1972), unrelated to any separate change in left ventricular function that it might cause.

3. Peripheral Resistance

The effects of changes in peripheral resistance are also complex. An increase in aortic pressure induced by methoxamine or angiotensin (HARRIS et al. 1967; SHAVER et al. 1968) prolongs ejection time and PEP while a reduction by amyl nitrate administration shortens both (SAWAYAMA et al. 1969).

4. Inotropic State

Systolic time intervals are changed by administration of drugs with a positive inotropic effect. Unfortunately this term is not well defined, but from common usage it implies one or more of a number of changes in left ventricular function occurring independently of any alteration in left ventricular filling. Such changes include an increase in the rate of tension development or in the rate of rise of pressure, an increase in peak wall tension developed, and finally, an increase in the peak rate of wall movement during ejection. The exact action of drugs with a positive inotropic effect differs from one to another and also between species. The effects of such drugs on the systolic time intervals however are consistent, showing a reduction in preejection and in QA2 interval. A reduction in ejection time usually, but not always, occurs, since associated haemodynamic changes such as an increase in stroke volume (WEISSLER and SHOENFELD 1970) may have the opposite effect. Similar changes in humans occur during erect exercise (PIGGOTT et al. 1971). AHMET et al. (1972) have demonstrated a close relation between changes in PEP in humans and a variety of indices of "contractility", including peak left ventricular dP/dt, and peak dP/dt divided by developed pressure, so-called V_{max} A reduction in PEP occurs after intravenous administration of 10% calcium gluconate (SHINER et al. 1969) or isoproterenol (HARRIS et al. 1967). PEP is prolonged by β-blocking drugs (HARRIS et al. 1967) which may also result in a reduction in ejection time. It will be apparent therefore that positive or negative inotropic drugs have predictable effects on PEP and QA2 interval, but not on ejection time.

5. Left Ventricular Disease

Left ventricular disease has significant and consistent effects on the systolic time intervals. The characteristic abnormality is a delay in the onset of ejection (JEZEK 1963), which causes prolongation of PEP and shortening of ejection time, and thus an increase in the ratio PEP/LVET, which is rate independent (GARRARD et al. 1970). The duration of electromechanical systole is usually unaltered, unless increased adrenergic activity is present, when it is shortened. This commonly occurs after acute myocardial infarction (TOUTOUZAS et al. 1969) when its extent has been shown to correlate with urinary catecholamine excretion in a group of patients with normal renal function (LEWIS et al. 1972).

The mechanism by which the onset of ejection is delayed in left ventricular disease is obscure. The lack of prolongation of QA2 suggests that it is not due to any negative inotropic effect in such patients. This clear difference from any acute, drug-induced alteration in left ventricular function is confirmed by other studies which demonstrate that indices of contractility perform very poorly in de-

tecting clinical left ventricular disease (PETERSON et al. 1974). The ratio PEP/LVET has been shown to be related to ejection fraction (GARRARD et al. 1970) which itself is a ratio and therefore dimensionless rather than time related. A second factor likely to prolong PEP and thus delay the onset of ejection is the presence of incoordinate left ventricular wall movement during isovolumic contraction. This has been shown in a previous study (GIBSON and BROWN 1976) to relate closely to reduced peak left ventricular dP/dt.

IV. Validation of Systolic Time Intervals

A number of studies have been performed in which externally measured systolic time intervals have been compared with corresponding values determined more directly. Estimates of ejection time derived from the indirect carotid pulse are virtually identical with those measured by micromanometer in the aortic root (BUSH et al. 1970; MARTIN et al. 1971). Estimates of PEP have been similarly validated against the interval between the Q were of the ECG and the onset of the upstroke of the central aortic pressure trace. Although there has been considerable discussion as to the exact mechanism of production of the second heart sound, the coincidence in time of A2 with aortic valve closure has been confirmed by echocardiography to within 5–10 ms (ANASTASSIADES et al. 1976; SABBAH and STEIN 1978).

V. Use of Systolic Time Intervals to Study Drug Action with Antianginal Preparations

The use of systolic time intervals to study antianginal drugs has been largely confined to β-blocking agents. One of the earliest studies by HARRIS et al. (1967) showed that stepwise increments in β-adrenoceptor activation induced by isoproterenol shortened the PEP in a dose-related manner and concluded that the amount of this shortening was therefore a function of the level of β-adrenergic activity. Increasing doses of propranolol shifted this isoproterenol dose–response curve to the right. The parallel nature of these shifts resembles those observed in pharmacological studies demonstrating competitive, antagonism between two agents for the same receptor sites. In the same study administration of propranolol to resting subjects lengthened the PEP, suggesting possible suppression of a basal level of β-adrenergic activity or possibly a myocardial depressant action.

HUNT et al. (1970) noted a shortening of PEP in the first 2 days of acute myocardial infarction with subsequent stepwise prolongation. In 14 such patients and 2 further patients with unstable angina, intravenous practalol caused an increase of PEP to normal levels with no significant change in LVET. Presumably the practalol abolished excess sympathetic activity with resultant increase in PEP. The constancy of LVETI may have reflected absence of change in stroke volume.

FRISHMAN et al. (1975) investigated patients with ischaemic heart disease who were being treated with propranolol (80–320 mg/day) for angina. Maximum improvement of exercise tolerance was found to occur at a dose of 80 mg and, above this level, exercise tolerance deteriorated again owing to fatigue rather than

breathlessness or chest pain. Increasing propranolol dose was associated with stepwise prolongation of PEP and PEP/LVET ratio. It was thus possible to define the effects of the drug in individual patients. The authors suggested that use of systolic time intervals might confirm a therapeutic action of the drug and also avoid limitation of exercise tolerance by inappropriately high propranolol dosage.

ESPER et al. (1975) assessed the calcium antagonist nifedipine in 20 patients with coronary artery disease by means of systolic time intervals. Before nifedipine was given, PEPI was increased and LVETI was reduced in the ischaemic patients as compared controls; the ratio PEP/LVET was thus increased. After nifedipine treatment, LVETI increased and PEPI shortened so normalising the ratio PEP/LVET. The authors interpreted these findings as demonstration of a beneficial action of calcium antagonists on myocardial function in patients with ischaemic heart disease.

VI. Place of Systolic Time Intervals in Clinical Pharmacology

The possible place of measurement of the systolic time intervals in the investigation of the effects of drugs in humans will have become apparent from the foregoing description. Their measurement is technically possible in the great majority of normal subjects and patients with heart disease, although it may present difficulties in the severely ill. As with all noninvasive methods, the value of the results is directly related to the technical quality of the records from which they are derived. A particular feature of methods based on the systolic time intervals is the simple way in which the results are presented, making them a very satisfactory means of determining the overall effect of individual drugs and of constructing dose–response curves. As shown in the studies involving β-adrenoceptor blocking drugs, they can also be used to give an elegant demonstration of the effects of competitive inhibition. Their main disadvantage is the sensitivity of each measurement to several haemodynamic variables, so that even in combination, they may not give unequivocal information about the mechanism of drug action. Thus, ejection time index may be shortened by positive or negative inotropic stimuli, a reduction in stroke volume or an increase in arterial pressure, while an increase in PEP may follow an increase in arterial pressure, a reduction in end-diastolic pressure or a negative inotropic stimulus. In general, the use of systolic time interval measurements to demonstrate possible cardiac effects of any drug with potent effects on the peripheral circulation may present difficulties. It is therefore useful to consider using the systolic time intervals in conjunction with noninvasive methods such as apex- or echocardiography which may allow drug action to be defined in more specific terms.

C. The Use of M-Mode Echocardiography in Assessing Antianginal Drugs

M-mode echocardiography is a method of using pulsed ultrasound to detect the position and movement of intracardiac structures. The technique itself, and its use in the study of left ventricular disease has been described in a number of recent

monographs and reviews (FEIGENBAUM 1976; ROELANDT 1977; MASON and FORTUIN 1978). It allows a number of aspects of left ventricular function to be studied. Of these, the simplest is the measurement of the transverse dimension of the left ventricular cavity at the level of the mitral valve apparatus. The technique has considerable potential advantages for clinical pharmacological studies in that it is noninvasive, has a repetition rate of 1,000 per second, compared with 50 per second for angiography, or even less for nuclear methods. It shows endo- and epicardial surfaces of the posterior left ventricular wall unequivocally throughout the cardiac cycle, and allows septal movement to be studied. In addition, it is totally safe, so that it can be used on normal volunteers.

I. Technique of Recording

Echocardiograms are most easily obtained with the patient in the 30 ° left oblique position, and the head raised. The mitral valve cusps are first located, with the transducer in the second to fourth left interspace. It is then rotated slightly

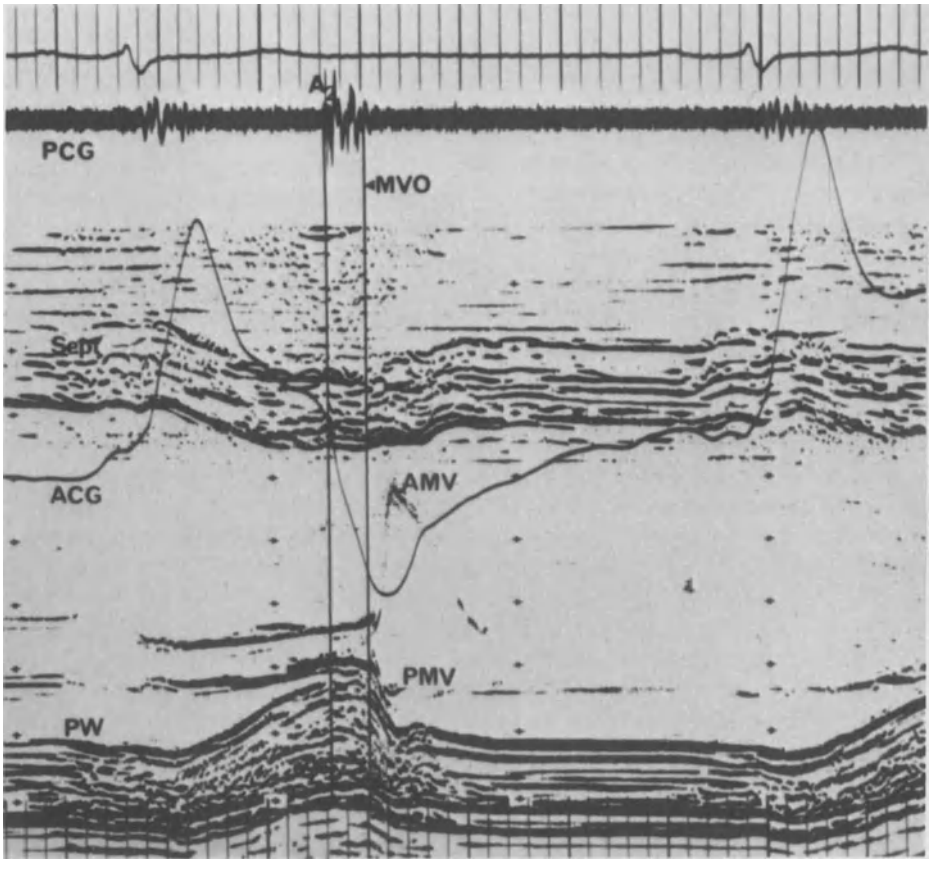

Fig. 2. M-mode echocardiography recording

towards the apex, so that a record of the interventricular septum and posterior wall is made at, or a little below the level of the mitral valve cusps (Fig. 2). Records taken at a higher level, towards the mitral ring, show a reduced amplitude of wall movement, while below the insertion of the papillary muscles, the cavity tapers towards the apex. Records must always show clear and continuous endocardial echoes, since experience with two-dimensional images has demonstrated that a series of overlapping echoes on the M-mode trace are often due to lateral movement of cardiac structures with respect to the ultrasound beam. Both sides of the septum should be demonstrated and also endo- and epicardial surfaces of the posterior wall, along with either part of the mitral cusps or chordae. Where possible, records should be taken throughout the respiratory cycle, but in some individuals, particularly those with chest disease, this may be impossible, and satisfactory tracings are only obtained in expiration. A strip chart recorder, operating at a speed of at least 50 mm/s, and preferably 100 mm/s should be used. It is essential to record a simultaneous ECG, and preferably a phonocardiogram and apex-cardiogram. Echocardiographic estimates of dimension have been validated against those derived from angiography in a number of studies (POMBO et al. 1971; FORTUIN et al. 1971; FEIGENBAUM et al. 1972; GIBSON et al. 1973).

II. Technique of Measurement

There is unfortunately no general agreement as to how even the simplest measurements should be made from echocardiograms. The following recommendations are based on those currently under consideration by the Working Group in Echocardiography of the European Society of Cardiology:

1. All measurements should be made from the anterior or leading edge of the echo on the tracing, since it is this, rather than the posterior edge that corresponds to the position in space of the structure giving rise to it. The thickness of an echo on the final trace depends on reverberations of sound within the structure and the gain settings of the instrument (ROELANDT 1977).
2. End-diastolic measurements should be made at the time of onset of the inscription of the Q wave of the ECG. Maximum dimension frequently follows this, occurring with a change in cavity shape during isovolumic contraction.
3. End-systolic dimension is measured at the time of minimum dimension, which almost corresponds to the time of maximum forward movement of the posterior left ventricular wall.
4. Measurements of cavity dimension should be expressed to the nearest 1 mm when ultrasound of 2.25 MHz is used, corresponding to the range resolution of the equipment at this frequency (WELLS et al. 1969).

III. Reproducibility of Dimension Measurements

Since it is likely that a clinical pharmacological study will involve measurement of cavity size, or derived information, before and after drug administration, knowledge of the reproducibility of the method is essential for adequate design of studies and interpretation of results. This has been studied by a number of authors. In normal subjects, BURGGRAF and PARKER (1974) found variation of up

to 4 mm at end-systole and up to 3 mm at end-diastole in duplicate determinations in normal subjects. GIBSON et al. (1973) noted a root-mean-square difference of 3.5 mm between duplicate determinations of dimension, made within a few minutes of one another, and almost identical results were reported by ROELANDT (1977). In measurements made over a time period of 1 h to 30 days, POMBO et al. (1971) found differences of 3 ± 2.6 mm at end-diastole and 3.4 ± 3.4 mm at end-systole. In an effort to reduce this variation, POPP et al. (1975) noted that even larger differences occurred when measurements were made from adjacent interspaces (0–13 mm) compared with those from the same interspace (0–4 mm). They therefore introduced the idea of the "standard" interspace as the one where the mitral echogram was obtained with the transducer perpendicular to the chest wall. However, STEFADOURAS and CANEDO (1977) noted that significant variation was possible even within the same interspace, and in order to improve reliability, they devised an instrument whereby the spatial orientation of the ultrasound beam relative to the chest wall could be standardised. Agreement between duplicate determinations using this instrument was ± 3.5 mm, significantly better than without it, when the range was up to 11 mm.

It must therefore be concluded that very significant differences may occur between duplicate determinations of ventricular dimensions in similar circumstances, and that these must be taken into account when studies are designed. They may be reduced by the following measures:

1. In individuals, all records should be made from the same intercostal space, with standardisation of the position of the subject.
2. Measurements should be taken at end-expiration, during quiet respiration (BRENNER and WAUGH 1978). If the patient is asked to stop breathing, it is likely that Valsalva's manoeuvre will be performed.
3. One the appropriate level in the ventricle with respect to the mitral valve has been identified, a lateral scan should be performed, and the maximum dimensions recorded and measured.
4. At least three beats should be measured, and mean values taken.
5. It detection of small differences in dimension is crucial to the experiment then consideration should by given to an instrument such as that described by STEFADOURAS and CANEDO (1977).
6. Echocardiograms should probably be measured "blind".

These questions cannot be regarded as settled, and there is appreciable scope for further studies in which factors causing variation in left ventricular dimension are critically examined.

IV. Derived Quantities

A number of quantities have been derived from dimension measurements.

1. Shortening Fraction

The extent of shortening, or shortening fraction, has been defined as

$$(D_d - D_s)/D_d,$$

where D_d is end-diastolic and D_s, end-systolic dimension. Shortening fraction thus represents the normalised reduction in end-diastolic dimension, and has been shown, in patients with coordinate left ventricular contraction patterns, to bear a close relation to ejection fraction (LEWIS and SANDLER 1971).

2. VCF

An estimate of the velocity of contraction can be gained from the quantity described as VCF, or velocity of circumferential fibre shortening (COOPER et al. 1971). The mean value is calculated as

$$(D_d - D_s)/(D_d \times t_e),$$

where t_e is left ventricular ejection time, measured from the indirect carotid pulse. This quantity is a normalised velocity, with the dimensions s^{-1}. It may also be regarded as shortening fraction divided by ejection time, and thus values are likely to be low under control conditions in a patient in whom left ventricular cavity size is enlarged and the amplitude of wall movement reduced. Changes in left ventricular ejection time with disease or drugs are relatively small. It is thus essential that ejection time is measured from the carotid pulse and not from the duration of inward movement of the posterior wall. This latter bears no clear relation to ejection time, and its use is subject to errors very much greater than changes occurring in ejection time as the result of disease or drugs and is therefore unacceptable.

3. Left Ventricular Wall Stress

It is possible to calculate values for meridional left ventricular wall stress with a knowledge of left ventricular minor axis, wall thickness and arterial pressure. The two former can be measured by echocardiography, and the latter derived either from cardiac catheterisation, or more simply, by sphygmomanometer. Wall stress is derived from the expression (MIRSKY et al. 1974)

$$\frac{pb^2}{(2b+h)h},$$

where h = wall thickness, b = echo dimension and p = peak systolic pressure in mmHg. Wall stress represents a force per unit area, and has the dimensions g/cm^2, or kN/mm^2. This derivation is based on the assumption that the ventricle is a thin-walled ellipsoid, and so is clearly an approximation, but it allows interrelations between the three variables of arterial pressure, cavity size and wall thickness to be conceived in a way that has clear physiological consequences in terms of myocardial oxygen requirements.

4. Left Ventricular Volume

At an early stage in the development of the subject, it seemed possible that left ventricular volume could be measured by M-mode echocardiography. Initially,

these were derived as the cube of the transverse dimension, but subsequently more elaborate regression equations have been proposed. These estimates have been subject to critical review by LINHART et al. (1975). In retrospect, these attempts were bound to have been unsatisfactory, although in patients with coordinate contraction patterns estimates were remarkably close to those derived from angiograms. Like those used for many years in angiography, these procedures assume that the left ventricular cavity is ellipsoidal, and that in addition, there is a constant relation between the major and minor axes. Attempts to allow for this latter source of variation by TEICHOLZ et al. (1976), by a regression equation lead to no improvement in accuracy of volume estimates. There are major changes in cavity shape, even during systole in normal subjects. The process of cubing itself leads to the amplification of small errors in the dimension that is measured, and it is in this form that the results should be quoted. Ventricular volumes and derived information such as stroke volume or ejection fraction will not be considered further.

5. Posterior Wall Thickness

Echocardiography has been used to estimate posterior left ventricular wall thickness, and estimates made in this way agree with those from angiography or directly at operation (SJOGREN et al. 1970; TROY et al. 1972). Wall thickening can be used as evidence of local contractile activity (DUMENSIL et al. 1974). In order to do so records must be obtained with an instrument of adequate dynamic range which shows separate epi- and pericardial echoes. The degree of thickening has been estimated as

$$(T_{ed}-T_{es})/T_{ed},$$

where T_{ed} is end-diastolic and T_{es} end-systolic thickness. Similarly, the rate of thickening can be estimated as

$$(T_{ed}-T_{es})/(T_{ed}t_e).$$

These quantities are more appropriate to study of patients with regional left ventricular disease than to investigation of drug action. Since the main determinant of dimension reduction during systole is an increase in posterior wall thickness, measurements of the latter should not be regarded as independent variables.

6. Isovolumic Relaxation Time

This is taken as the time interval from A2 – the onset of the first high frequency vibration of the aortic component of the second heart sound, recorded by phonocardiography – to mitral valve opening, recorded on the echocardiogram. This time interval has been shown to bear a constant, but inverse relation to left ventricular end-diastolic pressure (MATTHEOS et al. 1982) and is altered reliably by drugs such as nitrates.

V. Computed Quantities

The use of computers has made it possible to extend the study of ventricular dimension from repeated single measurements to continuous records (GIBSON and BROWN 1973). The echocardiogram is recorded in the usual way and the trace placed upon a digitising table, a device for rendering pictorial information suitable for digital handling.

Calibration points and relevant lines on the echogram, for example those representing the endocardial surfaces or epicardium, are traced with a cursor and the digitiser transmits a series of coordinates to the computer for storage and processing. Thus, by subtracting the ordinates for the septal and posterior wall traces, the continuous transverse dimension D is derived, and from this the first differential with time and the normalised first differential dD/Ddt which is the instantaneous VCF. The instantaneous posterior wall thickness and its rate of change can be studied in the same way. Peak rates of VCF and wall thickening can therefore be derived. Similarly, digitisation during the diastolic part of the cycle allows computation of maximal left ventricular filling rates and wall thinning.

VI. Effect of Physiological Manoeuvres

1. Heart Rate

An increase in heart rate caused by intravenous atropine caused a slight reduction in end-diastolic dimension, by 2 mm, and a rather more significant increase in peak VCF from 1.22 to 1.38 s^{-1}, attributed to a direct positive inotropic effect of rate (HIRSCHLEIFER et al. 1975).

2. Head-Up Tilt

Movement from the supine position to 80 ° head-up tilt in normal subjects caused a reduction in end-diastolic dimension from 4.8 to 4.2 cm, and from 3.2 to 2.75 cm in end-systolic dimension, with no change in mean VCF (REDWOOD et al. 1974).

3. Arterial Pressure

When arterial pressure was increased by phenylephrine administration, small increases in end-diastolic dimensions were noted by REDWOOD et al. (1974) and by HIRSCHLEIFER et al. (1975), but not by YIN et al. (1978), accompanied by either a small reduction, or no significant change in mean VCF.

4. Isometric Exercise

In normal subjects, isometric exercise (handgrip) caused no change in normal subjects in the control state, but small reductions in VCF have been observed in elderly subjects on propranolol treatment (YIN et al. 1978) and in patients with ischaemic heart disease and icoordinate left ventricular contraction (GIBSON et al. 1978).

5. Increase in Plasma Volume

An increase in plasma volume brought about by dextran infusion was associated with a 3–4 mm increase in end-diastolic dimension, but no change in VCF (QUINONES et al. 1975).

VII. Effects of Drugs

1. Nitroglycerin (Glyceryl Trinitrate)

The effects of nitroglycerin have been studied by a number of workers in both normal subjects and patients with ischaemic heart disease (REDWOOD et al. 1974; BURGGRAF and PARKER 1974; HARDARSON and WRIGHT 1976; MATTHEOS et al. 1982). The effects of sublingual nitroglycerin are similar in both groups with significant reduction in both end-diastolic and end-systolic dimensions of approximately 5 mm and an increase in mean VCF and heart rate. Nitroglycerin also causes a reduction in arterial pressure, which in combination with the reduction in cavity size, and slight increase in left ventricular wall thickness, causes a significant reduction in left ventricular wall stress from a mean value of 155 to 100 g/cm^2. These changes all reduce cardiac work and oxygen consumption and this is probably the mechanism by which anginal relief is produced. Similar results have been observed after treatment with nitroglycerin ointment, which caused a reduction in end-diastolic and end-systolic dimension and a slight increase in wall thickness (HARDARSON et al. 1977).

In patients with ischaemic heart disease nitroglycerin also prolongs isovolumic relaxation time, delays the O point of the apex-cardiogram with respect to A2 and reduces the relative amplitude of the F wave (MATTHEOS et al. 1982). There are no similar changes in normal subjects. These changes are explicable on the basis of a reduction in left ventricular end-diastolic pressure and reflect the sequelae of a reduction in pre- and afterload. These observations also have clinical significance since the prolongation of isovolumic relaxation time in patients with coronary artery disease presumably reflects some as yet unidentified aspect of left ventricular involvement in this condition.

2. Long-Acting Nitrates

Relief of angina by long-acting nitrate preparations is thought to be predominantly due to systemic venodilation with reduction of ventricular diastolic pressure and consequent relief of compression of deep left ventricular blood vessels so promoting diastolic coronary flow. Simultaneously left ventricular oxygen consumption is lowered by reduction of left ventricular dimensions (Laplace relationship) and by reduction of systolic pressure. Their action on the heart can therefore be monitored by observing changes in cavity dimension and left ventricular end-diastolic pressure. The first of these variables can obviously be measured directly from echocardiographic recordings and the second can be assessed using measurements of isovolumic relaxation time (see Sect. VII. 1; MATTHEOS et al. 1982).

Dimension changes can be seen in most patients with coronary artery disease after onset of nitrate therapy, but the greatest changes are seen in patients with

impaired left ventricular function secondary to ischaemia (GOMES et al. 1978). Thus GOMES et al. (1978) observed changes of end-diastolic dimension from 6.4 to 5.9 cm and of end-systolic dimension from 5.5 to 4.8 cm in such patients after treatment with 10 mg oral isosorbide dinitrate. There was an associated increase in shortening fraction and an increase in mean velocity of circumferential fibre thickening.

3. β-Blockers

β-Blockers have been demonstrated to be effective agents for treating patients with angina pectoris because they have the important physiological effect of reducing myocardial oxygen requirements during exercise. In proper doses they allow the patient to do work while requiring less myocardial oxygen delivery, thus delaying the onset if ischaemia and the occurrence of chest pain. However, although they may only be of considerable therapeutic effectiveness they are also potentially hazardous and caution must be used with these drugs, particularly in patients with impaired myocardial function. Since it is impossible to predict how an individual patient will respond to a single dose of β-blocker, noninvasive techniques have been used in association with these drugs for assessment of myocardial performance and in particular for early detection of ventricular dysfunction.

Probably the earliest study of this sort was carried out by FRISHMAN et al. (1975) who studied 19 patients with severe but stable angina pectoris in a double-blind manner to evaluate the effect of oral propranolol on exercise tolerance and left ventricular function measured by echocardiography and systolic time intervals. With a propranolol dose of 80 mg/day total work performance increased by 128%; at 160 mg/day total work performance decreased, but remained higher than at control levels. With propranolol left ventricular function decreased progressively with increasing doses of the drug; as measured from the echocardiogram maximal endocardial posterior wall velocity decreased 42%, ejection fraction decreased 13% and end-diastolic volume increased by 28%. PEP and LVET significantly increased with progressive dose increment. There was no correlation between blood level of propranolol and improved work performance. Exercise tolerance was maximally improved with propanolol doses of 80–160 mg/day. At higher dose levels left ventricular function deteriorated and exercise work decreased. The workers therefore concluded that noninvasive assessment of left ventricular function using echorcardiography and systolic time intervals proved more valuable than determination of drug blood levels in managing patients with angina pectoris and provided a guide to optimal adjustment of dosage.

CRAWFORD et al. (1975) used noninvasive investigation to try to establish the mechanism of action of β-blockers. It was postulated that many of these changes were due to a negative inotropic effect of the drug. However, Crawford's work demonstrated that when reduction in heart rate was prevented by atropine and reduction in arterial pressure reversed by phenylephrine, then changes in ventricular dimension and VCF did not occur, strongly suggesting that the observed effects of the β-blockers in other studies were due mainly to bradycardia.

Observations of this kind on haemodynamic effects of β-blockers are well documented, but VON BIBRA et al. (1980) in an interesting study recorded infor-

mation on the action of β-blockers on incoordinate left ventricular wall movement in patients with ischaemic heart disease. Patients were divided into two groups, depending on basal contraction pattern (i. e. coordinate or incoordinate). In patients with coordinate contraction at rest propranolol produced an early cessation of inward wall movement that could not be attributable to change in heart rate. There was no effect on diastolic events. In patients with incoordinate contraction, minimum dimension already occurred early. In these patients propranolol did not alter systolic events further, but increased delay in mitral valve opening, prolonged isovolumic relaxation, reduced the peak rate of dimension increase and aggravated the incoordinate relaxation. Complex drug effects in humans can therefore be assessed from the measurement of time intervals derived from multiple noninvasive techniques.

This differing effect of β-blockers on patients with ischaemic heart disease and coordinate or incoordinate left ventricular function was further investigated by GIBSON and WONG (1980) who compared the effects of sublingual nitroglycerin, propranolol and saphenous bypass grafting on left ventricular wall movement in patients with severe angina. Asynchronous onset of wall movement was unaffected by propranolol or nitroglycerin, but when present preoperatively, consistently improved after saphenous bypass grafting. Abnormalities of relaxation were aggravated by nitroglycerin or propranolol in patients whose contraction was initially incoordinate, but after operation, they tended to improve along with systolic abnormalities. The time interval between Q and minimum left ventricular cavity dimension was noted to be frequently reduced in patients with ischaemic heart disease, and treatment with propranolol increased the frequency of this abnormality. Saphenous bypass grafting however was associated with a consistent return towards normal.

Thus, two antianginal drugs (nitroglycerin and propranolol) with widely different pharmacological properties both have a similar effect on wall movement in shortening the duration of systole, thus reducing myocardial oxygen requirements and simultaneously increasing the time available for coronary flow. This effect appears to be at the expense of the normal mechanism by which cavity shape is maintained constant as ventricular pressure drops, so that both drugs increase the extent of incoordinate wall movement during relaxation. In addition, the action of both drugs is modified in the same way by asynchronous wall motion in the control state. One might thus predict that their therapeutic action in individual patients should be dependent on basal contraction pattern, and the existence of an antianginal action in addition to the well-recognised effects of reduction in heart rate and arterial pressure might explain therapeutic failures with these drugs. Such studes show that noninvasive techniques can be fundamental in understanding mechanisms of disease processes and drug actions.

D. Conclusions

These studies illustrate the use of systolic time intervals and M-mode echocardiography in assessing the effects of antianginal drugs. Their limitations are clear. The major disadvantage with systolic time intervals is the sensitivity of each measurement to several haemodynamic variables, so that even in combination they

may not give unequivocal information about the mechanism of drug action. The major problem with echocardiography is rather poor reproducibility compared with the size of the changes that are produced by drugs and this factor must be allowed for in experimental design. Both techniques are however noninvasive and therefore repeated measurements can be made in the same individual; in addition measurements can be made in control subjects. It is this latter feature which makes these techniques so attractive for use in clinical pharmacology.

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CHAPTER 6

Peripheral Circulation

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A. Assessment of Antianginal Drugs Through Studies of the Peripheral Circulation

In this chapter, consideration of the test methods that can be used to study the peripheral circulation will be confined mainly to those which can be applied to human limbs. The peripheral circulation could be defined in a much wider sense than this, to include the circulation through all the peripheral organ systems, but the chapter will be restricted to tests that can be used to assess skin and muscle blood flow. The human limbs are extremely well adapted for experimental vascular studies and have played an important part in the acquisition of clinical pharmacological knowledge.

While the symptoms of angina pectoris and their relief by antianginal drugs can be assessed only with reference to the sufferer, a full understanding of the mechanisms of action of antianginal drugs requires objective assessment of their circulatory effects, including those on the peripheral circulation. Such drugs can relieve anginal pain through reducing myocardial oxygen requirements by either cardiac or extracardiac effects (SCHARTL et al. 1982). The extracardiac effects involve the peripheral circulation by reducing preload or afterload. Preload is reduced when venous capacity rises owing to venous dilatation and hence venous return and cardiac filling are decreased. Afterload is reduced when total peripheral resistance falls owing to dilatation of arteriolar resistance vessels and hence aortic impedance and stroke work are decreased. In fact, reduction of preload and afterload is also a possible means of treating heart failure (COHN 1980; BRECKENRIDGE 1982) so that the same vasodilator drugs may be of benefit in both angina and heart failure. This convergence of interests strengthens the case for adequate assessment of the peripheral actions of the antianginal drugs.

Studies of the peripheral circulation can be used to compare or confirm vasodilator actions of various drugs and to compare the effects of a particular drug on the arterial circulation with its effects on the venous circulation. Drugs which affect the peripheral circulation may be studied through their direct effects on the circulation, such as increasing forearm blood flow (MILLER et al. 1976; ROBINSON et al. 1982), by their dilator action on vessels previously constricted, e. g. by noradrenaline (COLLIER et al. 1978) or by their effect on the characteristics of the peripheral pulse (SPÖRL-RADUN et al. 1980; IMHOF et al. 1980; ABSHAGEN and SPÖRL-RADUN 1981; SCHNELLE et al. 1981). Blocking of the vasodilation produced, e. g. by adrenaline, can also be studied in the case of drugs which may have this effect (BRICK et al. 1968). A vasoconstrictor drug may be used to "test the

system", as with the use of ergotamine to confirm that a venous preparation can show venoconstriction (SCHARTL et al. 1982).

Comparisons of the effects of particular drugs on the arterial circulation with their effects on the venous circulation have been made using strain-gauge plethysmography (arterial resistance) and pressure–volume relationships or vein diameter measurements (venous tone) by COLLIER et al. (1978), MILLER et al. (1976) and ROBINSON et al. (1980). In this way it has been possible to identify drugs with similar effects on the two vascular segments and others with disparate effects.

In all such studies it is important to test drugs in the same subjects and under rigorously standardised conditions if comparisons are to be valid. Thus reports of drug comparisons should indicate clearly that conditions have been standardised and that, where appropriate, baseline observations for comparative studies were similar. It is also useful to bear in mind the conditions in which the drug will be used in clinical practice. Sometimes the effects of drugs vary with the temperature of the limb to which they are administered. A drug may produce different effects in a subject in a comfortably warm laboratory than in an elderly patient in a cold apartment.

B. The Use of Human Subjects for Studies on the Peripheral Circulation

I. Anatomical Considerations

Human arms and legs make very suitable preparations in which to study the peripheral circulation. Large arteries and veins lie relatively close to the surface and can be identified easily by inspection or palpation. They can be catheterised with relative ease so that drugs may be infused into them or blood sampled from them with greater ease than elsewhere in the body. Even capillaries can be observed with relative ease as they come close to the skin surface in nail folds. It is possible to obstruct the arteries and/or veins in human limbs by applying pneumatic cuffs with appropriate cuff pressures to the limbs.

Since bone blood flow is relatively small the blood flow in human limbs is mainly to the skin and muscle tissues. In the hand and finger, skin is the predominant tissue and blood flow to these areas may be considered as largely skin blood flow. In the forearm and calf, however, blood flow will reflect muscle blood flow to a larger extent. The differentiation of skin and muscle blood flow in measurements of peripheral blood flow will be considered in detail later.

Perhaps the most important asset that limbs possess as experimental preparations is that they exist as paired symmetrical organs where fluctuations in blood flow due to alterations in vasomotor tone occur synchronously on both sides (BURTON 1939). This allows one limb to be used for control observations when experimental procedures are being carried out on the opposite limb.

The temperature of the peripheral parts of the limbs tends to be somewhat below that of the body core owing to their high surface : volume ratio and precooling of the arterial blood supply by the blood in the veins which run countercurrently alongside them. This permits estimation of blood flow in the peripheral parts of the limbs to be made from temperature measurements since the metabolic heat

production in these parts is low so that skin temperature is a function, albeit rather complex, of skin blood flow.

II. Ethical Considerations

Experimental procedures are usually too complex to allow them to be understood with their full implications by the experimental subject volunteering to take part in peripheral vascular studies. For practical purposes therefore, the doctor carrying out the work carries the moral responsibility for the investigations to be performed. Because of this the plan of the research should always be submitted for approval to a properly constituted ethical committee. This should apply even when the investigators use themselves as experimental subjects.

Codes of practice for the development of new drugs vary in different countries and investigators should by aware of those which apply in their areas. In the United Kindom, when a new drug is synthesised and some idea of its pharmacological activity is ascertained, a programme of chemical, toxicological and pharmacological work is carried out to evaluate the drug. The results of this work together with those of some controlled human pharmacological experiments are then submitted to the Committee on Safety of Medicines and permission to undertake clinical trials is requested. If the Committee is satisified it grants permission for a small number of controlled studies on patients. If the results of the first set of controlled studies on patients are satisfactory permission is given for further trials using greater numbers of patients. If these in turn are satisfactory, an application is made to the Committee for permission to market the drug. When asked by a drug company to carry out investigative work on a new drug, the investigators should establish clearly what is the stage of development of the drug in question and become familiar with the results of other work on the drug so that they may be aware of the possibility of side effects or other dangers that might result from using the drug.

When using drugs which can affect the cardiovascular system, it is useful from the safety point of view to have apparatus nearby which can be used rapidly to record the ECG and defibrillate the heart. The telephone number of the cardiology unit should be prominently displayed near the phone and any antagonists for the drugs being tested which are available should be kept in readiness for emergency use.

C. Administration of the Test Drug

I. Oral Administration

Unless the drug in question is very rapidly absorbed or has a spectacularly dramatic effect on the circulation, it is very difficult to study its peripheral vascular effects with oral administration. This is because the levels of peripheral blood flow vary greatly from person to person and in the same person from time to time. Blood flow in the skin and muscles of the extremities is normally subjected to varying degrees of vascoconstrictor tone depending on the metabolic and thermal state of the individual as well as upon the mental and emotional state and in the

female, the stage of the menstrual cycle. If the drugs have to be given by oral administration it is important that the control and experimental observations are made on the same subjects at the same time of day to allow for circadian variations in the level of flow (MANN et al. 1980). The subjects should be made to rest quietly in the laboratory equilibrating with their surroundings for a period of at least 2 h before observations are begun. Even with these precautions the range of variation in flow levels seen in the control measurements may make it difficult for any effects of the drugs to produce a change which will show up as significant.

II. Intravenous Administration

Intravenous administration of a drug presents it with such rapidity (usually less than I min) to the peripheral vascular system that its effects (if it has any) are readily seen. In getting to the periphery the drug has to traverse the lungs, where a proportion of it may be inactivated or destroyed, and the heart, where it may produce effects that cause reflex changes in the peripheral vasculature. Thus with intravenous administration one has the problem of separating the central effects of the drug on peripheral blood flow from the direct peripheral effects of the drug on the blood vessels. Indeed if the drug produces central effects such as awareness of a forceful heart beat or dizziness, the emotional consequences of these sensations may mask the direct effect of the drug on peripheral vessels.

When drugs are given intravenously (as opposed to intra-arterially) the concentration of the drug arriving at the tissues in the peripheral blood stays constant irrespective of changes in the rate of peripheral blood flow. If the blood flow rises the total dose being delivered to the tissues rises, but the concentration in the blood stays the same.

Although, with drug administration by the intravenous route, both limbs receive the same concentration of the drug in the inflowing blood, it is possible to design experiments where blood flow in one limb is used as a control for the other. If for example one limb has been treated with an "X" receptor blocking drug intra-arterially, the difference in the responses in the two limbs to inravenous injection of drug "Y" will be a measure of the effect of drug "Y" on "X" receptors.

One of the disadvantages of the intravenous route is that relatively large doses of the drug have to be given since allowance must be made for the facts that the dose will be diluted in the entire cardiac output before reaching the peripheral tissues and a considerable quantity of the drug may have been removed by the lungs or inactivated in the blood. To allow for these problems drugs may have to be administered in doses higher than would otherwise be desirable.

III. Intra-arterial Administration

Drugs may be administered quite conveniently to peripheral tissues via a catheter introduced into the brachial or femoral arteries. Both these arteries are quite easy to puncture percutaneously. The usual practice is to introduce a fine catheter through a plastic guide inserted into the artery. Puncturing the wall of the artery does not usually cause any sensation, painful or otherwise, provided the needle that is used is sharp. When the catheter is in place saline solution is usually infused

through it at a low constant rate (about 1 ml/min) to prevent blood from clotting within the catheter. Two variable rate infusion pumps are useful for this work, one for infusing the control saline solution and the second for infusing the drug solution. This allows the investigator to change the infusion fluid from the control saline solution to the drug solution without delay. The pumps should be outside the field of view of the subject who should be unaware when a change is made from control to drug infusion and vice versa.

One of the problems with intra-arterial infusion of drugs is that the infused solution may stream preferentially to certain branches of the arterial tree and therefore not be distributed uniformly to all the tissues. To test for uniformity of infusion, histamine in a dose of 1 μg/min can be infused. If the drug distribution is uniform, the histamine flush should be uniform over the skin of the hand and forearm. If it is not, the catheter should be manipulated in the arterial stream and the histamine test applied again. Streaming of the infused drug is less likely when the catheter is inserted centripetally rather than centrifugally. When infused upstream the catheter stream is more likely to set up turbulence and cause greater mixing of the infusate with the arterial blood.

One of the advantages of intra-arterial administration over intravenous administration of a drug is that much lower drug doses may be used to present the same drug concentration to the tissues. Since the total blood flow to the hand and forearm is only about 50 ml/min, i.e. 0.01 of the cardiac output, it is possible to achieve the same drug concentrations at the tissues with about 0.01 of the intravenous dose, using the intra-arterial route. When using potentially dangerous drugs such as potassium chloride (GLOVER et al. 1962) or curare-like drugs (BLAIR et al. 1961) the intra-arterial route permits a much greater safety margin. Another safety feature with intra-arterial infusions is the fact that a large proportion of the injected dose is inactivated or removed in one passage through the arm tissues. For example with noradrenaline infusions it is necessary to give 15 μg/min intra-arterially to mimic the effects of 2–4 μg/min intravenously (BRICK et al. 1967). Thus many potent drugs have little central effect when given intra-arterially.

A factor to be borne in mind when giving drugs intra-arterially is that the concentration of the drug arriving at the tissues will vary as the level of blood flow changes. Thus a vasodilator drug, by increasing blood flow, will result in a reduction in the concentration of the drug arriving at the tissues even when it is being infused at a constant rate. Similarly if the drug being infused causes vasoconstriction, the vasoconstriction will increase the drug concentration arriving at the tissues even though the total dose being delivered remains constant. This fact which may result in positive feedback may explain some of the differences in the effects of drugs on peripheral tissues when given by the intra-arterial and the intravenous routes (LOWE and ROBINSON 1964).

IV. Percutaneous Administration

Some drugs which affect the peripheral circulation are effective when applied directly to the skin. Rubefacients produce large increases in skin blood flow in the regions to which they are applied (CROCKFORD et al. 1962). When the hand is immersed in water saturated with carbon dioxide, vasodilation occurs in the areas

of skin immersed (DIJI 1959). Many drugs can be introduced into the skin by iontophoresis. Adrenaline can be introduced into the skin by this method to suppress the skin circulation in the forearm (EDHOLM et al. 1956; DETRY et al. 1972). The method has also been used for introducing drugs such as histamine, atropine and acetyl-β-methylcholine (MONTGOMERY et al. 1938) into skin.

D. Measurement of Blood Flow in the Peripheral Circulation

I. Venous Occlusion Plethysmography

The principle underlying this method was first described by BRODIE and RUSSEL in 1905 and first used to measure blood flow in human limbs by HEWLETT and VAN ZWALUWENBERG in 1909. The volume of a peripheral part is measured in a plethysmograph and the veins draining the part are periodically occluded by a pneumatic cuff. When the pneumatic cuff is inflated to a pressure which is lower than diastolic arterial pressure, arterial inflow will continue, but venous outflow will be obstructed until such time as the venous pressure rises to a level greater than the cuff pressure. Immediately after venous occlusion therefore, the part in the plethysmograph will swell and the initial rate of increase in volume will equal the rate of arterial inflow. There is no evidence that obstructing the veins causes any immediate change in the rate of arterial inflow to the part (FORMEL and DOYLE 1957). Figure 1 shows a typical forearm plethysmogram in diagrammatic form. For a period *B* following inflation of the venous occlusion cuff the forearm

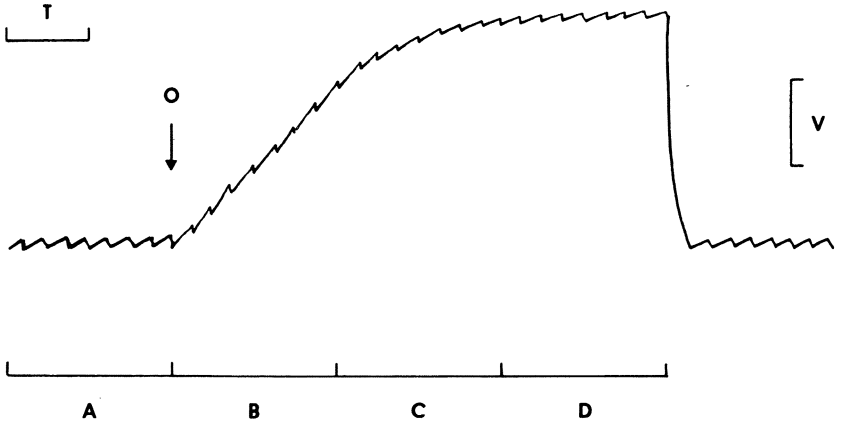

Fig. 1. A typical forearm plethysmogram. Period *A* shows the resting forearm volume, the small volume fluctuations being associated with each pulse; period *B* shows the phase of increasing volume after inflation of the venous occlusion cuff at *arrow 0*; period *C* shows the phase where forearm volume increases more slowly as the rise in venous pressure permits an increasing proportion of the arterial inflow to escape past the venous occlusion cuff; period *D* shows the phase when the venous pressure has risen to a level where blood escapes past the venous occlusion cuff at a rate equal to the entire arterial inflow so that the forearm volume remains constant

volume rises linearly. The slope of the plethysmogram during this phase can be used to calculate the volum flow per unit time using the time calibration T and the plethysmograph volume calibration V. A typical protocol would be 10 s occlusion with an interval of 5 s before the next occlusion, enabling rate of flow to be measured four times each minute. The segment of forearm enclosed in the plethysmograph is marked on the arm and its volume later measured by water displacement. Results can then be expressed as ml/min/per 100 ml forearm. Many good accounts of the method and estimates of its validity are available (LANSDOWNE and KATZ 1942; HYMAN and WINDSOR 1961; BARCROFT and SWAN 1953; FORMEL and DOYLE 1957; WILKINS and BRADLEY 1946; WALLACE 1958; GREENFIELD 1960a; GREENFIELD et al. 1963; GREENFIELD and FENTEM 1969; RODDIE and WALLACE 1979). Despite the theoretical simplicity of the method, its use requires a considerable amount of skill and attention to detail if the readings are to be meaningful. A number of points must be borne in mind.

1. Venous Drainage

Since the method depends on the ability of the veins to accomodate blood following venous occlusion, the veins must be able to empty quickly and effectively following deflation of the venous occlusion cuff. To ensure good emptying of the veins, the part enclosed in the plethysmograph must be above heart level so that the veins at rest are collapsed. Care must be taken that tight shirt-sleeves, over-tight wrapping of the venous occlusion cuff, awkward positions of the subject's shoulders (RODDIE and SHEPHERD 1956) or an over-tight fit of the plethysmograph itself do not so obstruct venous outflow that the capacity of the venous system to accomodate additional blood on inflation of the venous occlusion cuff is impaired. The effectiveness of venous drainage can be assessed from the rate at which forearm volume falls after release of the venous occlusion cuff (Fig. 2a). If emptying of the forearm veins takes more than a few seconds (Fig. 2b) factors that might be restricting venous drainage should be sought for and corrected.

2. Position of Venous Occlusion Cuff

The cuff should be sited close to the part enclosed in the plethysmograph since blood accumulating in the veins of a part may not stay where it arrives following occlusion of the veins. Thus when blood flow in the forearm is being measured, the venous occlusion plethysmogram will tend to underestimate flow if the venous occlusion cuff is placed close to the shoulder. This is because some of the arterial inflow to the forearm will run to the veins in the upper arm and not therefore be detected by the forearm plethysmograph. The type of plethysmogram seen would look like that in Fig. 2c where the initial filling rate is too low. However, some compromise has to be made since if the cuff is placed too close to the plethysmograph, a "jump artifact" will occur (Fig. 2d) owing to the cuff squeezing soft tissue and venous blood into the plethysmograph. This may not present much of a problem in flow interpretation when the flow rate is low and the jump artifact

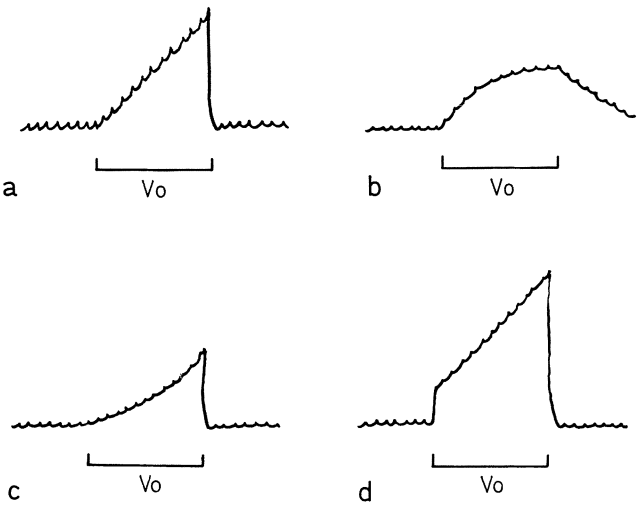

Fig. 2. a A satisfactory plethysmogram (Vo = venous occlusion). **b** An unsatisfactory plethysmogram where the poor capacity of the part to accomodate blood during venous occlusion and the slow venous emptying after release from occlusion suggest venous obstruction. **c** An unsatisfactory plethysmogram where the initial slow rate of volume increase would suggest that the venous occlusion cuff is too far from the plethysmograph. **d** An unsatisfactory plethysmogram where the "jump artifact" at the time of inflation and deflation of the venous occlusion cuff would suggest that the cuff had been placed too near the plethysmograph, the artifact could be due to the cuff inflation squeezing soft tissue or venous blood back into the plethysmograph

is easily recognised. It is a greater hazard at very high flow rates where the slope of the jump artifact and the actural flow rate may be similar enough to be confused.

3. Occlusion of Blood Flow Distal to the Plethysmograph

The necessity for this arises from the fact already mentioned that blood accumulating in occluded veins may not stay where it arrives. This was pointed out clearly by GRANT and PEARSON (1938) who showed that blood flow measured by a plethysmograph on the forearm was greater when the hand circulation was free than when it was occluded by a cuff inflated at the wrist to greater than systolic pressure. This was because when the circulation at the wrist was free, some of the arterial inflow to the hand accumulated in the forearm veins. Thus when flow is being measured in the forearm or calf the circulation must be arrested by a cuff inflated to above arterial pressure at the wrist and ankle respectively. The circulation to the hand and foot can be arrested for periods of 15–20 min without causing appreciable discomfort to the subject or danger to the tissues because the metabolic requirements of the hand and foot are so small. Inflating an arterial occlusion cuff may cause a transient ($\sim$1 min) disturbance of forearm (KERSLAKE 1949) or hand (RODDIE 1950) blood flow. The arterial occlusion cuffs should therefore be inflated at least 1 min before flow observations are made.

4. Speed of Inflation and Deflation of the Venous Occlusion Cuffs

Since flow measurements are usually made in the first few seconds after venous occlusion, it is important that the cuff filling time be as short as possible. This is helped by keeping the distended volume of the occlusion cuff small, having the cuffs inflated from a large pressure reservoir and having the tubing connecting the reservoir and cuffs as wide in bore and short in length as possible.

5. Leak Prevention

Plethysmographs are usually filled with water or air and the ability to hold water and air will depend on the integrity of the rubber and other seals in the apparatus. As the part in the plethysmograph swells, the positive pressure in the surrounding medium will accentuate escape of water or air through leaks. The water in a water-filled plethysmograph is usually contained by loose thin rubber sleeves, gloves or socks sealed to thick rubber diaphragms at the ends of the plethysmograph and kept in contact with the tissue by hydrostatic pressure (KROGH et al. 1932). If the baseline volume recorded by the plethysmograph tends to drift downwards at a near constant rate and this is accentuated by periods of venous occlusion, a leak in the system should be suspected and the rubber cuffs and seals should be tested. This may be done by recording volume during application of venous occlusion for ~ 1 min. If the baseline volume after release of venous occlusion is considerably lower than that before application of venous occlusion, a leak is almost certainly present.

6. Venous Occlusion Pressure

Since the apparent rate of arterial inflow using venous occlusion plethysmography is similar using a wide range of subdiastolic arterial pressures, the actual pressure chosen for use is not very critical. However, it is best to use a relatively high subdiastolic pressure since this will permit more venous filling to occur before venous pressure rises to equal cuff pressure. Thus the useful length of the plethysmogram slope will be increased. On the other hand one should be aware that certain procedures, such as reactive hyperaemia (PATTERSON and WHELAN 1955), lower body negative pressure (ARDILL et al. 1967) and drugs, may lower arterial pressure and the collecting cuff pressure may have to be lowered accordingly when these procedures or drugs are used.

7. Distensibility by the Part in the Plethysmograph

The more distensible the part, the more blood can be accommodated in the veins of that part following venous occlusion and the longer will be the useful part of the slope of the venous occlusion plethysmogram. When it takes the time of many heart beats following venous occlusion to raise the venous pressure to a level which exceeds cuff pressure it is much easier to estimate the inflow slope with confidence (Fig. 3 a). This situation applies in the forearm and to a decreasing degree in the calf, hand and foot. However in the fingers and toes where the skin is tough and the fascial sheaths which envelop the bone are tight, the tissues can not accumulate much additional blood following venous occlusion and estimation of

the slope of the inflow curve is more difficult since it has to be made over one or two heart beats (Fig. 3 b). This presents greater difficulties if the flow rates are high (Fig. 3 c). If the slope has to be estimated virtually over one heart beat a variety of estimations of the slope can be made and the possible contribution of a jump artifact to the initial slope may make the estimation more dubious. For these reasons, venous occlusion digital plethysmography is considered a difficult technique and requires considerable practice and experience on the investigator's part before its results can be interpreted with confidence. Despite the problems posed by the relatively nondistensible tissue of the digits, valuable measurements of blood flow have been made on them by venous occlusion plethysmography by a number of investigators (BURTON 1939; GOETZ 1946; BURCH 1954).

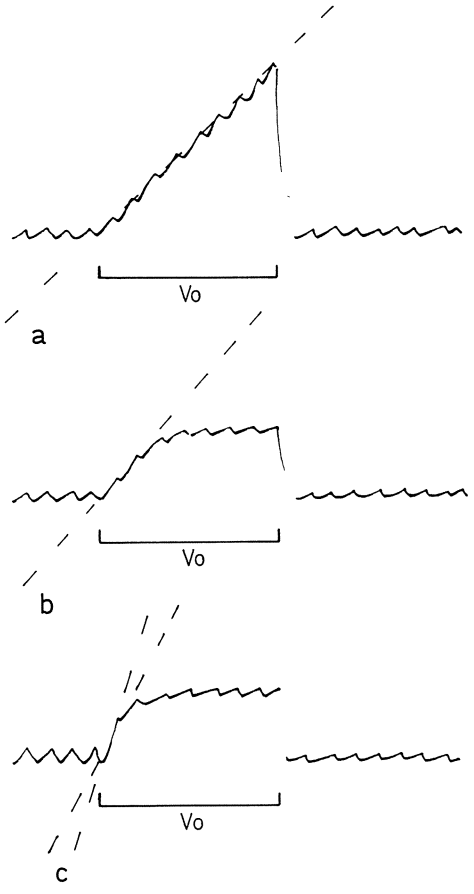

Fig. 3. a Venous occlusion plethysmogram in a distensible part such as the forearm (Vo = venous occlusion). **b** Venous occlusion plethysmogram in a less distensible part such as the finger at a low blood flow rate. **c** Venous occlusion plethysmogram in a less distensible part such as the finger at a high blood flow rate; it is possible to make various estimates of the slope of the inflow curve during venous occlusion in these circumstances and it is difficult to be sure which is correct

The problems of measuring particularly high flow rates in the face of rather poor distensibility have been discussed by WALLACE and JAMISON (1976). Pathological conditions such as burns, scleroderma or polyneuritis which can cause scarring or wasting of the parts can also make plethysmography difficult by limiting the distensibility of the parts concerned. Where possible it is best to choose subjects with relatively lax tissues to obtain easily interpretable plethysmograms.

8. Design of the Plethysmograph

There is no ideal plethysmograph suitable for all conditions and occasions. Water-filled plethysmographs are excellent for providing good temperature control and water volume is little affected by temperature change compared with air. The variety used in the authors' laboratory was designed by GREENFIELD (1954) and a cut-away diagram of the model is shown in Fig. 4. Though this is a very robust and stable instrument it is quite heavy and difficult to use outside the laboratory. Digital plethysmographs can be simpler and an example of one of these is shown

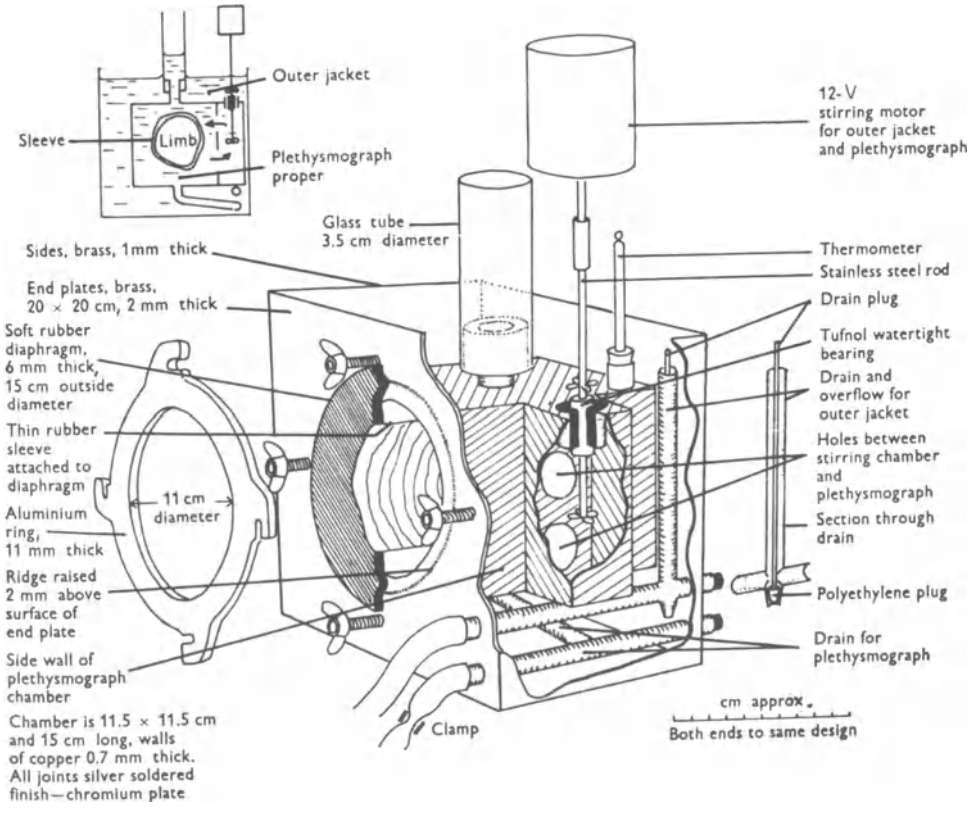

Fig. 4. Cut-away diagram of water-filled plethysmograph for forearm or hand, with a sectional diagram (*top left*) and a cut-away diagram of the overflow and drain plug (*right*). GREENFIELD et al. (1963)

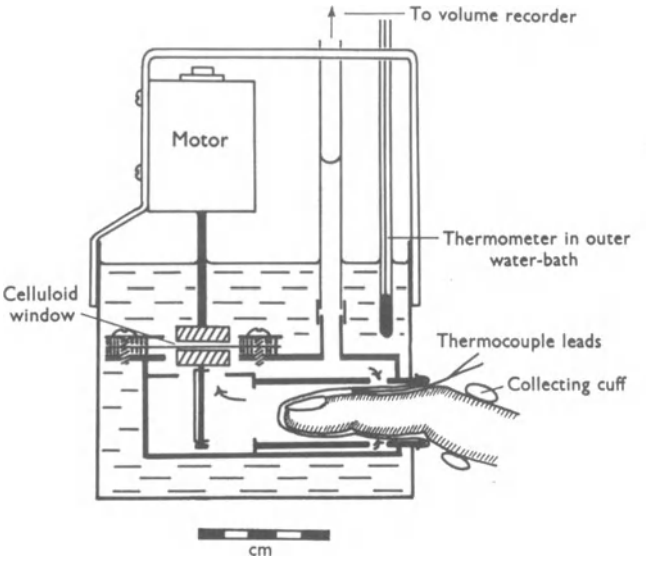

Fig. 5. The finger plethysmograph and surrounding water-bath. The driving magnet (*upper*) and driven magnet (*lower*) are shown by *cross-hatching*. The fingerstall is drawn separated from the finger, but in practice the external water pressure holds them in contact. GREENFIELD and SHEPHERD (1950)

in Fig. 5. For work outside the laboratory, light celluloid, air-filled plethysmographs may be used (LIVINGSTONE 1961), but temperature control is a difficulty with them.

9. Selection of Subjects

Measurement of blood flow by venous occlusion plethysmography requires considerable cooperation from the subjects concerned. It is important that they can lie quietly and patiently without moving their limbs or head. Body movements can cause large artifacts in the plethysmograms. In addition the subjects must not be frightened or over-concerned with the apparatus or the procedures being carried out upon them and they must be capable of responding to simple instructions without emotional stress. This is because stress can cause large changes in peripheral blood flow (BLAIR et al. 1959). For these reasons, better and more reliable results can be obtained in experienced subjects and conversely it is difficult to obtain good records in hospital patients who are unfamiliar with laboratory work.

II. Strain-Gauge Plethysmography

The principle underlying this method of estimating blood flow in a limb is that the rate of change in the circumference of a short segment of a limb following venous occlusion is directly related to the volume of the limb. The theoretical aspects of this relationship have been described by WHITNEY (1953). Changes in the volume of a limb can therefore be deduced from changes in its circumference. This has advantages since arm and leg circumference can be measured conveniently us-

ing mercury-in-rubber stain-gauges. Increase in circumference stretches the rubber tubing encircling the limb and alters the electrical resistance of the mercury contained within it. Using a Wheatstone bridge circuit, the change in resistence can be readily measured and calibrated by stretching the gauge by known lengths. Instructions on how to construct a mercury-in-rubber stain-gauge for limb plethysmography have been given by GREENFIELD et al. (1963). Good agreement has been found between the values for forearm blood flow when conventional venous occlusion plethysmography and stain-gauge plethysmography were used simultaneously (CLARKE and HELLON 1957).

The gauge has the advantage over a water-filled plethysmograph that it is much lighter and easier to apply. The lack of bulk and ease of application make it well suited for clinical use. However, it is a more indirect method of measuring limb volume changes than conventional plethysmography and its results must therefore be treated with greater caution. It has some advantages for studies in which the limb is directly exposed to the atmosphere since the limb does not have to be enclosed in an artificial medium. There is some indication that when the gauge is applied close to the wrist the values obtained represent mainly skin blood flow changes whereas when it is applied closer to the elbow, the measurements recorded are more representative of muscle blood flow. This idea is based on the relative proportions of the two types of tissue in the different parts of the forearm (CLARKE et al. 1958). The gauge is probably best for use where absolute quantitation of flow is not vital and convenience of use is essential. The gauge will give a good indication of relative changes in blood flow, but absolute values will always be questionable if only for the reason, as mentioned earlier, that blood may not stay in the veins where it arrives following venous occlusion.

III. Thermal Methods

Because of their large surface: volume ratios and countercurrent cooling of the arterial blood the temperature of the peripheral parts of the limbs are below body core temperature. In the digits, the metabolic heat production of the skin is so small that the temperature of the digit is largely a function of the local rate of blood flow.

If blood flow were to fall to zero, the skin temperature would approximate room temperature; if the flow were to rise, the skin temperature would approach core temperature. Estimation of digital blood flow from skin temperature methods is only useful over a certain range of blood flow. As the skin temperature approaches 37 °C very large increases in flow can occur without having any effect on skin temperature. Thus at higher flow rates, skin temperature is a very poor index of flow (SHEARD 1944; BURTON 1948; COOPER et al. 1949; FELDER et al. 1954). Nevertheless, skin temperature estimations of blood flow in fingers and toes are used frequently in sympathetic release tests (LEWIS and PICKERING 1931; GIBBON and LANDIS 1932) since they can be made with such convenience. In studies where changes in skin temperature in the hand are used to assess changes in blood flow, it is most important that environmental temperature be constant, since for example a rise in environmental temperature will automatically raise the temperature of a poorly perfused extremity.

More quantitative thermal methods depend on measuring the heat elimination from a peripheral part. This can be done by immersing a digit or hand in a calorimeter and measuring the temperature rise in water within it (STEWART 1911; GREENFIELD 1960b). In this case it is possible to be reasonably confident of the minimum flow which would account for the observed heat elimination, but the actual flow may be considerably underestimated at high flow rates where blood leaves the part before its temperature has equilibrated with that of the calorimeter (WALLACE and JAMISON 1978).

A variant of this approach is to measure heat transfer through copper–tellurium heat flow discs applied to the skin (HATFIELD 1950). These heat transfer methods will give estimates of blood flow even when the skin temperature has risen to equal that of the body core. Another approach is to use a heated thermocouple device mounted either in a skin applicator for surface use (HENSEL and BENDER 1956) or a needle for deep observations (GIBBS 1933; GRAYSON 1952; HENSEL and RUEF 1954; GREENFIELD et al. 1963). These devices depend on having a small heating element sited in the skin or deep applicator with a temperature sensing device nearby. The temperature recorded by the temperature sensor will be a function of local blood flow, an increase in flow tending to lower the local temperature by carrying away the heat gain and vice versa. These devices are again more appropriate where qualitative rather than quantitative changes are required. The performance of the heated thermocouples seems to depend on how near the device is to a large blood vessel. Thus the absolute value being recorded can change markedly if the position of the heated thermocouple is changed.

Estimation of blood flow in larger vessels can also be made using thermal dilution methods. If cold saline is forcibly injected through a catheter to produce turbulent mixing, the fall in temperature downstream will be a function of rate of blood flow (FRONËCK and GANZ 1960). However, this method is rather more invasive than those described previously and may be less acceptable to the subjects.

IV. Pulse Volume Methods

The volume of an extremity varies with each pulse beat because of the phasic differences between the arterial filling and venous drainage of the part with each cycle. It is difficult to record these pulsations accurately since they are likely to be modified by the characteristics of the volume measuring device and the tubing connections. The size of the pulsations will vary with the configuration of the arterial pressure contour and with the state of the vessels. BURTON (1939) found a linear relationship between pulsation volume and finger blood flow, but this is not always the case (HOLLING and VEREL 1957). It is possible to have virtually no flow with good volume pulses and vice versa (SHEPHERD 1950). Because of this it is not wise to use peripheral volume pulses as a measure of peripheral blood flow. However, the method can be used to study aspects of vascular behaviour in the extremities (WINDSOR et al. 1959).

The advantages of pulse volume measurement in clinical pharmacological investigations include the facts that the measurements can be made with relatively simple and reliable apparatus, by competent technicians, and cause little inconve-

nience, disturbance or pain to the patient or subject. The problems with the techniques lie mainly with interpretation of the precise meaning of the changes seen and the conversion of some parameter of the pulse contour into quantitative estimates of some specific circulatory event. Pulse volume changes have been measured by a great variety of methods and assessments of circulatory changes have been made from different aspects of the pulse contour or its derivatives.

IMHOF et al. (1980) analysed the digital pulse wave measured by a piezoelectric crystal sensor attached to the distal phalanx of a finger. The wave has a pronounced dicrotic form, especially in young people, and this has been ascribed to the reflection of the arterial pulse wave at the end of the aortofemoral system (KENNER and RONNIGER 1960). The amplitude and the position of the dicrotic wave on the descending limb of the peripheral arterial pulse contour is thought to be determined more by the wave reflection, resonance and damping in peripheral arteries, rather than by cardiac events. WETZLER (1941) produced evidence that when the dicrotic notch was high on the descending limb, peripheral resistance was high and vice versa. Thus the quotient of the height of the dicrotic peak from the pulse base to the height of the pulse peak from the pulse base has been used as an index of peripheral resistance, a rise representing arterial vasoconstriction and vice versa. Using this type of measurement and analysis IMHOF et al. (1980) were able to describe the relationship between plasma concentrations of nitroglycerin and arterial resistance. Another type of analysis was used by ABSHAGEN and SPÖRL-RADUN (1981). They made digital plethysmographic measurements of the volume pulses in normal volunteers before and after administration of isosorbide-5-mononitrate. The pharmacological activity of this compound was quantified by comparing the areas under the curves of changes of the amplitude of the first derivative of the α wave of digital plethysmograms during drug administration with those made before administration. SCHNELLE et al. (1981) have used the dimension of the first negative deflection in the first derivative of the finger pulse contour as the index of peripheral resistance in nitrate studies in humans; the rate of fall after the systolic peak in a digital plethysmogram can also be an index of the rate of "run off" of blood out of the arterial system and therefore the peripheral resistance. Rate of change can be recorded more graphically as the first derivative of the pulse volume changes.

Another pulse that can be studied with relative ease is the "carotid arterial displacement curve" recorded from a displacement transducer placed over the carotid artery (QUARRY-PIGOTT et al. 1973). The external ear is another part of the body where arterial pulsation can be recorded easily. The pinna is transilluminated and the light transmission recorded with a photoelectric device. With each pulse wave the light transmitted is reduced and is recorded as an "ear densitogram" (QUARRY-PIGOTT et al. 1973). Since estimation of circulatory parameters is often made from the rate of change of the pulse contour as recorded in the ear densitogram, a simultaneous record of the first derivative of the ear densitogram is usually made simultaneously.

In all this work it is worth remembering that the precise derivation of the contour of a peripheral arterial pulse is a most complex matter and attempts to explain the derivation contain many assumptions. In addition the characteristics of the measuring device and its connectors usually contribute to the final picture. All

this may not matter much if the object is to get an index of drug activity by comparing some specifically defined feature of the pulse before and after drug administration (SPÖRL-RADUN et al. 1980; ABSHAGEN and SPÖRL-RADUN 1981). The danger lies in attributing such a change with too much certainty to a specific circulatory effect.

Using computers, the work and time involved in converting the characteristics of the recorded volume pulse into circulatory parameters has been greatly reduced. SMOLEN and WILLIAMS (1976) in their guidelines for the pharmacological effectiveness of organic nitrate drugs describe how the contours of the digital plethysmogram can be used as an index of net arterial inflow, rate of run off of arterial inflow, apparent left ventricular ejection time, systolic pulse volume, relative cardiac output, net venous inflow, venous run off and diastolic pulse volume. The investigator should be careful to interpret these measurements with caution and realise that they can at best be an index of the quantity being estimated.

V. Isotope Clearance Methods

The rate of clearance of a depot of radioisotope introduced into a peripheral tissue has often been used as an index of local blood flow though clearance should not be affected by blood flowing through arteriovenous anastomoses or other shunt vessels (KETY 1948; BARRON and VEALL 1952; MCGIRR 1952; PALMER 1972). Radioactive sodium may be injected directly into the tissues for this purpose. However, the irritation caused by the injection may by itself alter blood flow. It has been suggested that the clearance of ^{24}Na may be limited by capillary permeability rather than the rate of blood flow (BRAITHWAITE et al. 1951) and similar objections have been made to the use of ^{85}K clearance for measuring blood flow.

SJERSON (1968, 1969) has used ^{133}Xe introduced by an atraumatic technique to avoid these difficulties. ^{133}Xe gas was introduced for about 3 min into a small chamber adhering to the skin after which the Xe remaining in the chamber was blown away. This allowed a small amount of Xe gas to diffuse into the skin in doses large enough to permit effective counting. Evidence showed that the amount of Xe diffusing out through the skin was negligible compared with that cleared by local blood flow. Clearance of Xe from the skin seems to have a slow and a fast component (YOUNG and HOPEWELL 1980). It has been suggested that the fast component is due to clearance by vessels in the papillary plexuses in the skin whereas the slow component is due to clearance by the deeper vessels.

VI. Differentiation Between Skin and Muscle Blood Flow

Most of the methods used for measuring peripheral blood flow measure the total flow in the skin, muscle and other tissues. However, it is known that the vasomotor control and vascular reactivity of skin and muscle blood vessels differ in many respects and it would be useful to have an experimental approach which would allow the separate estimation of each. There are a number of such approaches though no single one is perfect.

One way is to suppress the skin circulation in one limb by the iontophoresis of adrenaline into the skin (BARCROFT et al. 1943; COOPER et al. 1955; DETRY et al. 1972). The difference between the flow on the iontophoresed and the normal side should represent skin blood flow. The flow on the iontophoresed side should represent muscle blood flow. One of the problems here is to know whether the iontophoresis has completely or partially suppressed the skin circulation and if it has had any effect on the muscle circulation.

Another way is to compare the changes in oxygen saturation of blood from veins draining mainly muscle tissue with those in blood draining mainly skin. On the assumption that the drug or other stimulus has not affected the metabolism of the tissues the changes in oxygen saturation should reflect changes in blood flow in the two tissues (RODDIE et al. 1956, 1957; BLAIR et al. 1959, DETRY et al. 1972). This method has the disadvantage that the venous connections in the forearm tissues make it difficult to find veins which drain skin and muscle exclusively. Also it is difficult to translate the oxygen saturation changes into quantitative flow changes.

Another method which has been used is to apply heated thermocouple devices via a surface applicator to the skin and via a needle applicator to muscle (HENSEL et al. 1955). This can give useful qualitative results, but as mentioned earlier the extent of the changes recorded depend on how close the thermocouple is to a major vessel. Thus like the oxygen saturation changes the method is of limited value for quantitative results.

CLARKE and HELLON (1957) and CLARKE et al. (1958) have attempted to differentiate between skin and muscle blood flow using mercury-in-rubber strain-gauge plethysmography. Their results were consistent with the hypothesis that gauges placed near the wrist where there was little skeletal muscle gave blood flow estimations which reflected mainly flow changes in in skin. Conversely gauges placed on the upper forearm gave flow estimations which were more reflective of muscle blood flow changes.

Since the blood flow to the hand is mainly to skin and that in the forearm mainly to muscle, it is tempting to look at blood flow changes in these parts as representing changes in skin and muscle respectively. However, about half of the resting forearm flow goes to skin (COOPER et al. 1955; DETRY et al. 1972) and a certain fraction of hand flow goes to muscle. In addition the vasculature of the skin of the forearm may be quite different in its physiological and pharmacological responses from that in the hand (RODDIE et al. 1957). Certainly the skin of the hand with its high density of arteriovenous anastomosis (GRANT and BLAND 1931) has a very different pattern of vasculature from that in the forearm.

VII. Ultrasonic Flow Meters

SATOMURA (1959) was the first to attempt to measure blood velocity in an artery through the skin. Ultrasonic flow meters based on the Doppler principle are now readily available commercially and are used for estimating arterial or venous flow. Although there have been enormous strides in the technological excellence of these devices (GOSLING 1976), there are still difficulties in translating the signals generated into absolute units of flow.

Ultrasonic flow meters depend ultimately on the fact that the velocity of an ultrasonic beam when directed at an angle through a bloodstream will depend on the direction and velocity of the stream. Thus these devices essentially measure blood velocity. To convert velocity to volume flow it is necessary to know the velocity profile across the blood vessel concerned and estimate its cross-sectional area (GOSLING 1976; EIK-NES et al. 1980). Since both of these vary with the different phases of the cardiac cycle, many assumptions have to be made in making the method strictly quantitative in flow terms. However, the method may be useful for making qualitative estimations of flow in arteries or veins thought to be obstructed by disease. Calibration is usually carried out in an in vitro system where a fluid is pumped through tubes.

E. Measurement of Venous Tone

It is relatively easy to study vein behaviour in human limbs; in fact most of our knowledge of the human venous system comes from studies on human limbs. There have been three basic approaches.

I. Volume Measurement at Constant Pressure

The object here is to measure the volume of a part and construct a pressure–volume curve by applying stepwise increases in venous pressure and measuring volume at equilibrium. Venous pressure is measured as the pressure in a large forearm vein and the volume of the part is measured using a plethysmograph. However, the venous congesting pressure is sometimes taken as the venous pressure. The volume changes induced by pressure changes are assumed to be due to accumulation of blood in capacity vessels and only to a negligible extent to an increase in tissue fluid. It is also assumed that changes in the pressure–volume curves so recorded are due to active changes in the smooth muscle of the walls of the capacity vessels and not to passive changes in the walls of the veins. Using this type of technique it has been shown (GLOVER et al. 1958) that intra-arterial infusions of adrenaline, noradrenaline and serotonin decrease the venous capacity of the forearm.

A variant of this technique is to measure volume at a single constant pressure (say 30 mmHg) before, during and after the application of the stimulus (BEVEGARD and SHEPHERD 1965; ARDILL et al. 1968). SHARPEY-SCHAFER (1961) used the ratio of the initial increase in venous pressure during venous congestion to the initial increase in forearm volume as an index of venous tone in the forearm. This method may give invalid results since the rate of rise of pressure is different in different veins and it is not possible to measure mean venous pressure in the forearm.

II. Pressure Measurement at Constant Volume

The object in this case is to measure the pressure via a needle or catheter in a segment of vein which has been occluded at both ends and has no tributaries or branches. Thus with a constant volume, an increase in venous pressure indicates a venoconstriction and vice versa. This technique was used effectively by DUGGEN

et al. (1953) and BURCH and MURTADHA (1956). One of the problems of the technique is to find a suitable superficial vein where one can be sure that there are no branches or tributaries.

A variant of this technique is to occlude the circulation to a limb by inflating a pneumatic cuff on a proximal part to above systolic pressure and then to measure pressure in one of the large veins in the occluded segment; changes in venous pressure under these conditions are considered to be due mainly to alterations in venous tone since the venous volume is thought to remain constant (SAMUELOFF et al. 1966).

III. Vein Diameter Measurement

The principle of this method is to measure the expansion of a superficial skin vein in a direction perpendicular to the skin surface that results when a previously collapsed vessel is filled to a standard pressure by a congestive cuff (NACHEV et al. 1971). As a method it has the advantage that no catheters or needles need be inserted into the vein. The technique is illustrated in Fig. 6. A microscope is focused on a spot marked on the skin overlying a collapsed vein. Following venous congestion, the microscope is refocused on the spot and the distance travelled by the microscope measured. This noninvasive technique gives quite reproducible results and can be used for measuring venous compliance by either the pressure–volume method or the constant pressure method. Using this technique, ROBINSON et al. (1972) have been able to study the changes in venous compliance following myocardial infarction. Vein size may also be estimated by means of a lightweight lever connected to a displacement transducer (ROBINSON et al. 1980).

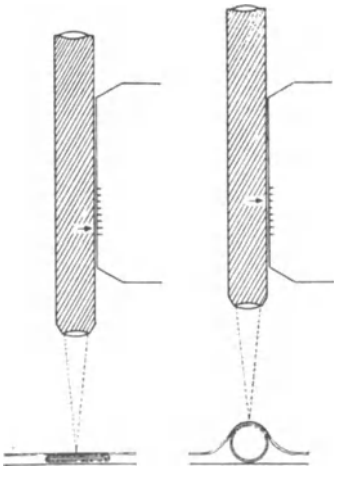

Fig. 6. Diagram showing principle of the method for measuring venous distensibility. The microscope is focused on the skin superficial to a collapsed vein and is then refocused when the vein has been distended by inflation of the congesting cuff. The distance travelled by the microscope, which is read from a vernier scale, approximates to the internal diameter of the distended vein. NACHEV et al. (1971)

F. Measurement of Vascular Permeability

The capillary filtration coefficient is an index of capillary surface area and capillary permeability. It is expressed in units of volume filtered per unit tissue weight per unit transcapillary pressure gradient per unit time. To make the measurements capillary pressure is raised by increasing venous pressure and the volume increase of the tissue concerned is measured over a time period (MELLANDER and JOHANSSON 1968).

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CHAPTER 7

Exercise Testing

D. REDWOOD

A. Introduction

The observations of BOUSFIELD (1918) and of PARDEE (1920) at the beginning of the century laid the groundwork upon which exercise testing has been based. These workers observed that acute, reversible changes in the ECG occurred during spontaneous attacks of angina pectoris. In 1928, FEIL and SIEGEL showed that similar changes in the ECG occurred when angina pectoris was precipitated by exercise. GOLDHAMMER and SCHERF (1932) later demonstrated the same exercise-induced abnormalities in over 50% of patients with angina pectoris and concluded that exercise would be of value in the diagnosis of patients presenting with chest pain.

These earlier studies formed the basis upon which Master's work provided a further important impetus to the widespread use of exercise testing in patients with ischaemic heart disease. Master's studies led to the well-known "two step test" which involved the patient performing 10–37 trips up and down two measured steps in 1.5 min, the number of steps being determined by the age, weight and sex of the patient (MASTER 1935; MASTER and JAFFE 1941; MASTER et al. 1957). Later, Master introduced the "double two step" in which double the number of trips was undertaken over 3 min. Criteria for an abnormal ECG response to this standardised exercise test evolved as Master gained experience and has resulted in the most commonly accepted abnormal ECG response – namely horizontal or downward sloping ST segment depression below the isoelectric line. However, the amount of depression that most reliably indicates myocardial ischaemia and will separate subjects with and without significant coronary arterial disease is still not clearly defined, although $\geqq 1$ mm is most commonly accepted as a discriminating degree of depression.

The reliability placed by Master and his colleagues on a negative ECG response to the two step test, in excluding significant coronary arterial disease was challenged by other workers, who also suggested that some subjects would have false-positive responses (MASTER et al. (1957), GAZES et al. (1964), SHEFFIELD et al. (1965), LEPESCHKIN and SURAWIEZ (1958). However, prior to the advent of coronary arteriography, the presence or absence of myocardial ischaemia was based upon clinical evaluation. More recent studies correlating the results of stress testing with the coronary angiographic findings have nevertheless confirmed these earlier doubts of the test reliability and have indicated that there is a significant percentage of false-negative and false-positive ECG responses. These studies defined an abnormal response as a horizontal or downward sloping ST

segment depression of at least 0.08 s duration below the isoelectric line. Using a criterion of 0.5 mm depression, false-negative responses varied in these studies from 12% to 52% and false-negative responses from 3% to 31%. With more stringent criteria, the specificity of the test improved (fewer false-positives), but the sensitivity decreased (more false-negatives). These studies, therefore, cast considerable doubt on the diagnostic value of the single stage type of test, of which the Master two step test is the best known example (COHEN et al. 1966; DEMANY et al. 1967; HULTGREN et al. 1967).

This doubt is based on sound physiological principles. It is known that myocardial ischaemia occurs at the time when increasing myocardial oxygen requirements induced by exercise outstrip the ability of stenotic coronary arteries to supply these requirements. The level of myocardial oxygen consumption at the point at which angina occurs is relatively constant in each patient, but varies considerably between subjects. Thus, in those patients with less severe disease, the level of stress needed to induce regional myocardial ischaemia may be higher than in those with more severe disease. In addition, the circulatory response to exercise shows considerable patient to patient variation and may also change in any given subject from time to time, being largely related to the degree of physical conditioning. SHEFFIELD et al. (1965) reported peak heart rates during the Master two step test ranging from 90 to 190 beats/min in a study of 216 men and KEYS et al. (1966) reported a range of 80–172 beats/min (peak heart rate) in 1,040 subjects walking on a treadmill at 5 mk/h and a 5% gradient for 3 min. REDWOOD et al. (1972) have the marked attenuation of the heart rate response to exercise that can be induced by a short period of physical conditioning in subjects with angina pectoris. Thus, both the variation in severity of disease and the variation in the subject's response to exercise are important factors influencing response to a single stage exercise test and account for the large percentage of false-negative responses (low sensitivity). Table 1 gives definitions of sensitivity, specificity, predictive accuracy and risk ratio.

These observations resulted in attempts to develop a more sensitive method for the detection of coronary arterial disease, in which the level of stress is increased until angina occurs or until the level of stress is relatively high. Since heart rate provides an approximate indicator of the level of myocardial oxygen consumption and is easily measured, one method to achieve a standardised level of cardiac stress would be to increase the external work load until a given percentage of predicted maximum heart rate is achieved. Early trials comparing these multistage tests with the standardised single load test of Masters suggested that the test based on heart rate response increased sensitivity. Thus MASON and LIKAR (1964) exercising patients on a bicycle ergometer to 90% of predicted maximal heart rate, or until chest pain occurred, found that 80% of 30 patients with typical angina pectoris had a positive ECG response (greater than or equal to 1 mm ST segment depression), compared with 57% using the Master double two step test. Similar findings were reported by SHEFFIELD and REEVES (1965) and by SHEFFIELD et al. (1965), using a target of 85% of maximal heart rate. Sensitivity with the multistage test was 79% compared with 65% using single stage exercise. Since, however, coronary angiography was not carried out in either of these studies the results do not indicate whether the apparent advantage of the graded test was really

Table 1. Glossary of terms

Sensitivity:	% of patients with disease who have an abnormal test $= \frac{\text{True-positives}}{\text{True-positives} + \text{false-negatives}} \times 100$
Specificity:	% of negative tests in subjects without disease $= \frac{\text{True-negatives}}{\text{True-negatives} + \text{false-positives}} \times 100$
Predictive Accuracy:	% of positive results that are true positives $= \frac{\text{True-positives}}{\text{True-positives} + \text{false-positives}} \times 100$
Risk ratio:	% of subjects with a positive test who manifest coronary artery disease / % of subjects with a negative test who manifest coronary artery disease

due to enhanced sensitivity or due to an increase in percentage of false-positives (decreased specificity). More recent studies using arteriographic evidence of coronary stenoses, have however confirmed that in symptomatic subjects, the presence of an abnormal ECG response to graded exercise indicates, with a high degree of probability, significant disease and that the sensitivity of the test is superior to exercise involving a single work load (HULTGREN et al. 1967; LIKOFF et al. 1966; ROITMAN et al. 1970; MCCONAHAY et al. 1971).

It should be emphasised, however, that despite using a multistage protocol, employing a multilead system both during and following cessation of exercise, the sensitivity remains unacceptable. This may be in part due to recording techniques. It has been shown that the abnormal ST segment response is largely confined to leads 2, AVF and V_3–V_6. Indeed, BLACKBURN et al. (1966) found that 89% of abnormal responses were found in lead V_5, and in a study of 100 men with ischaemic changes on exercise, the ratio of positive responses in the left lateral leads (1, AVL and V_4–V_6) to the vertical leads (2, 3 and AVF) was 10 : 1. Similar findings have been demonstrated using the Frank lead system. Some 65% of patients have abnormal changes confined to the X lead, 25% both X and Y and only 10% confined to Y. Many investigators have, therefore, simplified the recording system by using a bipolar lead CM_5, with the electrode over the manubrium and exploring electrodes at V_5 and CS_5, with an electrode over the right lateral subclavicular area and the exploring electrode at V_5. In contrast, other investigators have used analyses of the pattern of the ST segment changes, the slope and the area under the ST segment and the total of ST segment changes in a variable number of leads – standard modified bipolar and precordial maps – and have also included

changes in heart rate, blood pressure and exercise duration in multivariate analyses in an attempt to improve sensitivity of the test, but this has remained poor, varying from 45% to 95% (MCHENRY 1968; JACKSON et al. 1968).

More recently LINDEN et al. (1982) have published results of studies in which the rate of progression of ST segment depression related to increase in heart rate was measured in a 13-lead system, using 12 conventional leads and a bipolar CM_5 lead. The results using this analysis were then plotted as regression lines by calculating the changes in the level of ST segment depression and heart rate. The changes were calculated relative to the value at the initial point of the regression lines – at the value of initial heart rate. The findings of a study fo 120 patients with angina pectoris of whom 30 were on β-adrenoceptor blocking drugs and 90 were not, showed that these methods were able to distinguish between four groups of patients: those with insignificant disease and those with one-, two- or three-vessel disease and this applied equally to patients whether or not they were taking β-adrenoceptor blocking drugs. That this analysis is able to predict with 100% accuracy, not only whether or not significant arterial disease is present, but also its extent (one-, two- or three-vessel), is surprising since the data analysed are necessarily imprecise – for example, heart rate is only an approximate indicator of the changes in myocardial oxygen demand, the ST segment depression can only be a guide to the presence and severity of ischaemia, and coronary angiography, used as a "gold standard" in analysing the results, suffers from interpretative errors which are well known. The results also necessarily question the considerable variability of coronary arterial distribution, vessel dominance, presence or absence of coronary collaterals and the variability of coronary spasm, passive coronary collapse resulting from poor profusion and physiological alterations in vessel calibre. It seems unlikely when dealing with any test in a biological system that the results would be so precise, but further studies are necessary to confirm or refute this data.

Evaluation of the value of noninvasive techniques in the diagnosis of significant coronary arterial disease has to be judged against the value of clinical diagnosis. It has been shown that in patients presenting with chest pain, the sensitivity of the history when the patient has undoubted angina pectoris is about 95% (ROSS and FRIESINGER 1966). Similarly, if the chest pain syndrome was clearly not that of angina pectoris, the incidence of angiographically demonstrable significant coronary arterial disease is about 12%, i.e. a correct diagnosis is made in 88% of subjects. Clearly the most difficult group of subjects are those presenting with some but no all features of angina pectoris (atypical angina pectoris) and in these patients the clinical history was equivocal. Thus, the specificity and sensitivity of a careful history in patients with typical angina pectoris or in patients with chest pain definitely not due to angina was equal or superior to stress testing. However, in patients with atypical angina, a reliable noninvasive test would be of great value. At present, unless the findings of LINDEN et al. (1982) are confirmed by further studies, the presently employed stress tests are not sufficiently sensitive nor specific enough for this purpose.

It should be emphasised, however, that although the sensitivity of stress testing in symptomatic subjects is suboptimal, the predicted value of a positive test is excellent, i.e. if significant ST segment depression occurs with exercise in a

patient suspected of having coronary arterial disease, the probability of significant disease being present is very high.

B. Value of Stress Testing in Asymptomatic Subjects

In contrast to this good predictive value in symptomatic subjects, studies by FROELICHER et al. (1973) and BORER et al. (1975) have shown that predictive accuracy of a positive test is relatively low – Froelicher found that only 44%, and Borer only 37% of all positive tests were true-positives. These findings would suggest that the predictive accuracy depends on the population studied. It appears that the lower the prevalence of disease in the study population, the greater is the chance that a positive test will be false-positive. In contrast, when the prevalence of disease is high (as in a symptomatic population), predictive accuracy will be higher. This can best be appreciated by calculating predictive accuracy, assuming for example that specificity and sensitivity of the test in a population is 95%. If 1,000 symptomatic subjects are studied with a high disease prevalence (say 90%), then 900 would have disease and 100 would not. Since the sensitivity of the exercise test is 95%, 855 of the 900 patients with coronary arterial disease would show a positive test response to exercise and since specificity is 95%, then 5 of the 100 patients without disease would have a positive response. Thus, there would be 860 patients with a positive test of whom 855 actually had coronary disease and therefore predictive accuracy would be 99%. If similar calculations are carried out in a group of a 1,000 asymptomatic subjects with a very low prevalence of disease (say 4%) then only 40 would have disease and 960 would not. With a 95% sensitivity, 38 of 40 subjects with disease would have a positive response to exercise, but with a specificity of 95%, 48 (5%) of 960 subjects would manifest false-positive results. Therefore, of a total of 86 subjects with a positive test (48 + 38), 38 would be true-positives and predictive accuracy would be 44%. If, however, disease prevalence was only 2%, then predictive accuracy would only be 28%. Predictive accuracy may be enhanced if in serial studies of a group of asymptomatic subjects, an initial negative response to exercise converts to a positive response at subsequent testing. The study of DOYLE and KINCH (1970) suggested that this was in fact the case since, of 75 men having a normal response to exercise at first study, and who developed an abnormal response on subsequent exercise testing, 85% developed manifestations of coronary arterial disease during a 5-year follow-up period.

C. Value of Stress Testing in Epidemiology

Whilst debate still continues as to the value of stress testing as an aid to the diagnosis of ischaemic heart disease in an individual patient, its value in assessing the prognosis in epidemiological studies is firmly established. ROSS and MARKS (1967) analysed the results of the Master double two step test in applicants for life insurance and found that mortality from coronary arterial disease was eight times higher in the group of subjects with a positive result than in those with a negative result. Moreover, mortality rates increased with the increasing severity

Table 2. Incidence of subsequent development of manifest coronary artery disease in an asymptomatic population

Reference	Number, sex and age	Positive test	Coronary artery disease (%)	Follow-up	Exercise	Sensitivity	Predictive accuracy	Specificity	Risk ratio
BRUCE and McDONOUGH (1969)	221 M 24–67 years	22 (10%)	2.3%	5 years	Maximal treadmill ≧1.0 mm	60%	13.6%	91%	13.6
ARONOW (1975)	100 98 M, 2 F 40–67 years	13 (13%)	9%	5 years	Maximal treadmill ≧1.0 mm	66%	46%	92%	13.6
FROELICHER et al. (1973)	451 M 40–54 years	39 (8.6%)	3.8%	6.3 years	Maximal treadmill ≧1.0 mm	58.6%	25.6%	93.6%	15.1
CUMMING et al. (1975)	510 M 40–65 years	61 (12%)	5.1%	3 years	Maximal bicycle ≧2.0 mm	58%	24%	90.7%	10

of exercise-induced ST segment depression. The subjects included in this study, however, had been evaluated using the Master double two step test because of a suspicion of the presence of coronary arterial disease, aroused either by the history or by abnormalities on the resting ECG. In contrast, DOYLE and KINCH (1970) studied the incidence of ischaemic events in a totally asymptomatic population using either the Master double two step test or a standardised treadmill test. Of 75 men, 85% who had an initial normal stress test, but who subsequently demonstrated an abnormal ECG response to exercise, developed evidence of ischaemic disease in the next 5 years (angina pectoris, myocardial infarction or coronary death). The incidence of coronary events on the group of 1,928 men who had continued to have a normal exercise test at subsequent follow-up was only 1.5% in 5 years. BELLET et al. (1967) in their study of 264 asymptomatic men reported very similar findings and these results indicate therefore that an abnormal stress test is of high predictive value (Table 2).

It would appear that this apparently high predictability in epidemiological studies contradicts the results of the arteriographic correlative studies in symptomatic subjects. It also appears to contradict the low predictive accuracy of a positive exercise test in asymptomatic subjects – both the epidemiological group of study subjects and the asymptomatic group would have a similarly low prevalence of disease (about 2%–4%). However, the apparent disparity is readily resolved when the difference between risk ratio and predictive accuracy is appreciated.

Epidemiological studies show that a group of subjects with a positive test are 10–15 times more likely to develop coronary events than a group of subjects with a negative test. However, when the predictive accuracy is calculated in these positive responses, it is found to be quite low (13.6%–46% in subjects followed for 3–6.3 years).

The exercise test at present appears therefore of limited diagnostic value in symptomatic subjects presenting with typical angina pectoris since the presence of disease in this population is so high. Further studies are needed to establish whether or not new approaches to analysing the ST segment response to exercise are able to subdivide this group of patients into those with one-, two- or three-vessel disease. In subjects with atypical angina pectoris with a prevalence of disease of about 50%, predictive accuracy is good, although poor sensitivity would result in a significant number of patients with disease having a false-negative result. In contrast diagnostic studies of asymptomatic subjects show that predictive accuracy is very poor and if a firm diagnosis is to be established, coronary arteriography will be necessary.

D. Indications for Exercise Testing

Whilst it is evident that controversy still continues over the precise role that stress testing plays in the evaluation of patients with suspected coronary arterial disease, there are indications for its use, providing the investigator is aware of the interpretative pitfalls and reliability in diagnosis. The indications may be listed as follows: (a) diagnosis of the aetiology of chest pain syndromes; (b) evaluation of the efficacy of treatment, whether medical or surgical, of patients with angina pec-

toris; (c) evaluation of the safety and efficacy of rehabilitation programmes in patients with ischaemic heart disease; (d) epidemiological studies in asymptomatic subjects; (e) screening of asymptomatic subjects; and (f) evaluation of the incidence and response to treatment of disturbances of rhythm in patients with ischaemic heart disease. In general, ventricular ectopic beats which are suppressed by increase in heart rate induced by exercise, are benign and do not require treatment. In contrast, rhythm disturbances induced or made worse by exercise have more serious significance and should be suppressed with appropriate antiarrhythmic drugs and the patient reexercised to establish efficacy of therapy.

E. Safety of Stress Testing

I. Arrhythmias

Supraventricular or ventricular premature beats may occur in comparatively normal subjects and in patients with heart disease; as has already been emphasised, the occurrence or increasing frequency of ventricular ectopic beats during exercise has serious significance and will be an indication for termination of exercise. Supraventricular ectopic beats are of no significance and can be ignored. Occasionally atrial fibrillation will occur during exercise in normal subjects and in patients with ischaemic heart disease, but usually these episodes are brief and self-limiting. Ventricular fibrillation during exercise is rare (2 in 10,000 exercise tests at the University of Washington Hospital, Seattle). A defibrillator should always be immediately available during all exercise tests.

II. Hypotension

Exertional hypotension usually indicates the presence of myocardial disease and if this occurs, the exercise should be discontinued immediately. Occasionally, hypotension may occur as part of a vasovagal attack in apprehensive subjects either with or without heart disease, before or following exercise testing. Care should be taken not to keep the subjects standing still prior to and particularly following exercise when further ECG monitoring should be carried out with the patient supine.

F. The Use of Stress Testing in the Evaluation of Therapy in Patients with Ischaemic Heart Diseases

Whilst most studies of stress testing have concentrated on the evaluation of test sensitivity and specificity in the diagnosis of significant coronary arterial disease in symptomatic and asymptomatic subjects, a multistage exercise test, using either a bicycle ergometer or motor-driven treadmill, has proved of great value in: (a) assessing the patient's exercise-induced symptoms; and (b) assessing the effect of various interventions on exercise tolerance and haemodynamics. Most patients with angina pectoris due to coronary arterial disease will be treated initially or long-term with nitrates, β-blocking drugs or calcium antagonists, either singly or

in combination. The exercise response, both in terms of symptoms and ECG changes is of importance as a means to determine the efficacy of this treatment.

In the evaluation of the results of such testing, the design of the exercise protocol is of considerable importance (REDWOOD et al. 1971). For example if the changes in heart rate and blood pressure are measured during a single load type of exercise (e.g. the Master two step or a single load on the bicycle ergometer or treadmill), the initial response in heart rate and blood pressure levels off after a variable interval, depending on the circulatory response, the level of physical conditioning and other factors.

A change in exercise tolerance induced by drugs could not therefore be reliably assessed since the level of heart rate and blood pressure at which angina occurs, varying as it does from patient to patient, might for example, occur at *A* (Fig. 1) in which case the patient could exercise for a longer period at a subanginal

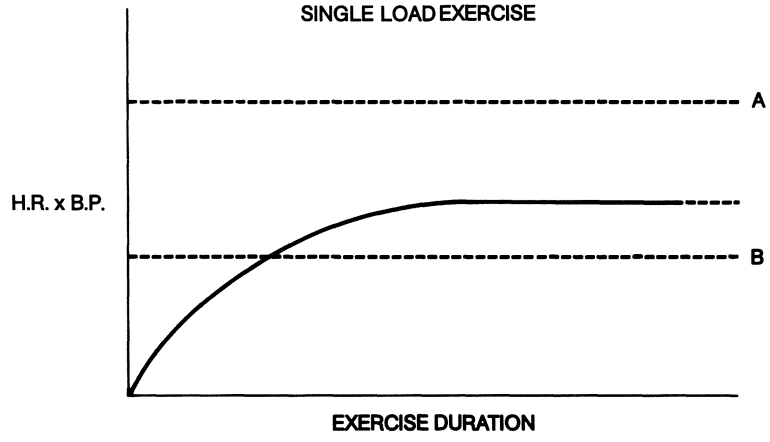

Fig. 1. Effect of a single exercise load on the circulatory response

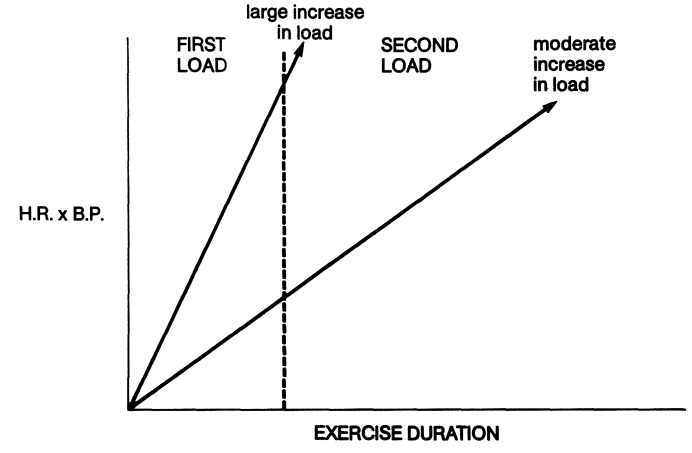

Fig. 2. Effect of varying loads on exercise response

Table 3. Exercise testing procedures

Type of exercise	Submaximal		Maximal
	Single stage	Multiple stage	
Protocol	1. Master two step or double two step	Treadmill	Treadmill
	2. Bicycle ergometer	Bicycle ergometer	
End points	Arbitrarily determined (age, sex, weight)	Symptoms, heart rate, rhythm disturbances, hypotension	Maximal exercise capacity
Observations	1. ECG (various leads) before, during and following exercise 2. Symptoms 3. Blood pressure		

level, or at *B*, when angina would occur soon after the start of the test. In contrast a multistage exercise protocol induces continuous changes in heart rate and blood pressure until a target heart rate is achieved or symptoms occur, but the periodic increase in work load should not be large since the rate of rise of haemodynamic variables will be steep (Fig. 2), and modest changes in exercise performance may be missed. Using various protocols in assessing the effect of small and large increments in load at variable time intervals, it has been shown that gradual and continuous changes in heart rate and blood pressure are induced by a 20 W increase in load very 3 min on the bicycle ergometer, or by similar changes in workload using motor-driven treadmill, e.g. the Bruce protocol (Table 3; REDWOOD et al. 1971).

G. Cardiac Response to Exercise

The Major determinants of myocardial oxygen consumption are heart rate and blood pressure. It has been shown that the product of heart rate and systolic blood pressure provides a convenient and easily measurable index of $M\dot{V}O_2$ (REDWOOD et al. 1971; GOLDSTEIN et al. 1971).

If a group of patients with angina pectoris exercise using identical exercise protocols, it is seen that:

1. Repeated bouts of exercise in any one patient will show remarkably consistent results, both in terms of total time of exercise to the point at which angina occurs, and also in terms of the level of myocardial oxygen consumption achieved at angina.

2. There will be considerable interpatient variation, which will reflect different circulatory responses to exercise from patient to patient. This is seen if the relationship between the time of exercise and work load are plotted against heart

rate or heart rate × blood pressure, or if $M\dot{V}O_2$ is plotted against $\dot{V}O_2$. This latter measurement gives what BERENYI et al. (1981) have termed relative cardiac efficiency.

H. ECG Response to Exercise

The commonest measurable alteration in the ECG during exercise is the ST segment deviation, which, whilst being suboptimal in terms of sensitivity, is highly specific in a population of patients with a high incidence of coronary arterial disease presenting with chest pain syndromes. In analysing results of exercise testing, the onset and magnitude of the ST segment depression below the isoelectric line can be used either singly or in combination with exercise time to angina, and the level of $M\dot{V}O_2$ achieved is calculated either at the onset of ST segment changes or at the onset of angina pectoris. As discussed earlier in this chapter the lead systems used in monitoring changes vary, but evidence would suggest a multilead system provides more information than any single lead system, and ST segment changes can either be monitored on individual leads or as a summation of changes in all leads employed (BARON et al. 1980). More recently changes in R wave amplitude have been assessed as a means of improving discrimination between patients with and those without significant coronary arterial disease. Thus BARON et al. (1980) demonstrated that all 14 patients with normal coronary arteries on ventriculography had a decrease in average R wave amplitude during exercise, whilst 61 of 62 patients (98%) with coronary arterial disease showed an increase in average R wave amplitude with exercise. The one patient with a decrease in R wave amplitude had one-vessel disease, and normal left ventricular function on ventriculography. The mechanism for these changes is unclear, but it is known that whereas in normal subjects, end-diastolic volume increases, and ejection fraction decreases with exercise to angina. It would appear therefore that there is a relationship between R wave changes and changes in ventricular volume. However, there appears to be no good correlation between changes in R wave amplitude and the degree of ST segment change induced by exercise, although there was greater ST segment change and increase in R wave amplitude in patients with widespread coronary arterial disease. It seems likely therefore that discrimination between patients with and those without coronary arterial disease may be enhanced by combining the results of ST segment deviation, and alterations of R wave amplitude brought on by exercise.

J. Evaluation of the Effects of Therapy

Using an appropriately designed exercise protocol on the motor-driven treadmill or bicycle ergometer, the effect of drug therapy on exercise performance and cardiac performance can be readily assessed. Prior to administration of the drug, the patient should be familiarised with the exercise protocol, and it is preferable for a practice session to be undertaken on the day prior to the test. It is important to distinguish between familiarisation and training effect. A patient introduced to an exercise laboratory will often be apprehensive, and this increased sympa-

thetic activity will affect the haemodynamic response to exercise, and will not therefore provide a reliable baseline response, both in terms of total exercise time and work load to angina pectoris, or in terms of haemodynamic changes during the exercise. Thus total time to angina will be shortened, and the rate of rise of blood pressure and heart rate will be steeper. Provided a practice session has been undertaken, exercise tolerance and haemodynamic response to exercise is consistent with repeated bouts of exercise (REDWOOD et al. 1971). However, with frequent exercise trials, carried out on successive days, a training effect may be observed in that there is a progressively improved circulatory response to exercise, so that at any given work load blood pressure and heart rate response to exercise will be reduced, and total time to angina and work load achieved at that end point will be increased (REDWOOD et al. 1972).

The patient should be exercised in the postabsorptive state (GOLDSTEIN et al. 1971). The time of day that the exercise is undertaken does not appear to be of any great importance (HANDLER and SOWTON 1984). With short-acting drugs (e.g. sublingual nitroglycerin) two bouts of exercise may be undertaken with the drug and placebo being administered prior to each bout of exercise, the order in which these are given being randomised. With longer-active drugs of course randomisation is not possible and the exercise after placebo administration will have to precede the drug exercise bout. The timing of the exercise test following drug administration is also of importance, and should be designed to coincide with the peak drug effect. If the duration of effectiveness of a drug on exercise performance is being studied, repeated bouts of exercise can be undertaken, providing sufficient time elapses between successive exercise trials to ensure that the patient is sufficiently rested, and that haemodynamic parameters and ECG changes have returned to a baseline stable state. Generally this interval should be of 15–39 min duration (GOLDSTEIN et al. 1971).

Once an appropriately designed exercise protocol has been formulated, the effect of therapy can be assessed, and this is best illustrated by using examples of the effect of commonly used antianginal drugs.

I. Nitrates

Within 2–3 min of the administration of sublingual nitroglycerin the product of heart rate × blood pressure will fall, and throughout exercise the value of this product will be less during any given work load than its value during nontreatment or placebo treatment exercise. It can be seen that the major change induced by the drug is a fall in blood pressure, which more than compensates for a baroceptor-induced increase in heart rate.

At he point of angina, the heart rate × blood pressure product will be approximately the same during the two exercise trials (placebo and nitroglycerin) indicating that the major beneficial change induced by the drug is through its peripheral effect in altering the haemodynamic response to exercise, thereby allowing the patient to exercise for a longer period, and to a higher work-load before angina occurs (Fig. 3; GOLDSTEIN et al. 1971). Moreover the degree of ST segment depression during exercise will similarly be reduced at any given work load, paralleling the haemodynamic changes, whilst at the end point of angina, ST segment

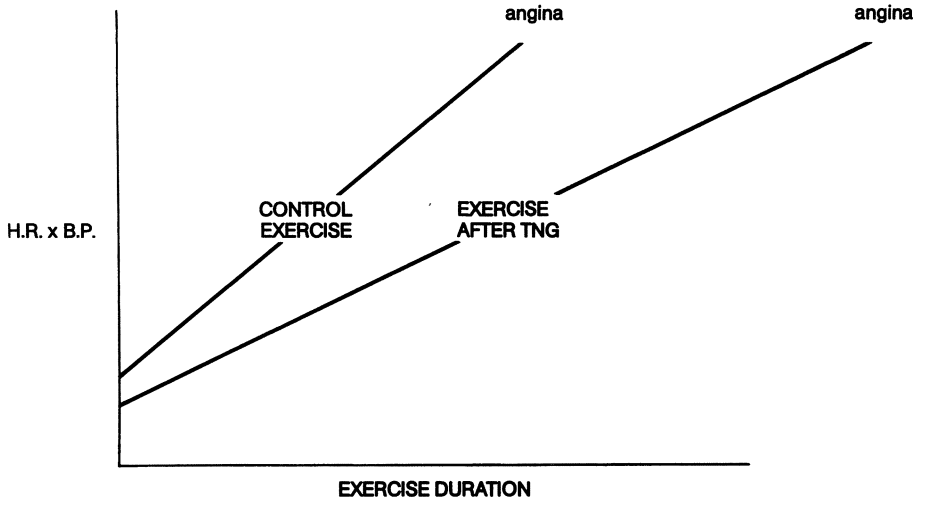

Fig. 3. Exercise response before and after sublingual administration of nitroglycerin

depression will be identical with pretreatment exercise. The evaluation of the efficacy of other nitrate preparations can similarly be undertaken with the timing of the test exercise bout coinciding with peak drug effect.

II. β-Adrenergic Blocking Drugs

In contrast to the haemodynamic affect of nitrates, β-blocking drugs attenuate the heart rate response to exercise, thus inducing an increase in exercise tolerance to angina by a different mechanism. Again the heart rate × blood pressure product as an index of $M\dot{V}O_2$ will be lower at any given work load, but its value at angina is the same as in pretreatment or placebo treatment exercise bouts. It can also be observed, of course, that if both a β-blocker and a nitrate preparation are used in combination, exercise tolerance will increase still further, since the reflex tachycardia effect of the nitrate will be attenuated by the β-blocker.

III. Calcium Channel Blocking Drugs

Both verapamil and nifedipine are examples of commonly used drugs for angina pectoris, and their effect is mainly through an attenuation of the blood pressure response to exercise. Again the improved haemodynamic response to exercise can be observed after administration of these drugs, and the mechanism for increased time and work load at angina measured.

K. Training

Exercise testing using a multistage exercise protocol can also be of value in programmes of physical conditioning (Redwood et al. 1972). Prior to such programmes, whether they are used in patients as part of a rehabilitation plan following

myocardial infarction or in patients with stable angina pectoris, exercise capacity should be assessed, first to design the appropriate protocol to fit individual patients' capabilities, second to demonstrate that the exercise programme can be undertaken safely (without rhythm disturbances or the production of hypotension during exercise), and third to provide patients with self-confidence that they are able to perform repeated bouts of graded exercises without harm. Reassessment of exercise duration and work load can be undertaken during the course of the programme and studies have demonstrated that a marked improvement in exercise capacity can be observed in patients incapacitated by angina pectoris. This improvement is probably entirely due to an improvement in the circulatory response to exercise (a purely training effect on the heart rate and blood pressure response to the work load), although is is possible that training also induces an improvement in myocardial oxygen supply, perhaps by promoting the development of coronary collaterals. The changes induced by an intervention which improves myocardial oxygen supply may be assessed using the same protocal design. For example, following coronary artery bypass grafting, the circulatory response to exercise will not change unless a training effect has occurred. However, the level of oxygen consumption at which angina or peak exercise capacity occurs is higher than preoperative levels.

L. Summary

In conclusion, stress testing can provide important information about patients with known or suspected ischaemic heart disease, providing the advantages and disadvantages of the test are appreciated. In the diagnosis of ischaemic disease in patients presenting with chest pain syndromes, the sensitivity of the test is frequently poor, and therefore patients with important disease will be missed (False-negatives). Whether the recent changes in recording techniques will enhance test sensitivity remains to be seen. In the screening of asymptomatic subjects, the high incidence of fals-positive responses limits the value of the test, unless coronary angiography is carried out to distinguish true- from false-positive results. Epidemiologically, the test has considerable value, but in these circumstances the predictive value of the test does not have to be high. Lastly, the stress test is essential in assessing a patient's exercise performance before and after therapy, whether medical or surgical.

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CHAPTER 8

Radionuclide Methods

W. E. ADAM and M. STAUCH

A. Clinical and Pathophysiologic Aspects of Testing Antianginal Drugs with Radionuclides

Radionuclide methods for testing antianginal drugs must fulfill the general prerequisites of evaluating coronary heart disease as well as special considerations of the particular method used:

1. Generally, they must allow performance at rest and under exercise under the same external conditions.
2. It should be possible to perform exercise in a supine as well as an upright position.
3. If radionuclide ventriculography is used, the time necessary for evaluation under exercise should be as short as possible. It is difficult to achieve a steady state of ischemia. If the "take" of the gamma camera necessary for a sufficiently high count rate is too long, there is the possibility that states of lesser and greater ischemia are mixed and yield a "diluted" result.
4. A critical condition for the design of the protocol is sufficient reproducibility, if the examination has to be repeated after such a length of time that patient and gamma camery have to be repositioned. For testing acute effects without moving cameray and patient, the reproducibility of technetium scintigraphy is usually sufficient.

There is hardly a method which gives evidence of ischemia at rest without intervention. Thallium scanning is a possibility, but without exercise not very sensitive. Presence of a scar from chronic infarction does not prove the presence of ischemic myocardium. Strictly speaking, methods for evaluating antianginal drugs need not necessarily give evidence of myocardial infarction, but only of myocardial ischemia. However, for several reasons it is necessary to know the effect of antianginal drugs on the heart with myocardial infarction, even if angina does not seem to be present:

1. Antianginal drugs are often used without specific indication in the postinfarction period, even if typical angina or other evidence of ischemia is absent or has disappeared. Therefore, their effects on parameters related to coronary blood flow and/or myocardial motility in diseased and normal regions, as well as hemodynamics, must be of interest.

2. Antianginal drugs may be prescribed specifically for different antianginal indications, e.g., secondary prophylaxis of infarction, congestive failure due to coronary heart disease, hypertension, and others.

3. The evidence of infarction should be included in the evaluation of the effect of antianginal drugs on cardiac function, if possible in a quantitative manner. Testing antianginal drugs may yield different results if there is a scar beside regions of ischemia. A scar increases the work load on the remaining myocardium, depending on the size of the scar. If large scars are present, the adrenergic drive to the remaining myocardium is increased to compensate for the impairment of the pumping mechanism. An important group of antianginal drugs, the β-blockers, will evoke a different reaction on the myocardium depending on the presence and size of scar, normally perfused tissue, and ischemic regions (see Sect. D.I).

4. Ischemic regions and infarcted areas are hardly ever so clearly separated that evidence of scar can be neglected in the evaluation of an antianginal drug on an ischemic region. Changes of perfusion or motility close to scars must be evaluated with more caution than clear new perfusion defects or new decreases of motility due to exercise in a region which is normal at rest.

From these considerations it follows that for the purpose of evaluation of antianginal drugs one must consider three different states of the myocardial wall: (a) normally perfused regions of myocardium, both at rest and during exercise; (b) normally perfused regions of myocardium at rest, with ischemia developing during exercise; and (c) areas of previous transmural infarctions. These three types may be present in all possible combinations. Intramural infarcts may have varying thickness. In addition, the quantity of each part of the combination may vary considerably. Under the assumption that the effect of an antianginal drug is different in each type of myocardial wall, the resultant net effect on global parameters of cardiac function may be rather inconclusive. For example, if in addition to an infarct scar an ischemic region and a normally perfused region are present in a ventricle during exercise, β-blockers may improve function in the ischemic region, but simultaneously exert a negative inotropic effect on the remaining, normally perfused myocardium. Improvement of left ventricular global function, i.e., an increase of ejection fraction during exercise, may not be discernible because ischemic areas exhibit increased motility after administration of β-blockers, but are balanced against the decrease of function after administration of drug in normally perfused areas with chronic overload. Scans of regional function, however, may give evidence of improvement of regional ejection fraction or Fourier amplitudes in a certain area. On the other hand, coronary disease is most commonly located in proximal portions of the large epicardial arteries, which leads to rather large ischemic areas. Therefore, even global parameters, e.g., the ejection fraction, are usually sensitive parameters of ischemia, on which antianginal drugs may be tested. For a number of patients, however, these considerations are valid.

Since we are dealing with antianginal drugs, the parameters of angina pectoris and ST-s segment depression must also be taken into account during the isotope examination. The combination of the three types of myocardium with these parameters results in a rather large number of possible situations. At any rate, it is important that exercise angina and ST segment depression do appear during the

isotope examination, if they have usually occurred during exercise. Angina may not appear for several reasons: selection of a lower exercise level; different position of the patient than previously used for exercise examinations; influence of other drugs, e.g., loop diuretics, falsely considered as not important for the evaluation of an angina patient. Loop diuretics such as frusemide and piretanide were shown to reduce preload and signs of ischemia in patients with angina pectoris (NECHWATAL et al. 1980a, b). If these drugs are administered before an isotope examination, the control examination may be influenced and thus the testing of the actual drug becomes questionable.

A lower exercise level may result from conducting the examination with a different "angina threshold", not of the patient, but of the examiners. If a patient is sent from a cardiology to a nuclear medicine department whose staffs are not in constant close contact with each other, the patient may be exercised considerably less intensively than in the cardiology department. Cardiologists tend to exercise patients to higher levels, mostly because they have seen them more often and have increased the level from time to time and are generally less "afraid" of an exercise ECG than other physicians. Experience in discussing results from varying laboratories has shown that this aspect is important.

The importance of considering the pathophysiology of coronary heart disease and its variability for the interpretation of results of isotope methods is discussed in connection with studies of antianginal drugs, mainly nitrates and β-blockers. A comprehensive review of the pharmacodynamics of these drugs will not be attempted here, since it is the subject of other chapters in this volume, but before going into detail, we need a comprehensive introduction to nuclear cardiology.

B. Some Important Definitions in Nuclear Medicine

The most comprehensive way to understand the information gathering process in nuclear medicine is based on considerations of the dimensions of space and time. What we want to know after application of a radioisotope is when and where it appears, and how it turns over in the body. This tells us something about the kinetics of the substance, which has been labeled with the radioisotope, and the radioisotope itself. The distribution of ^{201}Tl in the body images the distribution of blood flow when accumulation in the tissue depends only on blood flow. In this case, we only need an image of the distribution of the radionuclide in the body. This image is called scintigram or scan (Fig. 1, p. 222). However, the distribution of the radionuclide may change as a function of time, and in this case the scan depicts the momentary distribution at the time of scanning. The distribution may change after a short time. In this case, another scan reveals the shift of the radionuclide into another region. A sequence of scans in this way builds up the sequential scintigraphy picture. An example is the first-pass heart scan. The sequence of scans after intravenous injection of a radionuclide reveals the passage of the bolus of radioactivity through right atrium, right ventricle, pulmonary artery, lungs, left atrium, left ventricle, and aorta (Fig. 2). Finally, functional scintigraphy allows for more quantitative evaluation of the data. The procedure and its effects can be explained by help of the gated blood pool scan (GBPS). The result of a GBPS investigation is a sequence of scans which describe one heart cycle.

As will be outlined later on, showing the set of scans in rapid sequence yields a movie effect, in which the heart motion becomes visible. This is an example of sequential scintigraphy. Now, contraction and relaxation of the left ventricle can also displayed as a time–volume curve. Fundamentally, we only need to display the number of counts in the area of the left ventricle as a function of time. In this way, functional scintigraphy yields time–activity curves which describe the motion of the ventricles as functions of time. In conclusion, the distribution of the radiolabeled substance, radioactivity A, in space x, y, z and time t is the fundamental information in nuclear medicine. A refers to the radionuclide or the radiolabeled substance; x, y, z are the three dimensions of the body or the organ under consideration, and t is the time interval of the investigation. The distribution of the radioactivity in the body is registered and displayed by scintigraphy. The routine investigation by a gammas camera presents the true three-dimensional distribution $A = f(x, y, z)$, in a two-dimensional from $a = f'(x, y)$, whereas emission computer tomography allows for true three-dimensional presentation $A = f(x, y, z)$. The introduction of time $A = f(x, y, z, t)$ into the interpretation is possible by sequential scintigraphy (qualitatively), and by functional scintigraphy (quantitatively). After these basic definitions of imaging procedures in nuclear medicine, we are now prepared to look into the fundamentals of nuclear cardiology.

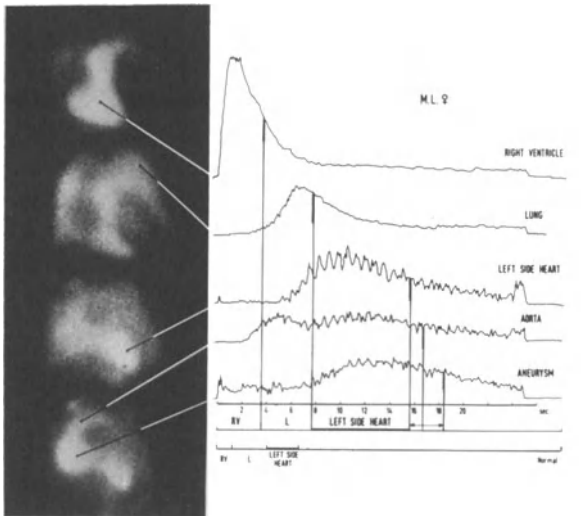


Fig. 2. Sequential scintigraphy of the first transit of 20 mCi (740 MBq) ^{99m}Tc through the heart immediately after injection into the antecubital vein. Imaging of the right ventricle (*above*), the lungs, and left ventricle with aortic aneurysm (*Below*). With help of the "region of interest" technique the time course of the radionuclide can be followed resulting in a time – activity curve, for each picture element (Pixel). The combination of these curves with the sequence of scans is called functional scintigraphy

C. Fundamentals of Nuclear Cardiology

The state of the heart depends on the function of the valves, the myocardium, and the excitation–conduction system. Nuclear cardiology claims to contribute to the diagnosis of all of these partial heart functions. With regard to antianginal drugs, we will focus on the myocardium and excitation–conduction system of the heart. The state of the myocardium is characterized by myocardial perfusion, metabolism, and function (myocardial motion). For each of these partial functions, which are interdependent, at least one radionuclide procedure is available.

I. Radionuclide Procedures for Imaging of Myocardial Perfusion

Ideally suited for perfusion imaging are substances with a distribution corresponding to perfusion, such as potassium (^{43}K), rubidium (^{81}Rb), and cesium (^{129}Cs). However, the standard substance nowadays is thallium (^{201}Tl) which meets requirements for handling and application of the radionuclide perfusion. Its relatively low energy photons allow the application of high resolution collimators, and the physical half-life of 73 h provides long shelf-life for practical clinical imaging. The concentration of thallous chloride in a dose of 2 mCi (74 MBq) is less than 4 μg. The LD_{50} is a factor 10^4 more. Thus, toxicologic considerations do not play a role (Carr 1962; Maseri 1972; Cannon 1975; Buell et al. 1977; Hoer et al. 1977; Lenaers et al. 1977; Strauss and Pitt 1977; Harper et al. 1978; Wackers et al. 1978; Ritchie et al. 1979).

Following an intravenous injection, ^{201}Tl accumulates in the myocardium very rapidly in accordance with myocardial perfusion. The initial extraction fraction is 87% (L'Abbate et al. 1979). This involves both passive and active membrane transport systems (Adolph et al. 1976). Having reached a plateau after about 20 min, Tl accumulation remains constant for about 60 min. Myocardial activity then decreases slowly through egress from myocardium. This is an important fact, because reflow of the substance into the blood pool and renewed distribution in the body according to perfusion distribution yields an image of perfusion of the organs at a later time. This fact is utilized by the redistribution scan: repetition of the Thallium scan 2 h later may reveal a change of myocardial perfusion. The classical example is stenosis of the coronary arteries with decreased coronary reserve, e.g., stenosis of the left anterior descending artery. Thallium is injected after exhaustion of coronary reserve during a stress test. The scan reveals a perfusion defect in the anterior wall of the left ventricle. Repetition of the scan 2 h later shows no defect at all, because now, during resting conditions, myocardial perfusion really is homogeneous. In contrast, in cases of myocardial scar, both images in this example of sequential scintigraphy reveal an anterior wall defect.

1. Protocol

Following intravenous injection of 1.5–2.0 mCi (55.5–74 MBq) ^{201}Tl, at least three views are routinely obtained within 30 min: 0° anterior, 45° left anterior oblique (LAO), anf left lateral (LL), with the patient supine. The accumulation of thallium is usually homogeneous in the left ventricular myocardium. Visualiza-

tion of the right ventricle is not usually possible, owing to its smaller myocardial mass. Visualization at rest is always abnormal, owing to increased ventricular work load. For exercise studies, patients undergo a graded stress test on a bicycle ergometer in the supine position. The patient exercises maximally to the end point of severe fatigue or chest pain, at which point the radionuclide is administered. Exercise is then continued for an additional 30–40 s to allow adequate distribution of the tracer. After this, the scan procedure starts. An ischemic defect in the scans requires additional scans 2 h later for a differentiation of transitory ischemia and myocardial scars (redistribution effect).

2. Clinical Results

The sensitivity to detect ischemic defects after acute myocardial infarction clearly depends on the time of scintigraphy. Within 6 h after onset of symptoms, all subendocardial and transmural infarctions are visualized in the thallium scan. Between 6 and 24 h, 34 of 35 transmural infarctions revealed clear defects, whereas in 1 case the defect was questionable. In 17 patients with nontransmural infarctions 1 scan was negative, whereas 4 results were questionable. The sensitivity decreases after 24 h. The correlation between the size of scanning defects and size of infarction postmortem was 0.72 (WACKERS 1980). Detection of transient ischemia by thallium stress scans in coronary artery disease is clearly superior to stress ECG. Whereas sensitivity and specificity of the stress ECG range between 55% and 70%, stress scans with thallium reveal a sensitivity and specificity between 75% and 95% (Table 1; POHOST et al. 1980; SIMOONS and HUGENHOLTZ 1980; SAUER and SEBENING 1980; LOOGEN and LÖSSE 1980). It is now obvious that the distribution of thallium in the myocardium is not only a function of perfusion, but also of metabolism. However, fortunately for clinical reasons and also for the testing of drugs, the metabolic changes in hypoperfused areas reinforce the symptoms of hypoperfusion. Decreased flow with decreased extraction means a more significant thallium defect in the myocardial scan. This indeed is true for most of the myocardial radiopharmaceuticals. However, the thallium scan is an effective procedure for testing myocardial perfusion. The positive imaging of hypoper-

Table 1. Sensitivity and specificity of stress–ECG and stress–thallium scans for the detection of coronary artery disease

Reference	No.	^{201}Tl		ECG	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
POHOST et al. (1980)	1077	82	90	61	82
SIMOONS and HUGENHOLTZ (1980)	118	75	86	59	76
SAUER and SEBENING (1980)	120	91	94		
LOOGEN and LÖSSE (1980)	169	99	69	79	69

fused myocardial regions by pyrophosphate, which has been applied for infarct diagnosis, does not play an essential role for pharmaceutical investigations, and therefore will not be discussed in detail in this chapter, but it should be mentioned that besides conventional scintigraphy, single photon emission computer tomography (SPECT) and positron emission tomography (PET) are now acquiring an increasing share in coronary artery disease diagnoses. These devices play a more important role in Sect. C.II, which deals with imaging of myocardial metabolism.

II. Radionuclide Procedures for Imaging of Myocardial Metabolism

Radiopharmaceuticals for the visualization of myocardial metabolism are in general physiologic substrates, and hence are assimilated into the metabolic pathways which we have considered in the preceding sections. The most important substrates for myocardial metabolism are glucose, fatty acids, and lactate. Indeed, analogs of two of these substrates have been successfully used, ^{18}F-labeled 2-deoxyglucose (FDG) as an analog of glucose (PHELPS et al. 1978), and, as an analog for free fatty acids ^{11}C-labeled palmitic acid (APA), or long-chain fatty acids labeled with ^{123}I (VYSKA et al. 1979). The turnover rate of the radionuclide primarily reflects the hydrolysis of triglycerides and subsequent β-oxidation of free fatty acids. Under anaerobic conditions β-oxidation is not possible and turnover rate decreases significantly, whereas glycolysis is the last reservoir for energy liberation. For this reason, glucose and glycogen are essential for survival of the ischemic myocardium. FDG behaves like glucose in relation to its movement through the interstitium and across the cell membrane. The initial metabolic steps are comparable to glucose. It is initially phosphorylated by hexokinase to FDG-6-phosphate, but then becomes trapped. It does not enter glycolysis nor is it stored in the form of glycogen. Metabolically unbound FDG subsequently leaves the myocardium. Images obtained by PET reflect the local distribution of metabolic rates for glucose, when they are obtained at equilibrium. We have to bear in mind that using these radiopharmaceuticals and PET leads to truly quantitative results. Cross-sectional images permit quantitative assessment of the local distribution of the radioindicator in μCi/g and thus resemble "in vivo autoradiographs". This makes possible physiologic modeling, e.g., mathematical formulation of a multicompartment model. However, myocardial perfusion abnormalities and failures of metabolism soon become apparent. They cause motion abnormalities in the hypoperfused region within seconds. Frequently, the ischemic portion of the ventricle bulges outward with systole, impairing the heart's pumping function. Imaging of these subtle and frequently small regional wall motion abnormalities (RWMA) with sufficient reliability is one of the most rewarding and challenging tasks cardiology requires from imaging techniques.

III. Failures of Myocardial Function

Myocardial function can be described in terms of volume and pressure and their time derivatives, but assessment of global volume alone does not fulfill completely the requirements of cardiology. The heart is more complicated than a mechanical

pump and description of its function by global parameters, like ejection fraction may yield false-negative results. Hypokinesis of one myocardial region may be compensated for by hyperkinesis of another region, preserving a normal stroke volume and ejection fraction. The requirement for the exact definition of RWMA by a noninvasive procedure has provoked increased developments in nuclear cardiology, ultrasonography, and digital imaging. The subsequent sections will focus on the problem of how radionuclide procedures work for imaging and quantitative evaluation of influence of drugs on RWMA.

1. Imaging and Quantitative Evaluation of RWMA

Detailed description of RWMA requires the exact localization x, y, z of each myocardial region m_i as a function of the heart cycle t. The approach of nuclear cardiology is based on the assumption that the cyclic motion of each myocardial region can be described as a set of time-dependant count rates $C(t)$, forming a representative time–activity curve, which corresponds to the time–volume curve of the respective region. This can be attained by a gating procedure which produces a set of heart images describing one heart cycle (sequential scintigraphy). After radiolabeling the blood pool (e.g., with 20 mCi ^{99m}Tc), the myocardial count rate depends on the volume changes of the heart.

For statistical reasons, a gating procedure has to be applied, which ensures that some hundred heart cycles are superimposed (HOFFMANN and KLEINE 1965; ADAM et al. 1969; STRAUSS et al. 1971). We started with two heart regions, left and right ventricle. Finally, a set of regional curves is obtained, each one representing the cardiac cycle of one small region corresponding to or smaller than the resolution of the camera computer system (ADAM et al. 1970, 1979; BITTER et al. 1971). The sum of the time–activity curves of all regions of the heart contains all information concerning myocardial motion [the so-called pixel or picture element

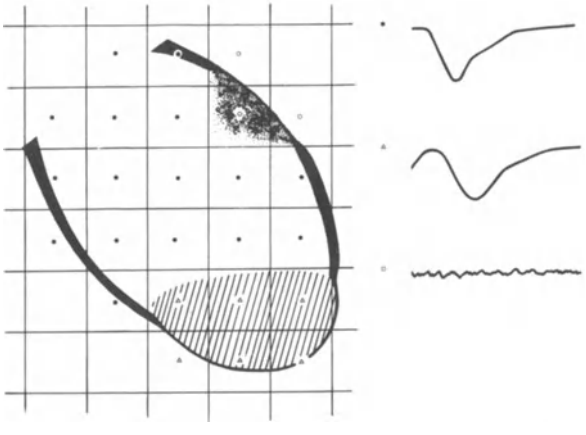


Fig. 3. The time–activity curve (TAC) of each pixel of the heart reflects myocardial motion. TAC in normokinetic regions equals the normal left ventricular volume curve (*above*). The pixel TAC in the dyskinetic apical region reflects paradoxical motion, whereas akinetic pixels show no motion at all (*below*). ADAM et al. (1979)

curve (Fig. 3)]. A prerequisite for quantitative evaluation of the pixel curves is reliability, which has been proven in the following way. The similarity of each pixel curve to the global left ventricular curve was evaluated by comparison of corresponding curve points. The resulting correlation coefficient r is a measure of the similarity of both curves. The plot of all correlation coefficients is called the correlation scan. Investigation of more than 20 normokinetic subjects showed that the correlation between the pixel time–activity curves and the left ventricle global curve was extremely high. In more than 78% of the left ventricular pixel curves, r was better than 0.9. This shows that pixel curves reflect very well the synchronous motion of the left ventricle and suggests that even small local deviations within the behavior of time–activity curves may have statistical significance. Within infarcted regions, the correlation coefficients may drop to low values, of the order of zero, and even may become negative in aneurysms. Thus, the correlation scan figures outline very clearly regions with wall motion abnormalities, but do not indicate which kind of RWMA is present. For this reason, we do not use the correlation scan in routine investigations, but we have learned and can prove by this special form of parametric scans, that the pixel curves are reliable and can be used for further data processing (GEFFERS 1977).

2. Imaging of Myocardial Function Abnormalities

The complete assessment of heart function (wall motion) includes the regional position as a function of time (x, y, z, t). Imaging in nuclear cardiology results in a set of scans, each one representing the heart in a short interval of the heart cycle, or a matrix of pixel curves. This is the basic information for further data handling to yield more or less quantitative data.

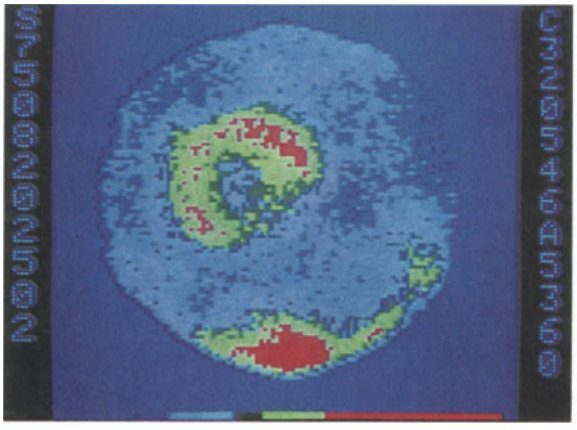
a) Qualitative Assessment of Myocardial Function (Regional Wall Motion)

The simplest procedure is to show the scans, in rapid sequence so that the heart motion becomes visible. RWMA can be detected immediately. This is of special interest for drug administration because after administration of ^{99m}Tc labeled erythrocytes, the heart motion can be observed for about 5–7 h. Improvement of RWMA after application of antianginal drugs becomes apparent immediately. More sophisticated data processing leads to parametric scans and finally to a true quantitative assessment of RWMA. Fundamentals of this procedure are outlined subsequently.

b) Semiquantitative Assessment of Myocardial Function (Myocardial Motion)

These procedures are based on the pixel concept, outlined in Sect. C.III.1. The disadvantage of the resulting matix of pixel curves is its abstract presentation. It is impossible for the eye to reveal the huge amount of information hidden in the multitude of curves. Parametric scanning can solve the problem, by choosing various essential features of the regional curves as parameters. A parametric scan shows the regional distribution of one parameter in the heart (Fig. 4). The selection of parameters should follow the criteria of clinical demands and reliability. The parameters chosen should reveal abnormalities of myocardial motion and, if possible, differentiate between functional or anatomic lesions and conduction

abnormalities. The cardiologist utilizes the contrast angiogram to detect RWMA, differentiating akinetic, hypokinetic, and dyskinetic regions. Diagnosis of conduction abnormalities is based on the ECG. Nuclear cardiology based on the concept of parametric scanning facilitates the diagnosis of RWMA and conduction



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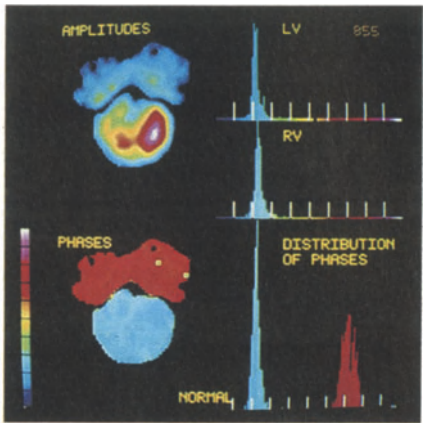

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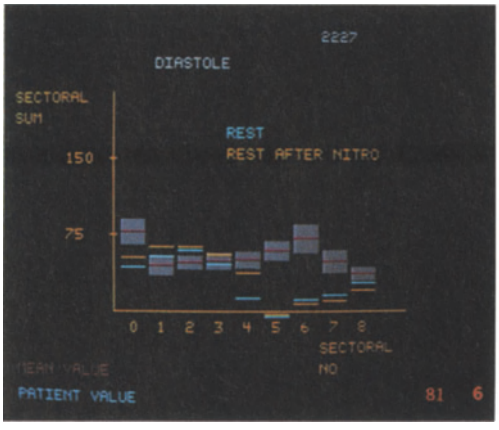

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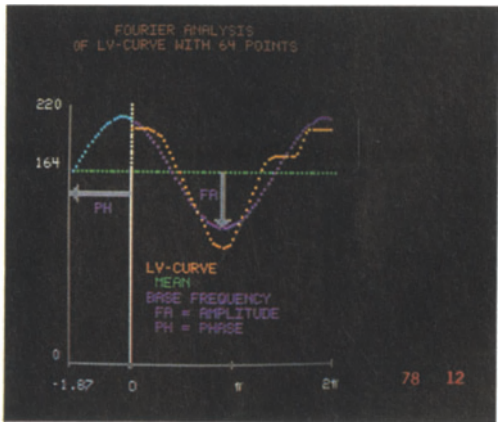

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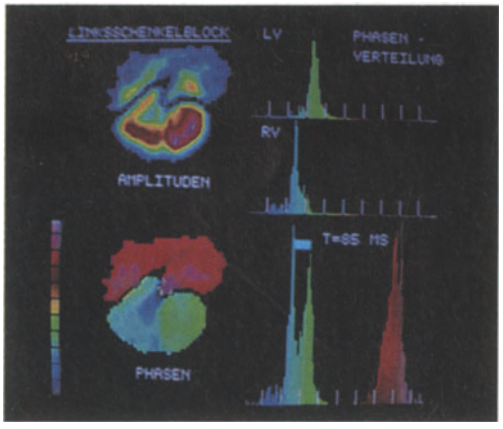

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abnormalities (GEFFERS et al. 1975, 1977; ADAM et al. 1979; BOSSUYT et al. 1979; PAVEL et al. 1980; NOELPP et al. 1977).

Hypokinesis and akinesis show decreased or absent systolic–diastolic differences and dyskinesis is revealed as asynchronous motion, e.g., delayed end-systole. Left bundle branch block (LBBB) shows delayed contraction of the whole left ventricle. This can be demonstrated in a parametric scan utilizing the interval "R wave–end-systole" (IRE) as parameter (end-systolic time). Similar results are possible by utilizing amplitude and phase of the base frequency after Fourier analysis. The amplitude corresponds to the systolic–diastolic differences, the phase to the IRE. However, beyond the scope of conventional angiography, parametric scanning yields additional information [e.g., the peak filling rate (maximal relaxation velocity) scan], which may prove to be of importance in early stages of myocardial insufficiency. The parametric scan procedure in fact yields semiquantitative data. For this reason, further data processing for complete quantification of gated blood pool investigations is necessary.

c) Complete Quantification of Myocardial Motion

Complete quantification can be obtained in two ways:

1. Presentation of the distribution of one parameter within the heart as a histogram and comparison with the histogram of a normal group. The set of all histograms then yields the complete picture. Our results show a gaussian distribution for the phases, but an empirical distribution with negative skew for the amplitude and regional ejection fraction.

Fig. 1. Stationary scan of the heart 15 min after intravenous injection of 2.0 mCi (74 MBq) ^{201}Tl in left anterior oblique 30°. The normal heart shows an ovoid closed shape corresponding to the left ventricular myocardium. An accumulation defect between 3 and 7 o'clock is proof of an extended myocardial perfusion defect (inferior wall infarction)

Fig. 4. Example of parametric scans of a normal heart. The *extent* of regional myocardial motion is reflected by the amplitude scan (*top left*). The *red color* reveals good contraction of the left ventricle. The phase – related to the time course of contraction – shows simultaneous contraction of both ventricles (*homogeneous blue*) and, later on, of atria (*Homogeneous red*). The phase histograms (*right*) show the distribution of contraction during one heart cycle

Fig. 5. The LV is divided into one central segment and eight peripheral sectors. The central segment (0) and the peripheral sectors (1–8) are outlined on the abscissa, the size of the respective parameter on the ordinate. Mean and standard deviation of regional motion of a normal group ($N=20$) is presented by the *violet columns*. Hypokinesis in segment 0 and akinesis in sectors 4–8 are evident in a patient with anterior wall infarction (*blue*). After nitroglycerin application, there is no significant improvement, except in sector 4. Diagnosis: extended anterior wall scar after infarction

Fig. 6. Approximation of the pixel curve by the basal frequency after Fourier analysis of the original curve. The approximation is very rough, but has the advantage of definition by only two parameters: phase (*PH*), time course; amplitude (*FA*), extent of motion

Fig. 8. Left bundle branch block. "Double tower sign" of the ventricle complex in the phase histogram. The motion of the left ventricle has a delay of 85 ms compared with the right ventricle (*green color*). The amplitude scan shows normal extent of motion of both ventricles

2. The end-diastolic left ventricular area is divided into sectors. Comparison of the sector sum of the various parameters with a group of normal subjects reveals pathologic areas (Figs. 5 and 6).

For intra- and interindividual comparison, a normalization of the parametric scans is necessary. The distribution of the ventricular phase is arbitrarily normalized to 0.5, provided a bundle branch block can be excluded. Normalization of the amplitude, ejection fraction, and regional ejection fraction is based on the left ventricular ejection fraction. Within the last few years two-dimensional ultrasonography has made great progress in the recognition of RWMA. The best results are obtainable in children. Limitations exist for adults because only approximately 60%–70% of the myocardial wall can be visualized sufficiently. Most difficult is assessment of the left ventricular apex. Comparison of five wall segments by angiography and two-dimensional ultrasonography showed agreement in 70% of 105 patients. This agreement could be improved to 80% after revision of the ultrasonographic results (KISSLO 1978). However, radionuclide procedures in patient with coronary artery disease are presently more useful than ultrasonography. Digital angiocardiography has a surprisingly high degree of similarity with radionuclide ventriculography. "Image subtraction" corresponds to background subtraction, "image integration" to gated imaging, and "subtraction image enhancement" to contrast enhancement. Even the parametric scan mode finds its analog in "functional imaging" of digital angiocardiography, extracting a single parameter from the "pixel densitogram". The data array obtained by applying this operation to the pixel densitogram can be rescaled and displayed as an image. This functional image may describe the distribution of transit times or other parameters. Their clinical utility has not been described up to now.

3. Fourier Analysis in the Diagnosis of Myocardial Motion Abnormalities

This procedure (GEFFERS et al. 1975, 1977; BOSSUYT et al. 1979; VERBA et al. 1979) has presently a predominant role in quantitative evaluation of myocardial motion, and therefore will be explained in detail. Fourier analysis leads to a spectrum of sine and cosine curves of different frequencies. The combination of all these curves results in the original pixel curve. The basal frequency is an approximation of the pixel curve (Fig. 7). Though this approximation is a very rough one, it has one important advantage: the shape of the curve is defined by only two parameters. The amplitude determines the altitude and the phase the temporal position of the curve. In this way the amplitude describes the motion of a pixel in space, and the phase describes motion in the time domain. This fact elucidates the clinical applicability of this concept:

1. Hypokinetic and akinetic regions are clearly outlined by decreased amplitudes of the respective pixel curves.
2. Dyskinetic (aneurysmatic) regions are revealed and outlined by a phase delay of the respective pixel curves (Fig. 8).

In this way, the most important RWMA are imaged by Fourier analysis. The amplitude scan is an image of hypokinetic and akinetic regions, the phase scan is an image of dyskinetic areas. The phase scan has obtained additional impor-

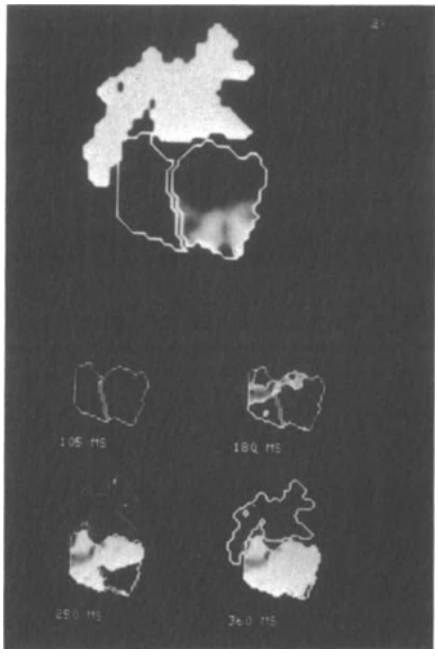

Fig. 7. Aneurysm in the left ventricular apical region, outlined in the phase scan (*top*). The sequential presentation of the phase scan shows 180 ms after the R wave motion in the base of both ventricles, after 250 ms in both ventricles except the left ventricular apex. Delay in the aneurysma region (360 ms)

tance by its ability to image excitation–conduction abnormalities of the heart. This is the topic of the next section.

IV. Failures of the Conduction System of the Heart and Techniques for Their Imaging

Conduction abnormalities can be imaged with sufficient exactness using the phase scan (Fig. 8). This is due to the conformity of the phase scan with the end-diastolic time scan and to the fact that the electromechanical linkage of the myocardium preserves the correspondence of mechanical contraction and electrical activation. Differentiation between conduction abnormalities and regional dyskinesia is clinically possible by the typical pattern of conduction abnormalities.

Additionally, the phase scan provides an accurate means of detecting and localizing abnormal foci of ventricular contraction. FRAIS et al. (1981) observed foci of earliest contraction either in the anterior wall of the left ventricle or in the septum, in patients with Wolff–Parkinson–White syndrome. This corresponded exactly to the sites of preexcitation determined on electrophysiologic mapping. Similarly, among eight patients with pacemakers, the site of earliest excitation was localized to the right ventricle in seven patients and to the left ventricle in one. Within each ventricle the site corresponded to the radiographic location of the

pacemaker electrode; similar results were also reported by BYROM et al. (1981). A typical pattern of LBBB with characteristic changes in the phase histogram became apparent. Changes of the pacemaker from the upper to the lower septum showed corresponding pattern changes in the phase scan. In conclusion, with each case serving as its own control phase, images clearly showed the effect of different activation patterns.

D. Application of Radionuclides for Testing Antianginal Drugs

I. β-Blockers

Thallium scintigraphy is difficult to use for testing antianginal drugs, mainly because an acute test (control and drug intervention study in one session) is not possible. After the control examination, a relatively long time has to go by until radioactivity can be applied again. Repositioning of the patient and gamma camera is necessary which affects reproducibility. More important, the patient has to be exposed to another dose of radiation. This is more significant for the patient than a second dose of ^{99m}Tc.

Some studies have been performed with thallium and β-blockers, with different results. In an acute study, the effect of 5 mg intravenous β-blocker, atenolol, on stress-induced perfusion defects was examined in 14 patients with angina and ST segment depression of 0.1 mV or more (CHLUP et al. 1981). At identical work loads, perfusion defects were unchanged in 11 of 14 patients. Clinical improvement was observed not only in the three patients with improved perfusion, but also in six patients with unchanged stress scintigram. The lack of change in perfusion defects in these six patients was explained on the basis of a better perfusion of endocardial layers of myocardium which cannot be recognized in transmural perfusion scintigrams. Normalization of ECG need not necessarily coincide with a normalization of the transmural perfusion gradient. In this study there were four patients without infarct. The authors do not state whether the scintigraphically improved patients came from this group. From our experience with radionuclide ventriculography, these patients are the best candidates for improved function.

Another point is the level of stress used in this study. The average exercise level was 133 W, ranging from 50 to 200 W. This high level indicates that in a number of patients perfusion was not very much impaired. It seems unusual that all patients should really have suffered from typical angina. Even the interpretation of exercise ECGs is rather difficult and limited in patients exercised at very high levels. Testing antianginal drugs should focus on patients with a really symptom-limited exercise tolerance at levels around 50–100 W.

In another recent thallium study, evaluation of perfusion was combined with the study of global function after the chronic administration of propranolol in a dose of 4×40 mg. All patients complained of angina pectoris. The authors divided the patients into two groups: one with previous infarction and one with no history of infarction (RAINWATER et al. 1982). In addition to the perfusion images, ejection fraction was measured with a scintillation probe. Even though all

patients had angina pectoris, only 8 of the 15 with previous infarction showed ST segment depression of 0.1 mV during exercise and 13 of the 15 in the group without infarct. Perfusion was changed differently in these two groups; 13 of 15 patients without infarction improved against only 5 of 15 in the infarct group, 5 others did not show any change and 5 did show a decrease in perfusion imaging. The authors do not differentiate between patients with or without ST depression in relation to the perfusion changes. From our experience with radionuclide ventriculography, we would expect the patients with improvement to be the ones with marked ST depression or those in the infarct group with posterior infarction (STAUCH et al. 1981 a).

The change of ejection fraction seems to parallel the perfusion findings in this study (RAINWATER et al. 1982). In the noninfarct group, 10 of 15 patients increased ejection fraction by more than 5% (absolute percentage), the other 5 remained within $\pm 5\%$. In the infarct group, only 7 of the 15 patients showed a significant increase of ejection fraction of more than 5%. It would be interesting to know, if these seven patients came from the group of eight patients with ST depression, or, more generally, whether the quantity of new perfusion defects during exercise correlated with the fall in ejection fraction in the control examination and the improvement of perfusion correlated with improvement of ejection fraction. The great variability of coronary heart disease as to quantity and distribution of the three types of myocardial areas should render this approach particularly useful. The authors discuss the possibility that propranolol increases ventricular dilatation with corresponding increase in myocardial oxygen requirements in some patients with infarction. They did not measure left ventricular end-diastolic volume so that this point remains unclear. From this study, it seems evident that antianginal drugs should be withdrawn before doing thallium examinations. This is not always the case, as demonstrated by a study which compares thallium scintigraphy with cardiac function during exercise in patients with coronary heart disease, partly under medication with propranolol (KIRSHENBAUM et al. 1981).

Cardiac function studies are more suitable for evaluating antianginal drugs. Either first-pass radionuclide angiography or radionuclide ventriculography are used. Testing propranolol on normal volunteers with radionuclide angiography showed significant decrease of left ventricular ejection fraction and cardiac output at comparable work loads. If comparable heart rates were tested, there was no longer any difference in hemodynamic parameters (PORT et al. 1980). In another study on volunteers, comparable heart rate–blood pressure products were used to compare hemodynamic parameters. In this study, left ventricular ejection fraction and mean normalized systolic ejection rate were depressed not only at peak exercise, but also at comparable heart rate–blood pressure products (MARSHALL et al. 1981). It seems doubtful whether the inclusion of blood pressure really makes a difference compared with the study of PORT et al. (1980), which examined ejection fraction at the same heart rate.

Patients with coronary heart disease did not show a change in resting ejection fraction after propranolol administration in this study (MARSHALL et al. 1981). At peak exercise, only eight patients showed a decline in ejection fraction during control exercise. Four patients even showed increased ejection fraction by more than 5% and six patients did not change more than $\pm 5\%$. Of these, 14 patients

with an abnormal response at control, i.e., decreasing ejection fraction or increase below 5%, 10 patients showed improvement of ejection fraction which was statistically significant. In the four patients with normal response to exercise at control, there was no significant change of ejection fraction after β-blockade, only a small decrement. Since 16 of 18 patients with coronary heart disease had positive stress test and angina as well, the result of this study should be relatively uniform. That this is not the case can be related to the lack of quantitative parameters of ischemia for the selection of patients for a study. One may assume that the results of this study follow the scheme that the presence of larger ischemic areas will lead to an improvement of function by propranolol. If function under exercise is already very little impaired, zero or small negative changes are to be expected. In other words, one cannot conclude that propranolol "failed" to act positively in the four patients mentioned, but rather that relatively little ischemia was present so that a positive reaction could not be expected. Sine the average ejection fraction at rest was 57% in the patients and only little more, 63%, in the volunteers, it may be concluded that not many patients with large infarctions or severely impaired function were included. This also implies that negative effects of β-blockade were not to be expected either.

In another study, ejection fraction at rest did not change much after administration of 3 mg penbutolol. It decreased significantly, but only from 58.8% to 55.6%. With exercise there was no statistical difference in the 12 patients with coronary heart disease (NECHWATAL et al. 1980 b). After additional administration of frusemide, the resting values still did not change, but they increased significantly and to a large extent with exercise. Chronic application of β-blockers seems to change ejection fraction very little at rest. This was found with propranolol (BATTLER et al. 1979), as well as with acebutolol (KATZ et al. 1981). The negative effect on normal segments seems to have decreased during chronic therapy, but regional analysis was not performed. Contradictory results in evaluating β-blockers can mainly be traced to wide differences in the patients' diseases. Additional variability is introduced by differences in method, doses, routes and duration of administration, etc.

In a recent study, the most important one of these factors, disease variability, was minimized by selecting only patients with one-vessel disease of the left anterior descending coronary artery (LAD), with either critical stenosis or transmural infarction due to LAD disease, i.e., with anteroseptal infarction (PFISTERER et al. 1983). This selection of patients yielded two groups, one with infarction and no ischemia, and one with ischemia and no infarction, both in the same area, leaving the lateral portion of the left ventricle free of disease as a control area. The global ejection fraction of the whole left ventricle did not show an impressive change from control to metoprolol. At rest there was a small decrease only in the ischemic group; during exercise there was no change in either group. However, regional ejection fraction over the anteroseptal (diseased) area showed a large decrease of ejection fraction during exercise at control in the ischemic group. After metoprolol treatment, resting values decreased and exercise values increased significantly. On the contrary, in the lateral (more or less normal) region, ejection fraction increased during the control period and decreased after administration of the β-blocker. In the infarct group, there was a slight decrease at control and a small

increase after metoprolol administration. The absolute values between 20% and 30% in this anteroseptal region show the reduced function due to the infarct. In the lateral region, ejection fraction increased strongly at control and much less after β-blockade. Nifedipine and nitroglycerin were also tested in this group of patients.

II. Vasodilators

Nitroglycerin was examined first with radionuclide ventriculography with regional analysis performed by visual examination of the radionuclide cineangiogram (BORER et al. 1978). In the control examination, the fall in ejection fraction during exercise is very marked, as in most patients without angina. The effect of nitroglycerin is also similar in the coronary heart disease patients with and without angina. The normal subjects, however, did not show a change. The studies with nitroglycerin are hampered by the quick attenuation of the effect of the drug. The authors start with 0.4 mg and repeat this if heart rate or blood pressure do not change adequately. After the study at rest, the dose is repeated with exercise. This makes evaluation and comparability a little difficult, at least if other longer-acting nitrates are used.

In our own studies, the effect of nitrates on ejection fraction is relatively uniform, even between normal subjects and patients, if effects at rest and exercise are compared (Fig. 9). Ejection fraction is increased by 10 mg ISDN or 5-ISMN in both examinations. There is a difference in that patients have a greater increase in ejection fraction under exercise than at rest, in normal subjects it increases slightly less during exercise. The effect of the nitrate is evident by comparing the course of ejection fraction under placebo, it changes very little in both patients and normal subjects (STAUCH et al. 1981 a, 1983). The difference between nitrate

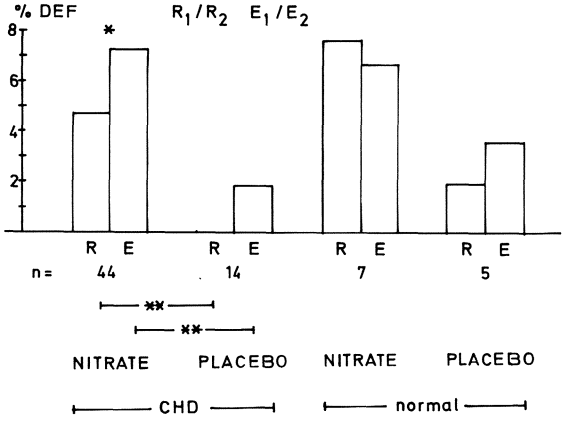

Fig. 9. Absolute differences of ejection fraction (*DEF*) from the first (*R*1, *E*1) to the second examination (*R*2, *E*2) with medication of 10 mg ISDN or 5-ISMN orally, comparing differences at rest (*R*) and those during exercise (*E*) in 58 patients with coronary heart disease and 12 without heart disease. *, $P<0.05$; **, $P<0.01$

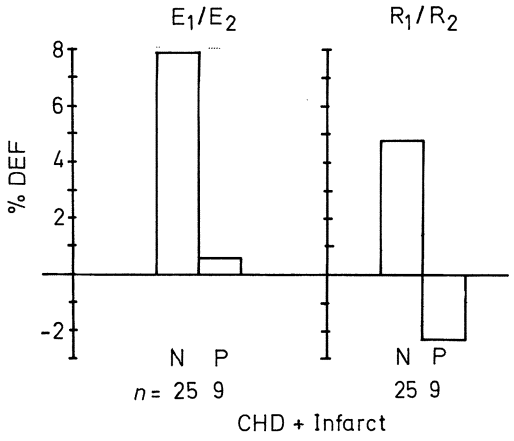

Fig. 10. Absolute differences of ejection fraction (*DEF*) between control exercise (*E*1) and after medication (*E*2) of nitrate (*N*) or placebo (*P*) and the corresponding values during both resting periods (*R*1/*R*2) in 34 patients with old infarction

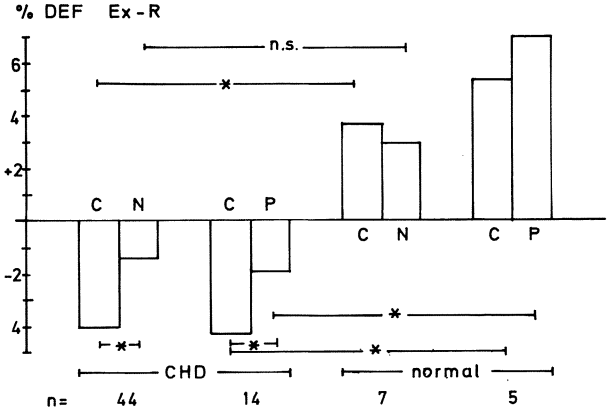

Fig. 11. Absolute differences of ejection fraction (rest minus exercise) in the control examination (*C*) compared with the second examination under nitrates (*N*) or placebo (*P*) in patients with and without coronary heart disease

and placebo is more evident, if only patients with previous infarction are compared (Fig. 10).

If one compares the difference between rest and exercise in the control group with the second examination after nitrate administration, the decrease in ejection fraction due to exercise in coronary patients is substantially diminished (Fig. 11). However, in the placebo group, this difference between control and placebo is also significant. This is partly due to the fact that the resting values at the second examination are higher than at the first examination so the difference becomes smaller. Generally speaking, the differences are relatively small for the whole large group. The reason for the small difference becomes evident by comparing

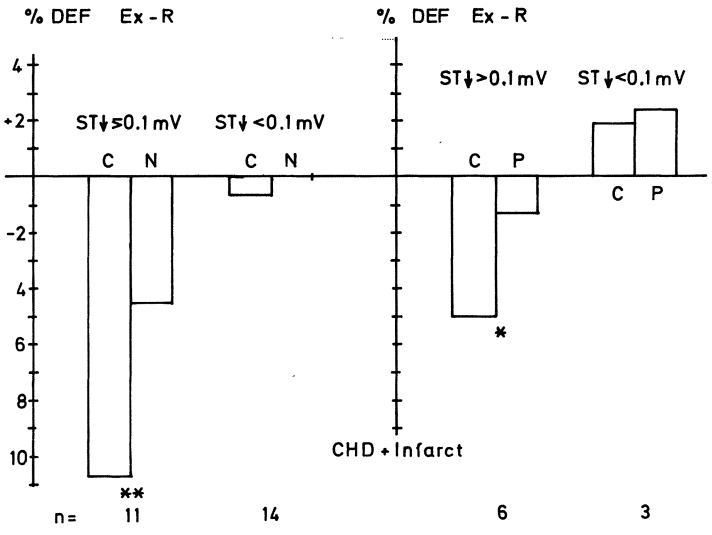

Fig. 12. Absolute difference of ejection fraction (exercise minus rest) in patients with coronary heart disease and old infarction, separated according to the presence or absence of ST segment depression in the exercise ECG. *C*, control; *N*, nitrate; *P*, placebo

patients with signs of exercise ischemia with those with chronic infarction, but without signs of ischemia. In the ischemic group, of 11 patients receiving nitrate, the decrease of ejection fraction due to exercise amounted to over 10% (absolute values), which was significantly diminished at the second examination. The group without ischemic signs did not show and difference from rest to exercise at control or under nitrate, only the level of ejection fraction was raised by ISDN (Fig. 12).

The decrease of ejection fraction during exercise is quite a reliable measure of ischemia. A coronary "ischemia score", based on coronary stenoses supplying functioning myocardium only and disregarding coronary lesions leading to infarcted areas, showed good correlation with the difference between rest and exercise ejection fraction. Correlation with ST depression was poor (STAUCH et al. 1981 b).

Radionuclide ventriculography also allows determination of volumes, at least if controls with placebo are examined. In this study, the stroke volume increased significantly after administration of nitrate in comparison with control. At rest it decreased, during exercise it increased after nitrate administration. There was no change after placebo administration (STAUCH et al. 1983). Absolute values for volumes can be obtained by simultaneous determination of cardiac output with the thermodilution method and the gamma camera. With ejection fraction, cardiac output, and stroke volume, enddiastolic volume can be calculated (NECHWATAL et al. 1981).

The effect of ISDN was also demonstrated with thallium scintigraphy (WOLF et al. 1979), who found that 64% of new perfusion defects which appeared during exercise showed normalization after nitrate application. Quantification is difficult with thallium, but was attempted by calculating the average impulse rate of the

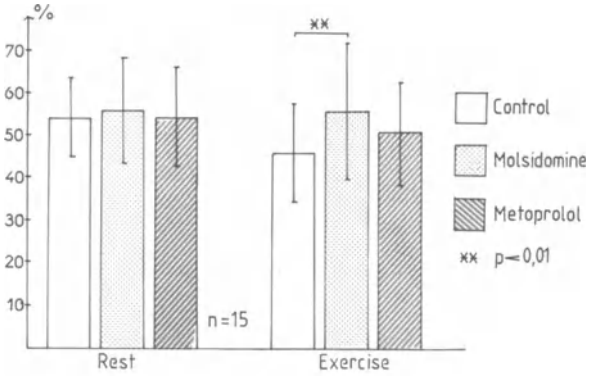

Fig. 13. Ejection fraction of the left ventricle in 15 patients with coronary heart disease at rest and during exercise at control, and after administration 4 mg of oral molsidomine and 10 mg intravenous metoprolol. *, $P < 0.01$

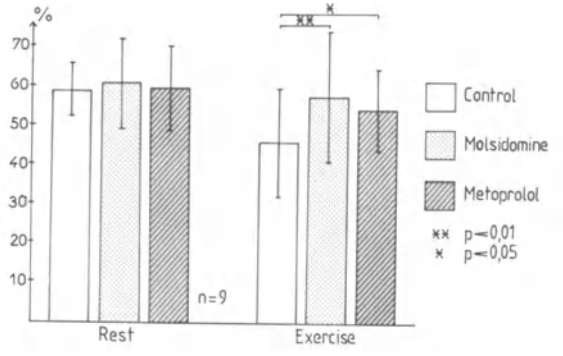

Fig. 14. Nine patients with exercise angina and ST depression of 0.1 mV or more from the group of Fig. 13

matrix points. Among calcium channel blockers, nifedipine shows a similar effect to nitrates (PFISTERER et al. 1983).

The consequences of a combination of nitrates and β-blockers on hemodynamics and myocardial wall motility can be examined with radionuclide ventriculography in a satisfactory and noninvasive manner. In a recent study on 15 patients, 9 of whom has ST depression of 0.1 mV or more and angina pectoris, 4 mg molsidomine was applied after control examination and in the same position 10 mg metoprolol was administered intravenously after 30 min. Figure 13 shows the ejection fraction of all patients. At rest there was only a slight elevation after molsidomine administration; during exercise the increase after molsidomine administration was significant, but reduced after metoprolol administration. Figure 14 shows the results of the ischemic group. Here the increase is retained after metoprolol administration, whereas in the group without ischemia, i.e., with chronic infarction, ejection fraction returns to the control level (Fig. 15). The regional analysis in nine segments of the left ventricle confirms this for the Fourier

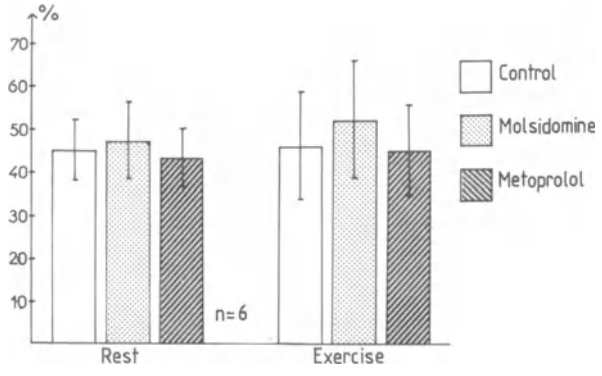

Fig. 15. Six patients without exercise angina or ST changes, but with previous infarction

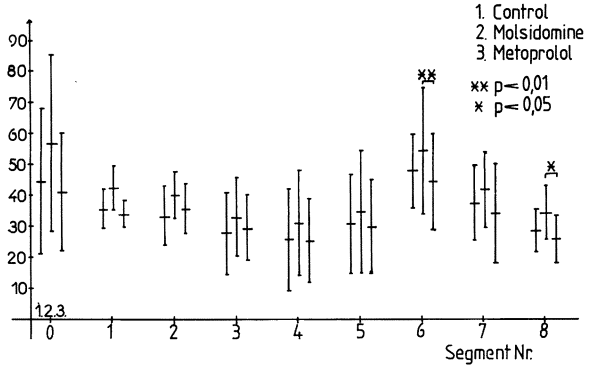

Fig. 16. Fourier amplitudes during exercise of the six patients without signs of ischemia in nine different segments of the left ventricular image. Mean values and standard deviation

amplitudes. In the nonischemic group, there is even a significant decrease after metoprolol administration in two segments (Fig. 16). In the ischemic group, the effect of molsidomine is more marked and the amplitudes hold the same level after β-blockade as after treatment with the vasodilator (Fig. 17; STAUCH et al. 1983). A study with the combination administered in the reverse order, (10 mg metoprolol first, followed by 10 mg ISDN) has been reported by NECHWATAL et al. (1982). These patients all had angina pectoris, but some had evidence of poor ventricular function. In these, ventricular function became worse after metoprolol administration, but improved with ISDN. Generally, the improvement during exercise after metoprolol administration could be further increased by ISDN:

Studies with antianginal drugs using isotope methods improve the evaluation of pharmacodynamic effects of β-blockers on the heart, but also help shed more light on the pathophysiology of coronary heart disease. The different aspects of testing antianginal drugs may be summed up as follows. Motility of left ventricular ischemic regions is significantly improved by β-blockers as well as by nitrates and calcium channel blockers. The study of PFISTERER et al. (1983) seems to sug-

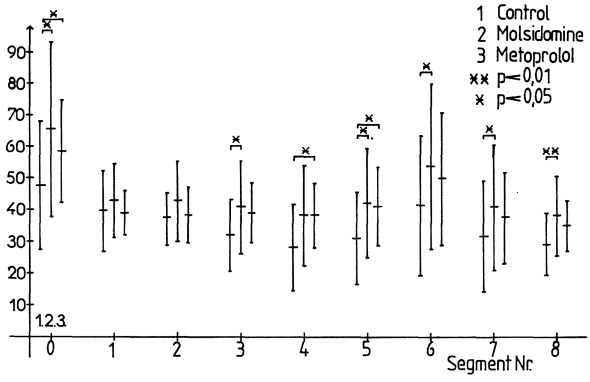

Fig. 17. Fourier amplitudes during exercise in nine patients with exercise ischemia as in Fig. 16

gest, however, that β-blockers alone effect the least improvement. this is not fully conclusive since in radionuclide ventriculography parameters of regional function are the result of motility of the myocardial segments opposing each other, e.g., in the ischemic anteroseptal region, the anterior and posterior segments. The motility of the ischemic wall may be improved as much as with other drugs, but owing to both the lack of volume reduction (as with nitrates) and a possible reduction of the motility of the normal posterior segment, regional ejection fraction of this ischemic ragion may improve less than with nitrates.

Normal segments are not influenced negatively by the other antianginal drugs, but show a small reduction of ejection fraction by acute β-blockade. This situation is due to the fact that β-blockers act directly on the myocardium, whereas nitrates and calcium channel blockers act mostly on the vascular system. Thus, they do not influence normal segments directly, but by reducing ventricular volume and afterload, may increase ejection fraction which is usually interpreted as improved function. It should be borne in mind though, that ejection fraction is only the relation of diastolic volume to stroke volume.

The other antianginal drugs act mainly on ischemic and normal segments in the same direction, whereas β-blockers do so in opposite directions, at least in acute studies. This is particularly true if work load is chronically increased on normally perfused segments, owing to a reduction of the whole working muscle mass as a consequence of large infarctions with consequent increase of sympathetic drive.

Radionuclide methods show, impressively, the contribution of β-blockers to the saving of myocardial oxygen consumption, provided the indication for their use is adequate. Possibly a combination with peripheral vasodilators is preferable in patients with impaired ventricular function. Considering the unlimited variability of coronary disease, in the light of different effects on different myocardial segments, it is easy to imagine that contradictory results must be common in the evaluation of β-blockers.

Still, isotope methods make tools available for differentiating the effect of antianginal drugs on a regional basis; with a regional disease this is adequate.

Measurements of hemodynamics yield global results only. Angiographic data give regional information, but the important effect of exercise, particularly with repeated examinations after drug treatment, is difficult to evaluate. Isotope methods seem to be particularly useful for the evaluation of antianginal drugs, provided one keeps in mind that obtaining the answers to specific questions depends on the clear definition of the patient's state of disease.

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CHAPTER 9

Assessment of Coronary Artery Disease and Myocardial Ischemia by Invasive Methods

C. NIENABER and W. BLEIFELD

A. Parameters for the Assessment of Cardiac Function in Ischemic Heart Disease

I. Introduction

Chronic ischemic heart disease, like short-lasting ischemic attacks and acute myocardial infarction, is the result of a fluctuating state of impaired coronary perfu-

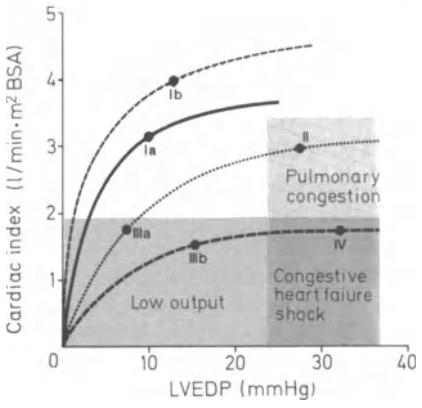

Fig. 1. Left ventricular function curves. Relationship between left ventricular filling pressure, i.e., left ventricular end-diastolic pressure (LVEDP) assessed as pulmonary artery wedge pressure (PWP) and cardiac index (CI) in the setting of acute myocardial infarction (AMI) with related clinical symptoms.
Ia Normal left ventricular function curve. Normal increase of cardiac index with increasing left ventricular filling pressure. LVEDP < 14 mmHg and CI > 2.8 l/min per m^2 BSA (body surface area). 30% of patients with AMI from this group.
Ib Hyperdynamic function curve in uncomplicated AMI as found in 5% of patients with AMI. Sympathetic stimulation by circulating catecholamines is thought to be the reason for elevation in systolic blood pressure and CI with normal or slightly elevated LVEDP.
II LVEDP > 25 mmHg is associated with signs of pulmonary congestion; CI is still normal with values clearly above 2 l/min per m^2 BSA.
IIIa Low output syndrome with low LVEDP and no signs of pulmonary congestion due to hypovolemia.
IIIb Low output syndrome with increased LVEDP > 18 mmHg. In the setting of severe AMI, volume load does not increase CI adequately and signs of pulmonary congestion or cardiogenic shock occur.
IV Cardiogenic shock with low output and LVEDP > 22 mmHg associated with a very poor prognosis

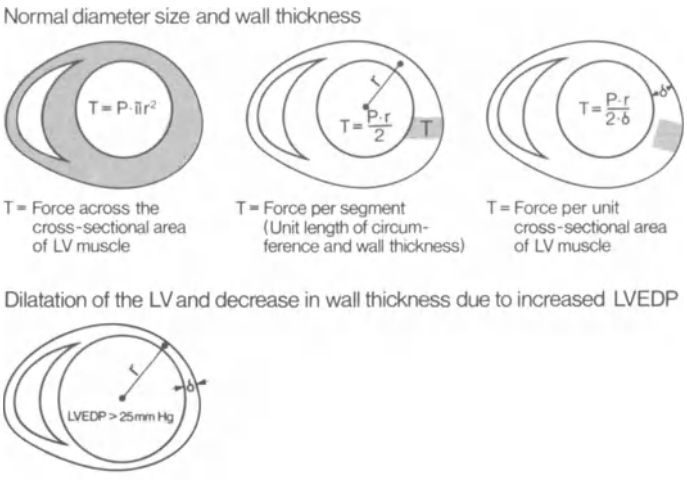

Fig. 2. Three definitions of contractile force in the myocardium and their formulas based on Laplace's law. *T*, contractile tangential tension or force in the left ventricular wall; *P*, transmural pressure accross the left ventricular wall; *r*, average radius of the ventricle assumed to be a sphere; *g*, ventricular wall thickness. The lower panel shows a patient with heart failure and increase in myocardial systolic wall tension owing to Laplace's law. With increased wall tension, myocardial oxygen demand raises at the same time as subendocardial perfusion is impaired owing to increasing left ventricular end-diastolic pressure

sion and a consequence of circulatory insufficiency, directly related to the compromised pump function of the left ventricle. Hemodynamically, pump failure is defined as low cardiac output usually following or associated with inadequately elevated left ventricular end-diastolic pressure (LVEDP) and pulmonary wedge pressure (PWP) (Fig. 1; GORLIN 1976; RACKLEY et al. 1974).

Elevated left ventricular filling pressure itself has an adverse effect on coronary perfusion. Owing to Laplace's law, increased left ventricular diastolic pressure results in augmentation of left ventricular volume and both in increased left ventricular wall tension and oxygen consumption (Fig. 2; GORLIN 1976; RACKLEY et al. 1974, 1979). Elevated wall tension greatly impairs myocardial perfusion, especially in the subendocardial layer, and can provoke additional ischemia secondary to impaired ventricular function on the basis of coronary heart disease, i.e., critical stenoses or complete obstruction of a coronary artery (MORASKI et al. 1975). With more myocardium at risk, angina may develop as a symptom of critically underperfused tissue (MORASKI et al. 1975; RIVAS et al. 1976; COHN 1972). The mismatch of myocardial oxygen requirements and blood supply can result in severe hemodynamic effects on coronary perfusion as well as whole body perfusion, which can be assessed by right heart catheterization monitoring central venous pressure, PWP, and subsequently cardiac output (Fig. 3; GANZ and SWAN 1972; SWAN et al. 1970).

With the technique of flow-directed right heart catheterization, first introduced by DOTTER and STRAUBE (1962) and adapted for clinical use by SWAN et al. (1970), the events occurring during an anginal attack as well as the effects of

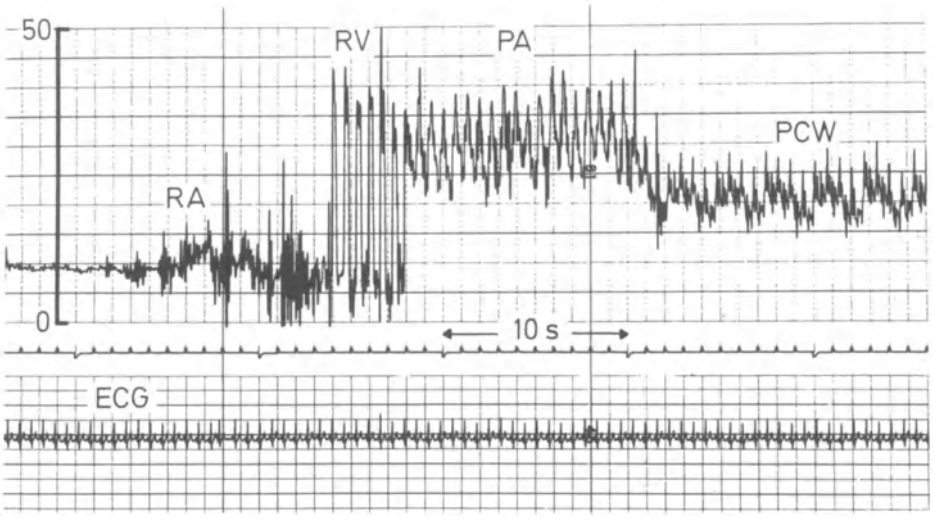

Fig. 3. Normal pressure tracing during insertion of a flow-guided balloon-tipped Swan–Ganz catheter. *RA*, right atrial pressure; *RV*, right ventricular pressure; *PA*, pulmonary artery pressure; *PCW*, pulmonary capillary wedge pressure representing the left ventricular end-diastolic pressure in the absence of mitral valve disease. The scale calibrates pressures from 0 to 50 mmHg. Assessment of *PCW* can provide important information about left ventricular hemodynamics in a variety of clinical settings

catecholamines and antianginal medication on cardiac output and LVEDP can readily be quantitated and monitored at the bedside throughout any medical intervention (SWAN and GANZ 1973; WILLIS et al. 1976; DALEN 1979).

II. Technical Aspects

1. Pressure Measurements

Pressures measured by flotation catheters must be referred to an appropriate zero point, related to the level of the tricuspid valve, which is usually located in the supine position at the upper border of two-thirds of the transversal diameter of the thorax, measured from the table surface. Different catheter types are available ranging from 4 Fr. end-hole latex systems for single pressure recording to 7 Fr. double-lumen flotation catheters (Swan–Ganz type) used for double-chamber diameter pressure recordings and evaluation of cardiac output by thermodilution. With careful maintenance of the zero reference point and exact calibration, pressure may be recorded with an accuracy of ± 2 mmHg under clinical conditions. Appropriate corrections for respiratory influences, especially assisted ventilation, are necessary. The influence of intrathoracic pressure should be minimized. If possible, pressures should be recorded with slight inspiration in apnea. A frequency response of the recording system, flat to 8–10 Hz with a rapid increase at higher frequencies, provides an optimal record of right heart pressures.

2. Cardiac Output by Thermodilution

Thermodilution is the most common technique for the determination of cardiac output in humans because of its convenient approach and its precision. Ice-cold water is injected into the right atrium; the change in temperature is detected by a thermistor located 4 cm from the catheter tip, which is positioned in the main stem of the pulmonary artery. No blood need be withdrawn, in contrast to other indicator dilution techniques, e.g., indocyanine green. The procedure is easily carried out at the bedside by one person.

The thermodilution technique meets the assumptions of Fick's law of diffusion if homogeneous temperature mixing is present. A minimal quantity (10 ml) of negative heat (usually ice-cold saline) transferred to the right heart chambers during initial passage of the bolus of cold saline is mixed with the bloodstream and detected by the distal thermistor (FORRESTER et al. 1972). Portable computer devices providing rapid data display are commonly used for uniform sampling and calculation of the transient changes in blood temperature. To improve precision repeated (at least three consecutive) measurements of the same conditions are advisable and the mean value should be taken. The cardiac index normally ranges from 2.5 to 4 l min^{-1} m^{-2}, with a mean value of 3.2–4 l min^{-1} m^{-2}. Hemodynamic monitoring and assessment of cardiac output has proven to be very useful in cardiac patients with acute myocardial infarctions, heart failure, and cardiogenic shock (SWAN and GANZ 1973; DALEN 1979).

III. Hemodynamic Monitoring

Hemodynamic measurements are extremely useful in assessing cardiac function and the response to various forms of treatment. In acute myocardial infarction, a slow spontaneous recovery of the cardiac index is frequently observed during the initial 3 days, if there are no complications (MATHEY et al. 1974). However, complications with development of pump failure may be observed within 12 h in 30% of patients with acute myocardial infarction (BLEIFELD et al. 1974).

Changes in left ventricular preload, afterload and systolic performance can be assessed by serial measurements of cardiac index. After expansion of the blood volume, some patients experience ischemic chest pain due to impaired subendocardial perfusion, reflected in decreased ventricular function and elevated pulmonary arterial end-diastolic pressure (PAEDP), illustrated by a decline in cardiac index. Relief of the angina, e.g., with sublingual nitroglycerin, is accompanied by a fall in PAEDP and increase in cardiac index; these hemodynamic changes persists for some hours when long-acting nitrates are applied (WILLIS et al. 1976). Also in ischemic heart failure, hemodynamic improvement with long-acting nitrates was reflected in markedly reduced severity of ischemic signs and symptoms (WILLIS et al. 1976; EMANUELSSEN and HOLMBERG 1983). With the use of hemodynamic monitoring, vasodilating agents and nitrates have gained widespread application in any form of acute or chronic ischemic heart disease. Serial assessment of the PAEDP and cardiac index help find the optimal individual dose of drug to reduce PAEDP and increase cardiac output efficiently (DALEN 1979; CHATTERJEE et al. 1975; HANRATH et al. 1975).

Recently, the mechanism of the antianginal action of nifedipine in patients with coronary heart disease was demonstrated by hemodynamic monitoring (EMANUELSSEN and HOLMBERG 1983). Sublingual nifedipine significantly lowered systemic vascular resistance by inducing a drop in systolic afterload. During right atrial pacing, a nifedipine-induced decrease in PAEDP was monitored, reflecting a corresponding fall in LVEDP. If diastolic dimensions were reduced, as this implies, a decrease in tension development in systole will result according to Laplace's law. Beside afterload reduction, this "ventricular unloading" could be the major factor for reducing myocardial oxygen consumption and preventing angina pectoris at the same heart rate that produced severe angina in the control situation. By lowering LVEDP, nifedipine at the same time causes a decrease in myocardial backpressure, resulting in an improved perfusion pressure distal to a coronary artery stenosis.

IV. Parameters to Evaluate Cardiac Loading Condition

1. Central Venous Pressure

It is now widely accepted that the absolute values of the central venous pressure (CVP) do not reliably reflect pulmonary artery pressure or LVEDP, and may not reliably reflect left heart failure (HANRATH et al. 1973). A CVP line, however, offers several practical possibilities:

1. A constant route of administration of drugs and fluids in very ill patients.
2. An access to right atrial blood samples for mixed venous blood gas analyses.
3. A guide to gross fluid overload or failure in patients with low or normal venous pressure during fluid challenges.
4. An index of right heart failure if distended neck veins are not well seen.
5. Means for recording intracavitary electrocardiograms for arrhythmia diagnosis.

Certain hazards may attend the use of CVP lines including phlebitis, thrombosis, and parenteral infections (DALEN 1979).

2. Left Ventricular Filling Pressure

Today, a closer view of hemodynamic function is possible by additional physiologic measurements available from hemodynamic monitoring by flotation catheters (CHATTERJEE et al. 1975; HANRATH et al. 1975); LVEDP is reflected by the pulmonary end-diastolic pressure in wedge position, if both mitral stenoses and pulmonary hypertension are absent (DALEN 1979; BLEIFELD et al. 1974). The normal left ventricular filling pressure is less than 12 mmHg (see Fig. 3). In a variety of different clinical settings of coronary artery disease, i.e., acute myocardial infarction, chronic stable angina, exercise-induced angina, and congestive heart failure due to coronary artery disease, left ventricular filling pressure is often found elevated which may have deleterious effects by two mechanisms:

1. Even a modest elevation in pulmonary capillary pressure leads to transudation of fluid into the lungs and subsequent elevation of pulmonary artery pressure.

2. Increased subendocardial wall tension as outlined before (see Fig. 2), may impair subendocardial perfusion even more, especially if aortic diastolic pressure is reduced (i. e., aortic insufficiency).

Left ventricular filling pressure as assessed by PWP more than 25 mmHg is followed by pulmonary congestive symptoms and indicates the immediate need for venous pooling and diuretics (BLEIFELD et al. 1974). In patients with acute myocardial infarction without evidence of heart failure, PAEDP is elevated about 12 mmHg in 75% and the cardiac index significantly reduced in 20% of patients (see Fig. 1; BLEIFELD et al. 1974). Anterior infarctions tend to present higher values of PAEDP than inferior infarctions (CHATTERJEE et al. 1975; HANRATH et al. 1975). In most of the patients in cardiogenic shock, left filling pressure is usually elevated beyond 20 mmHg. In contrast, cardiogenic shock caused by hypovolemia is accompanied by low PWP (BLEIFELD et al. 1972). The response of the LVEDP and cardiac index to volume expansion describes a ventricular function curve and is an indicator of myocardial reserve. Small infarctions react to a volume challenge with an immediate increase of cardiac output and an only slight elevation of PWP, whereas large infarctions with impaired pump reserve show a rapid increase of PWP in the presence of only small increases of cardiac output, indicating a marked flattening of their ventricular function curve (HANRATH et al. 1975; SCHEIDT et al. 1970). The slope of the ventricular function curve correlates (see Fig. 1) with the ejection fraction and is altered by the size of the myocardial infarction. The optimal left ventricular filling pressure in acute infarction is around 20 mmHg, higher values lead to pulmonary congestion without increases in cardiac output (see Fig. 1); RACKLEY et al. 1974; BLEIFELD et al. 1974; SCHEIDT et al. 1970).

By sequential measurements of these parameters, the effect of therapeutic approaches to aid the ischemic myocardium and for the relief of angina in acute myocardial infarction can be evaluated. Symptomatic as well as asymptomatic episodes of ST segment elevation or depression or T wave pseudonormalization or peaking are common when appropriately searched for in patients with ischemic heart disease. Evidence of concomitant LVEDP elevation during the majority of ischemic events – either with anginal attacks or painless and unrecognized by the patient – may be provided by hemodynamic monitoring. Even short periods of ischemia are reflected in a transient elevation of PAEDP and in a reduction of left ventricular peak contraction and relaxation (CHIERCHIA et al. 1983).

In severely and acutely ill patients, hemodynamic monitoring provides management and recognition of complications and beneficial effects, i. e., physiologic information on left ventricular function, prognostic information (RACKLEY et al. 1979; BLEIFELD et al. 1974; CHATTERJEE et al. 1975) in acute infarction and cardiogenic shock, and the only objective evaluation of the response to pharmacologic agents (DALEN 1979; EMANUELSSEN and HOLMBERG 1983; MANTLE et al. 1976).

Right ventricular infarction can be suspected if right atrial pressure is equal or higher than PAEDP (COHN et al. 1974). A ventricular septal defect as a consequence of acute myocardial infarction may be confirmed by an increased oxy-

gen saturation in the right ventricle and/or the pulmonary artery blood as compared with a right atrial sample (DAVIS et al. 1979).

Acute mitral regurgitation due to papillary muscle infarction is recognized by a large V wave with the catheter tip in pulmonary wedge position. Cardiac tamponade has to be suspected if PAEDP, right ventricular end-diastolic, and right atrial pressure are similar and a dip phenomen is present (RACKLEY et al. 1979). Pulmonary embolism has to be considered if the pulmonary end-diastolic pressure is about 5 mmHg higher than the pulmonary capillary pressure as a sign of arteriolar vasoconstriction (RACKLEY et al. 1974) and if the pulmonary pressure amplitude is abnormally high. The combination of hemodynamic monitoring with noninvasive measurements of ventricular performance (such as shortening fraction as taken from the echocardiogram, radionuclide ventriculography, and wall motion analysis) can probably sufficiently follow up a patient after discharge from the hospital.

B. Assessment of Functional Significance of Coronary Artery Disease

With regard to the patient with ischemic heart disease, the exact knowledge of presence, extent and functional significance of atherosclerotic lesions is necessary for the process of therapeutic management and any further prognosis (FRIESINGER et al. 1970; ABRAMS and ADAMS 1969 a, b).

I. Indications for Coronary Arteriography

Although the most widely accepted indication for coronary arteriography is angina pectoris, the philosophy of the individual cardiologist in the framework of the patient's history, complaints, and treatment as well as the individual risk–benefit balance may vary the diagnostic management. Convincing agreement exists on the indications for patients with unstable angina, severe angina with low

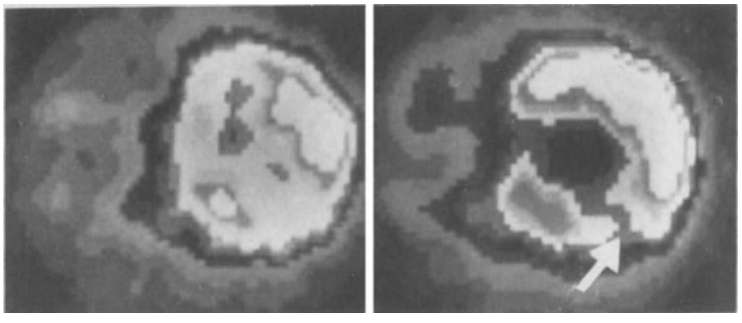

Fig. 4. Biphasic ^{201}Tl perfusion scan, revealing exercise-induced myocardial hypoperfusion, suggestive of right coronary artery stenosis. Subsequent angiography is advisable even if no angina is present

exercise, and variant angina, as well as those with evidence of complicated myocardial infarctions (i.e., cardiogenic shock, congestive heart failure and aneurysm).

In the presence of stable angina, most cardiologists favor coronary arteriography in the younger age group (i.e., <50 years), whereas older patients should be followed conservatively. Another reason for diagnostic catheterization is to exclude coronary heart disease in the presence of atypical chest pain of unknown etiology.

With the increasing utilization of noninvasive screening stress tests in search for coronary artery disease such as exercise ECG, rest and exercise ^{201}Tl perfusion scans, and exercise radionuclide wall motion studies, the so-called silent angina has become an accepted indication for coronary angiography (Fig. 4; FROEHLICHER et al. 1978; ERIKSSEN et al. 1976).

In our institution, coronary angiography is performed if significantly positive exercise tests are detected, i.e., either >2 mm ST-T segment depression in the exercise ECG, or reversible exercise-induced perfusion defects on stress ^{201}Tl scans, or exercise-induced wall motion abnormalities on gated blood pool scans, in this diagnostic order (Fig. 5; MCNEER et al. 1978; BRUCE 1974). Hypotension during

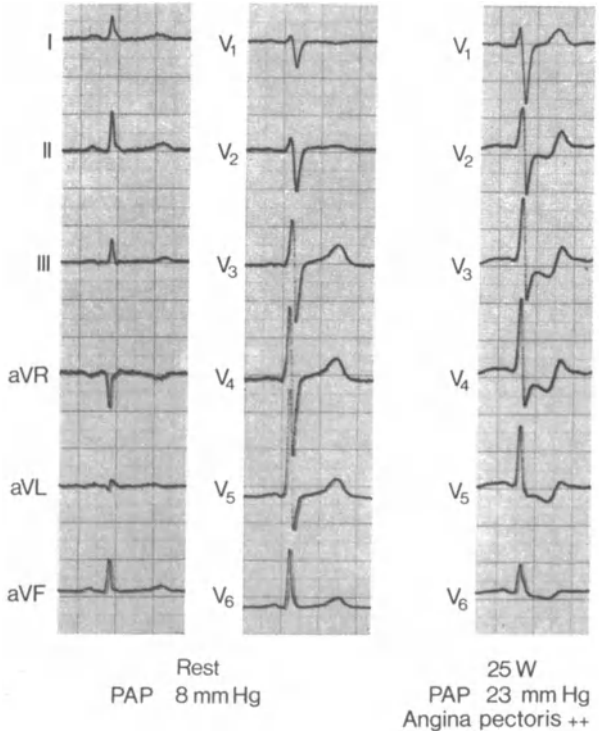

Fig. 5. Twelve-lead ECG of a patient with 95% proximal stenosis in the left anterior descending coronary artery. Marked ST segment depression in leads V_2–V_6 provides clear evidence of left ventricular anterior wall ischemia with increasing pulmonary artery pressure and angina pectoris at mild exercise

exercise may be an indicator of left main coronary artery disease, even if signs of ischemia in the previously mentioned tests are absent (IRVING and BRUCE 1977); accordingly, angiography should be considered. In addition, coronary arteriography in patients with aortic or mitral valve disease should be emphasized in the presence of previous anginal pain and in careful judgment of risk factors and age (ROBERTS et al. 1973).

II. Information Gained from Coronary Angiography

Coronary arteriography is the "gold standard" by which all methods of diagnosing coronary artery disease are measured, since it defines coronary anatomy in the living patient. To accomplish this technique safely and reproducibly, certain principles of performance and interpretation have to be observed. Besides the static anatomic map of the coronary system, contrast arteriography provides information about the dynamic severity of stenotic lesions, th distal vessel bed, including the significance of collateral supply, the poststenotic radiopaque run off and a rough estimate of the regional coronary blood flow (RACKLEY et al. 1979; RIVAS et al. 1976; SONES and SHIREY 1962). By provocative maneuvers such as ergonovine infusion and/or the cold pressor test, variant angina may be documented (COHN 1972; GANZ and SWAN 1972).

Left ventriculography allows visual analysis of global and segmental wall motion; systolic and diastolic volumes and ejection fraction can be readily calculated (Fig. 6). Left ventricular catheterization and left ventricular angiography provide further functional information if performed under stress such as atrial pacing or physical exercise or after administration of pharmacologic agents. Combined analysis of the coronary arteriogram and left ventriculogram can identify the functional severity of a stenosis and bypassable coronaries supplying still viable myocardium.

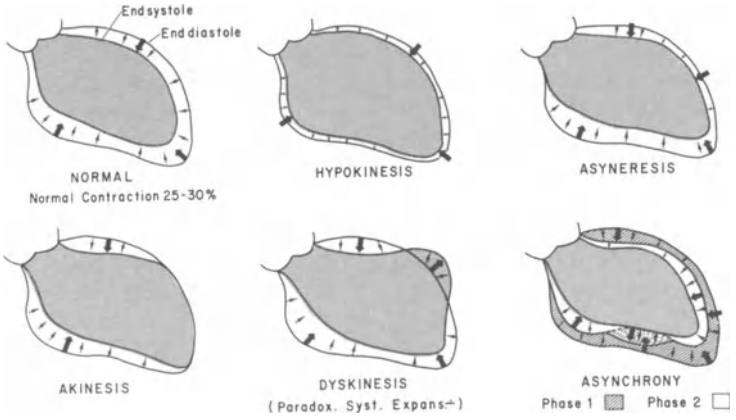

Fig. 6. Variety of contraction pattern of the left ventricle in RAO view. Segmental hypokinesis or severe hypokinesis is often seen with severe ischemia or nontransmural infarction. Akinesis or dyskinesis reflects transmural infarction

With atrial pacing or physical exercise as well as with increased left ventricular contraction by administration of nitrates, catecholamines, or induced postextrasystolic potentiation, left ventricular wall motion abnormalities may be detected since a particular stenosis can become "critical", i. e., it produces evidence of ischemia under stress conditions (HELFANT et al. 1974; DYKE et al. 1974; HORN et al. 1974). In patients after revascularization surgery, patency of bypass grafts and the native coronary circulation can be ascertained. Associated valve disease will be found as well as abnormalities in the coronary system (DABIZZI et al. 1980).

III. Techniques of Coronary Arteriography

1. Brachial Approach

The Sones technique uses an antecubital cutdown to the brachial artery, which is exposed and entered by a woven Dacron catheter (Sones, Positrol UCSI Billerica, Massachusetts). After passage through axillary and subclavian artery, the catheter enters the ascending aorta; there, the soft tapered catheter tip is deflected off the valve cusps up the coronary orifices. The advantages of the Sones technique is the use of a single catheter tip, owing to its proximity (SONES and SHIREY 1962). Disadvantages are the need of an antecubital dissection, arteriotomy, and arterial suture.

2. Femoral Approach

Percutaneous arterial catheterization, introduced by SELDINGER in 1953, was first used for coronary arteriography in 1962 by RICKETS and ABRAMS. Different catheter systems were introduced; among them, the Judkins technique gained widest acceptance and use, although three different catheters are required, one specially made item for each coronary, and a pigtail catheter for ventriculography. Attempts to avoid serious complications of catheter emboli such as systemic heparinization and catheter debridement techniques help to keep the number of complications low. The percutaneous femoral approach using a single catheter (SCHOONMAKER and KING 1974) may combine the advantages of the Sones and Judkins technique.

3. Catheter Types

For diagnostic purposes, there is a wide selection of preformed disposable catheters in a wide range of sizes, shapes, and lengths with both end- and/or side-holes (AMPLATZ et al. 1967; JUDKINS 1967). The ideal nonpreformed catheter allows bending as individually required and holds its shape under in vivo conditions owing to specific material properties and incorporated wire. All surfaces should be smooth and regular to prevent thrombus apposition. For more detailed description of catheter hardware and specific purpose items such as transseptal catheters, bioptomes, loop-snare catheters, and flow-probe-equipped types it is advisable to refer to a handbook of cardiac catheterization (GROSSMAN 1980).

4. Pressure Measurements

During any invasive procedure, phasic pressure recording is routinely required. For this purpose, a properly responding pressure recording system should have a high natural frequency and optimal damping as checked by a sine wave generator to prevent phase lag and amplitude distortion. If the maximal rate of rise of left ventricular pressure expressed as peak dP/dt (first derivative) is of interest, a high fidelity catheter-tip transducer is necessary instead of a fluid-filled one (NICHOLS et al. 1978). The index dP/dt represents the contractile state best, but is influenced by the actual preload and by left ventricular hypertrophy (SONNENBLICK et al. 1970). LVEDP is recorded on a high sensitivity scale and is measured at the coincidence point of the left ventricular pressure wave downslope with the initial upstroke of the left ventricular pressure, or more easily at the peak of the R wave of the ECG. Elevated LVEDP is indicative of a dilated left ventricle, but can also reflect an acute ischemic event in a normal-sized heart. It generally reflects a decreased diastolic compliance of the ventricle, i.e., a disturbed left ventricular pressure–volume relationship (BRAUNWALD et al. 1976).

5. Performance of Coronary Arteriography

Once all medical and pharmaceutical precautions and all technical facilities for emergency care and resuscitation are provided according to international standards, catheterization is performed according to the guidelines which are extensively discussed in specific handbooks (GROSSMAN 1980). Essential to any coronary arteriography technique is a thorough knowledge of the aortic root anatomy. The left coronary artery usually rises from the left sinus of Valsalva, whereas the right coronary artery normally originates from the right sinus positioned anteriorly. Owing to the wide anatomic variation of position, size, and number of the coronary arteries, considerable experience is necessary to identify the complete coronary tree.

IV. Risks and Complications

The risk–benefit balance of heart catheterization is primarily influenced by the severity of the disease detected by catheterization, but also by other factors such as accompanying diseases, instability of the clinical symptoms and, the skill of the angiographer (CONTI 1977; KING et al. 1980; MCMAHON 1979; KALTENBACH and MARTIN 1975) complications (Table 1) has decreased in active centers and seems to be inversely related to the case load of the cardiac catheterization laboratory (ADAMS et al. 1973). Comparing the standard procedures, the Sones and the Judkins techniques, local complicating events at the puncture site (arterial stenosis, hematoma, false aneurysm, nerve lesion, or infection) occur more often with the brachial approach, whereas thromboembolic events as well as acute myocardial ischemia and infarction are more often related to multiple catheter and guide wire exchanges, probably owing to release of thrombus material from the catheter surface (TAKARO et al. 1973; DAVIS et al. 1979).

The routine use of heparin was not found to decrease the incidence of thromboembolic events (FORRESTER et al. 1972). To prevent these and especially cere-

Table 1. Complications of coronary arteriography

	DAVIS et al. (1979)			ABRAMS and ADAMS (1975)			
				Femoral		Brachial	
	Femoral	Brachial	Total	H	NH	H	NH
Death	0.0015	0.0050	0.0020	0.0016	0.0015	0.0010	0.003(
Myocardial infarction	0.0022	0.0042	0.0025	0.0018	0.0023	0.0014	0.002:
Cerebral emboli	0.0002	0.0008	0.0003	0.0008	0.0010	0.0008	0.000(
Arterial complications	0.0040	0.0290	0.0080				
Ventricular fibrillation			0.0063				

H = systemic heparin; NH = no systemic heparin

brovascular complications, a proper technique of catheter flushing and wiping guide wires free of blood before reuse is absolutely necessary. Also the time for continuous use of a wire has to be limited; after 2 min, careful wiping is advisable (ABRAMS and ADAMS 1975).

C. Quantitative Approach to Coronary Artery Disease by Invasive Methods

I. Introduction

Ischemic heart disease is defined by the World Health Organization as myocardial impairment due to the imbalance between coronary blood flow, i.e., oxygen supply, and myocardial flow demand caused by changes in the coronary circulation (RJISFC 1979). Atherosclerotic coronary artery disease is the most important pathophysiologic factor causing myocardial ischemia in humans (HEART FACTS 1980; DIAMOND and FORRESTER 1979). Currently, the coronary arteriogram is the essential and most accurate tool to determine the presence and functional severity of ischemic coronary artery disease. The use of this invasive technique is clearly dependent on specific indications which have already been mentioned. The clinical manifestation of myocardial ischemia, however, can already be suspected in the presence of chest pain (WEINER et al. 1979; MCNEER et al. 1978; GORLIN 1965), electrocardiographic alterations (BRUCE 1974; BERMAN et al. 1978; COHN et al. 1979; BRUCE 1977), regional myocardial perfusion defects (STRAUSS et al. 1977, GOULD 1978 a; BODENHEIMER et al. 1969), and with the release of specific metabolic products like lactate (CURRY et al. 1978; KRASNOW and GORLIN 1963). A state of severe ischemia or impending infarction may be heralded by the presence of intracellular enzymes like creatine phosphokinase in the peripheral bloodstream as an early sign of irreversible cell damage. Nevertheless, invasive angiographic studies are the only reliable current method to evaluate the anatomic extent and severity of coronary artery disease, but they cannot identify the presence or absence of ischemia at the time of the study (BARTEL et al. 1974).

II. Assessment of Left Ventricular Function

1. The Resting Ventriculogram

Cardiac catheterization and angiography at rest is very unlikely to provide information about the presence of ischemia, whereas ventriculography during maneuvers resulting in high oxygen demand and/or limited oxygen supply often provides evidence of decreased ventricular function in a state of ischemia (HAMILTON et al. 1972). The resting ventriculogram is useful to estimate the prognosis of a particular patient and can direct the physician to the appropriate medical or surgical therapy (NELSON et al. 1975, COHN et al. 1974). Besides the coronary arteriogram, the ventriculogram is the fundamental data base for the surgeon, when a bypass operation is considered (GROSS et al. 1978). Since ventricular function is the most important factor to provide prognostic information in coronary artery disease, it has been proven useful to assess the global and regional ejection fraction from left ventricular and right ventricular angiograms (HAMILTON et al. 1972; COHN et al. 1974; HAMMERMEISTER et al. 1979). The ejection fraction is derived from planimetric measurements with the assumption that the ventricle is ellipsoidal in shape (see Fig. 8).

The definition of the ejection fraction is

$$\frac{\text{end-diastolic volume} - \text{end-systolic volume}}{\text{end-diastolic volume}} \times 100\,[\%]$$

In addition to the measurement of the global ejection fraction of the left ventricle, it is also advisable to assess the regional ejection fraction from the ventriculogram to detect wall motion abnormalities (RENTROP et al. 1975). The wall motion may be normal or may show decreased inward movement (hypokinesis), absent movement (akinesis), or paradoxical movement (dyskinesis) (see Fig. 6; HERMAN and GORLIN 1969; SPILLER et al. 1974; SHARMA and TAYLOR 1975).

According to several studies, the patient mortality rate correlates negatively with the resting ejection fraction, i. e., the patient's survival is low with a high degree of left ventricular dysfunction due to previous infarctions or highly compromised myocardial perfusion (MORASKI et al. 1975; NELSON et al. 1975; BRUSCHKE et al. 1973). The mortality associated with coronary artery bypass surgery in the presence of severely depressed ventricular function is also increased. Besides the various degrees of ventricular dysfunction, the ventriculogram may also demonstrate a left ventricular aneurysm causing congestive heart failure, ventricular dysrhythmias, or systemic embolism (HOROWITZ et al. 1980). All findings may lead to surgical intervention. Finally, in patients with coronary artery disease, the ventriculogram provides information about other left ventricular abnormalities such as the papillary muscle syndrome causing mitral insufficiency or a ventricular septal defect after myocardial necrosis.

2. The Intervention Ventriculogram

The presence of a hypokinetic or akinetic segment on the resting ventriculogram may not necessarily indicate fibrous scarring after infarction, but can also be

caused by severe underperfusion of still viable myocardium (HAMILTON et al. 1972; HERMAN and GORLIN 1969). The regional wall motion can be readily improved after acute reduction of preload by vasodilating drugs such as nitroglycerin or nifidepine, or during the positive inotropic state of postextrasystolic potentiation (HORN et al. 1974; BANKA et al. 1976; HERMAN 1976; RAFFLENBEUL et al. 1976; STADIUS et al. 1980).

Nitrate-induced venous pooling has beneficial effects both on myocardial oxygen supply and demand, especially when ventricular diastolic pressures are elevated. In addition, when coronary conduit vessels are narrowed by atherosclerotic lesions or by spasm, relaxation of normal or increased smooth muscle tone at the site of the stenosis by nitrates may increase native and/or collateral flow, enabling critically underperfused territories to reestablish contractile function. Depressed regional left ventricular ejection fraction due to regional ischemia will normalize if the oxygen supply: demand ratio is normalized by any pharmacologic intervention.

In general, a postintervention improvement of wall motion is considered indicative of still viable myocardium functioning at a depressed state owing to critically reduced myocardial blood flow. In addition to the pharmacologic intervention, "ischemic" asynergy has been shown to improve significantly with successful recanalization of acute coronary artery thrombosis, by either surgical nonsurgical treatment, probably owing to reperfusion of reversibly damaged myocardium (see Fig. 18; WEBSTER et al. 1974; RENTROP et al. 1976; MATHEY et al. 1981 a).

3. Techniques to Evaluate Left Ventricular Function from Angiograms

Selective injection of contrast material is essential to obtain the image of the opacified left ventricular cavity in either monoplane or biplane views (frontal and lateral), or right anterior oblique (RAO) and left anterior oblique (LAO), or half-axial left anterior oblique and conventional right anterior oblique views (RAFFLENBEUL et al. 1976; DODGE et al. 1960; WYNNE et al. 1978; ALS et al. 1978). In the single plane mode, the frontal or right anterior oblique view has been shown to be reliable (KENNEDY et al. 1970; SANDLER and DODGE 1968). The formulas appropriate to calculate the left ventricular volume and ejection fraction have been

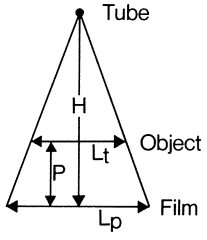

Fig. 7. Correction for nonparallel X-ray beam distortion requires knowledge of the tube-to-film distance H, the object-to-film distance P and the relationship between the three lengths of the object L_t and its projected length L_p on film

validated by comparing true volumes of left ventricular casts with calculations from cine frames of these casts, which truely represent the dynamic geometry of the left ventricle. Correction for X-ray magnification and image distortion is essential (Fig. 7). In the classical biplane area–length method of DODGE et al. (1960), each shadow of the left ventricular chamber is seen as an ellipse and its volume is calculated from the formula

$$V = \frac{4}{3}\pi \frac{D_a}{2}\frac{D_l}{2}\frac{L_m}{2},$$

where: D_a = minor axis in the anteroposterior view; D_l = minor axis in the lateral view; and L_m = major axis.
Using a monoplane approach, the longest measurable axis and one short axis are measured. A second nonvisible short axis is assumed to equal the first

$$V = \frac{4}{3}\pi \left(\frac{D_l}{2}\right)^2 \frac{L_m}{2}.$$

In either the biplane or the monoplane approach, the short axis dimension can be derived from both the long axis and the area of the "elliptical" left ventricle, since, the area is easily determined by planimetry using either a hand planimeter, an electronic scanning device, or an *xy* plotter (Fig. 8).
The two axes D_a and D_l are calculated as follows

$$D_a = \frac{4A_a}{\pi L_a}$$

$$D_l = \frac{4A_l}{\pi L_l}$$

where: A_a = area of the anteroposterior image derived from planimetry; A_l = area of the lateral view image derived from planimetry; L_a = longest axis in the anteroposterior view; and L_l = longest axis in the lateral view. Complicated correction procedures for magnification caused by the divergence of the X-ray beam and al-

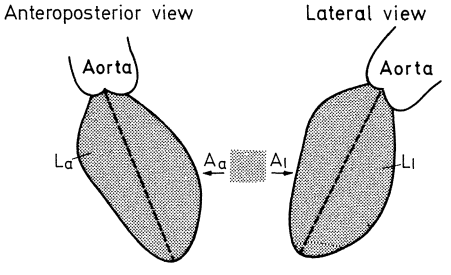

Fig. 8. Area–length method of DODGE et al. (1960) for left ventricular volume calculation from biplane angiograms. The diagram depicts the longest measured axis L_a and L_l in two orthogonal views and the corresponding areas A_a and A_l. Calculations are based on an elliptical model (see text for details)

so for pincushion distortion (i.e., greater magnification at the image periphery than in the center) are overcome by filming an overlying calibrated grid at the estimated level of the left ventricle.

From ventricular cast studies, DODGE et al. (1960) derived the following regression equation by correlating the calculated volume and the known volume of nine postmortem human left ventricles

$$V_t = 0.928\ V_c - 3.8,$$

where: V_t = true volume; and V_c = calculated volume after correction for nonparallel X-ray distortion.

In practice, it is advisable to use the following formula, taking into consideration the nonparallel X-ray distortion and the regression equation (DODGE et al. 1966)

$$V_t = 0.787 \frac{C_m^2\, C_s\, A_a\, A_l}{L_s} - 3.8$$

where A_a = uncorrected area of the projected image in the anteroposterior view (cm^2); A_l = uncorrected area of the projected image in the lateral view (cm^2); L_s = the smaller of the major axes (cm), uncorrected; C_m = correction factor for nonparallel X-ray distortion in the projection with the longest measured length;

$$C_m = \frac{L_t}{L_p} = \frac{H - P}{H}$$

L_t = true length; L_p = projected length; H = tube-to-film distance; P = object-to-film distance; and C_s = correction factor for the other projection.

Despite these corrections, estimates from angiographic techniques tend to overestimate the actual volume of the left cavity owing to the systolic displacement by inner cavitary structures. Besides the regression equation for biplane (anteroposterior and lateral) angiography ($V_t = 0.928\ V_c - 3.8$) there are several other equations in the literature to correct for volume overestimation (DODGE et al. 1960; WYNNE et al. 1978).

The limited availability of biplane angiography equipment stimulated the development of regression equations for the single plane approach. An equation developed by SANDLER and DODGE (1968) is

$$V = 0.951\ V_{AP} - 3.0.$$

For the single RAO view KENNEDY et al. (1970) developed the formula: $V = 0.81\ V_{RAO} + 1.9$, which correlates well with the volume estimate from biplane angiography using Dodge's equation (GORLIN 1976). New semiautomatic computer systems and data aquisition modes greatly facilitate the rapid determination of ventricular volume at different cycle frames. Therefore, ejection fraction, left ventricular muscle mass, ventricular wall stress, and regional changes in the ejection fraction can be easily assessed. Normal values in humans are shown in Table 2. De-

Table 2. Normal left ventricular function values in humans

Left ventricular end-diastolic volume	70 ± 20 ml/m^2
Left ventricular end-systolic volume	24 ± 10 ml/m^2
Left ventricular ejection fraction	$0.67\% \pm 0.08\%$
Diastolic left ventricular wall thickness	9 mm in women 12 mm in men
Left ventricular mass	76 g/m^2 in women 99 g/m^2 in men

creasing left ventricular volume or increasing left ventricular ejection fraction are seen with increased myocardial blood flow after successful coronary artery bypass grafting or other revascularizing procedures (WEBSTER et al. 1974; MATHEY et al. 1981 a).

4. Right Ventricular Function

The complexity of the right ventricular internal geometry has discouraged the use of angiocardiography to determine the right ventricular volume and ejection fraction. But despite the geometrical difficulties, the area–length method of DODGE and SANDLER has also been validated for the right ventricle (Fig. 9; SHIMAZAKI et al. 1980; GENTZLER et al. 1974). Its modification, the parallelepiped H_1-method has proven to be of comparable accuracy (Fig. 10; ARCILLA et al. 1971). Simpson's rule is widely used for calculation of the right ventricular volume (GENTZLER et al. 1971; GRAHAM et al. 1973).

The right ventricular volume is calculated according to the formula (Simpson's rule)

$$V_c = \frac{\pi h'}{3}\left(\sum^{\text{odd}} A'_i B_i + \sum^{\text{even}} \frac{1}{2} A'_j B_j\right)$$

$$= 1.047 h'\left(\sum^{\text{odd}} A'_i B'_i + \sum^{\text{even}} \frac{1}{2} A'_j B'_j\right)$$

where: h' = segment height corrected for image distortion (cm); A', B' = antero-posterior and lateral measured axes, corrected for image distortion (cm); i = odd numbers; and j = even numbers.

Other methods with different geometrical models also have been utilized to calculate the right ventricular volume with acceptable accuracy including the two-chamber method (GRAHAM et al. 1973), the prism method (FISHER et al. 1975), and the three-sized pyramid method (FERLINZ et al. 1975). The end-diastolic right ventricular volume in normal persons is 81 ± 12 ml/m^2 (GENTZLER et al. 1974), and the right ventricular ejection fraction is about $50\% \pm 10\%$.

Right ventricular infarctions or ischemia in the coronary artery supplying parts of the right ventricle may cause deterioration in right ventricular function expressed by decreasing right ventricular ejection fraction or increasing right ventricular end-diastolic as well as end-systolic volume (RATLIF and HACKEL 1980).

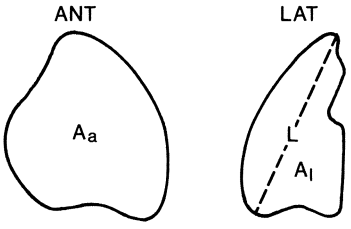

Fig. 9. $V = 0.848\ (A_a A_l / L)$. Modified area–length method for measurement of right ventricular volume. The diagram depicts the area of the projected plane in anterior A_a and in lateral projection A_l as well as the longest measured length L in the lateral view cm

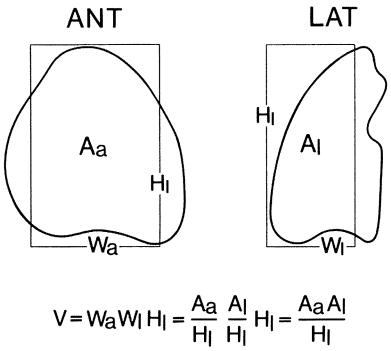

Fig. 10. Parallelepiped H_l method for right ventricular volume measurements. This diagram depicts imaginary rectangles so constructed that their areas are similar to those of the respective ventricular planes in the anterior *ANT* and lateral *LAT* views. The height H_l is identical to the superior–inferior axis in the lateral view. W_a = width of the rectangle in anterior views; W_l = width of the rectangle in the lateral view. Volume is calculated according to the formula above

III. Assessment of Coronary Artery Morphology

1. Evaluation of the Functional Severity of Coronary Artery Stenoses

When coronary angiograms are analyzed, a systematic view in each standardized projection is essential. Because coronary anatomy can be quite variable, the first approach is to view the film with the naked eye in order to detect either homogeneous perfusion or significant defects of perfusion suggestive of occluded or anomalous coronary arteries. Areas of foreshortening and overlap should be examined in other views to exclude hidden lesions. After reviewing each segment, a systematic scoring and recording system is useful for complete analysis of the coronary perfusion pattern.

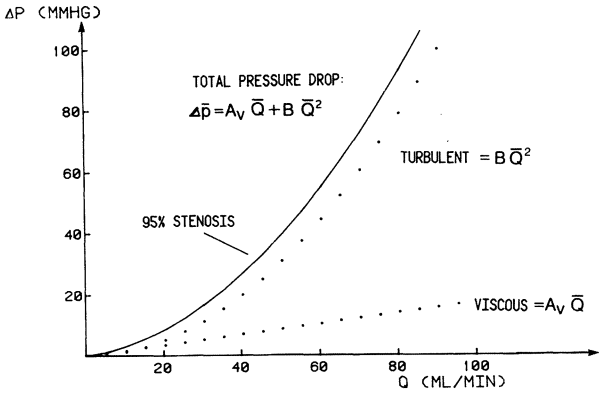

Fig. 11. Nonlinear relationship between pressure drop ΔP and flow Q with a 95% area stenosis. At a flow of 40 ml/min ΔP is about 29 mmHg, whereas at 80 ml/min ΔP is as much as 90 mmHg

The analysis of coronary angiograms also requires assessment of stenosis location and severity; the latter is often expressed as the percentage decrease in the luminal diameter of the vessel, as emphasized by an international coordinating council (AUSTIN et al. 1975). The corresponding reduction in the intraluminal cross-sectional area is proportional to the square of the decrease in diameter (FIDDION et al. 1964). From experimental animal studies, we learn that a 85% decrease in luminal diameter is necessary before a stenosis becomes physiologically critical, i.e., compromised resting coronary flow (MAY et al. 1963; YOUNG and TSAI 1973; SYDORAK et al. 1972). The cross-sectional area reduction is 98% under these conditions. For example, at a 95% area stenosis under resting conditions the mean pressure drop would be approximately 29 mmHg. However, with increased demand for blood flow, as would occur with exercise or vasodilating drugs, the pressure drop would increase to 88 mmHg (Fig. 11; FIDDION et al. 1964). Stenosis flow resistance is shown to increase with increasing turbulence at the stenosis exit and decreasing distending pressure owing to ischemic vasodilation of the poststenotic peripheral vascular bed. It is obvious that, with increasing myocardial oxygen and flow demand, a coronary stenosis can easily become the limiting resistance to blood flow, whereas the same lesion may not significantly impair myocardial perfusion under more normal or resting conditions. In humans for instance, a 72% luminal diameter stenosis which is a calculated 92% decrease in cross-sectional area, has been estimated to result in myocardial ischemia at rest (GOULD and LIPSCOMB 1974; KLOCKE 1976). With increasing length of the stenosed segment and in the presence of multiple lesions, coronary flow is more markedly reduced than in the case of discrete single short lesions (GOULD and LIPSCOMB 1974). In addition, the geometry of the stenosis exit and entrance angle has a flow-dependent influence on stenosis severity so that turbulent resistance increases with the steepness of the exit angle and the velocity of flow (YOUNG et al. 1977; SEELEY and YOUNG 1976). The complexity of these relationships makes it difficult to predict the precise physiologic effect of multiple lesions observed on routine angiograms.

2. Problems in Judging the Severity of Coronary Artery Disease

Several studies have demonstrated an astonishing intra- and interobserver variability in assessing the severity of lesions and also in defining the number of coronary vessels involved in a particular patient (ZIR et al. 1970; DEROUEN et al. 1977; DETRE et al. 1975). The most common method to evaluate the distribution and severity of coronary lesions is joint review by the angiographer and the surgeon, both examining the film simultaneously. Other methods include independent reading by two or more observers with a subsequent joint meeting to resolve disagreement and review by a panel of experts. Assessment of coronary lesions by any method can be judged in the light of two interrelated criteria: accuracy and consistency. Accuracy asks the question "how truly does the evaluation reflect actual coronary morphology?" Accuracy is influenced by all factors involved in the production and interpretation of films and has been evaluated in several reports by comparing angiographic structures with postmortem findings (GRONDIN et al. 1977; HUTCHINS et al. 1977). The second criterion, consistency, asks the question "how reproducible is the interpretation of a single angiogram?"

Generally, there are two ways to evaluate angiograms by a panel: group opinion or consensus opinion. For group opinion, panel members read films independently and the estimates are averaged later. According to ZIR et al. (1970) interobserver variability is a significant limitation in the group opinion method owing to the lack of uniformity in assigning the location of stenoses. This problem is reduced when all panelists review films simultaneously for consensus opinion, i.e., to achieve a common judgement. Interestingly, duration of experience and practice in reading angiograms does not influence the degree to which nonprofessional readers agree with the panel (BROWN et al. 1977). In our institution, we emphasize the consensus opinion method, since in our experience it provides the lowest overall variability in estimating the severity of left main coronary stenosis or first diagonal branch stenosis, well known to be the most difficult sites in the coronary circulation to judge the degree of narrowing.

In some institutions, it has been proven useful to differentiate stenoses with significant lesions (more than 70% area stenosis, i.e., 50% diameter reduction) from nonsignificant stenoses with a diameter reduction of less than 50%. Narrowing the judgment to this extent limits the use of coronary angiography to describe the natural history of ischemic heart disease, neglects a lot of important information, and severely overestimates the consistency of the panel.

3. Automated Evaluation of Coronary Angiograms

In order to reduce variability associated with the naked eye technique (albeit with systematic reading, multiple projections, and panel consensus), an alternative approach with semiautomated computer-assisted stenosis estimates seems to provide better consistency in grading stenoses. A quantitative procedure described by BROWN et al. (1977) and some other groups is based on manual tracings of normal as well as stenosed coronary artery segments and has been shown suitable for clinical use (SMITH et al. 1981; SIEBES et al. 1982). A fully automated instrumental procedure for computerized vessel edge detection, based on densitograms across the vessel border, has been introduced by LEDBETTER et al. (1978). Currently,

quantitative coronary angiography is gaining growing clinical interest since it improves consistency and quality and may allow a closer look at the slow progression of arteriosclerosis with time. According to studies comparing angiographically estimated stenoses with measurements made of vessels at postmortem examination, it is evident that human readers often underestimate the severity off an obstruction (VLODAVER et al. 1973). However, experienced readers seem to overestimate the amount of narrowing caused by relatively severe stenoses compared with a quantitative computer reading of the lesion (BROWN et al. 1977). Despite these discrepencies, subjective and automated evaluation have provided important prognostic information related to survival from one-, two-, and three-vessel disease as well as from main left coronary involvement (WEBSTER et al. 1974; MCNEER and ROSATI 1978; TAKARO et al. 1976).

4. Dynamic Changes in Stenosis Severity

It has recently been reported that both the area of stenosis and the cross-sectional area of a normal segment can dilate with infusion of slow calcium channel blockers like verapamil or nifedipine (DHEW et al. 1980; SCHAPER 1979). This indicates that the presence or absence of certain drugs can significantly alter the result of quantitative coronary angiography. Some other drugs are also known to influence stenotic or normal segment diameter heavily (VATNER et al. 1982). With infusion of nitroglycerin, for instance, BROWN et al. (1981) showed an increased in luminal area in normal segments, especially in large epicardial vessels. Furthermore, diseased segments of a coronary artery system showed evidence of a 22%–36% increase in stenotic area. Stenosis dilation resulted in an average 25% reduction of estimated stenosis flow resistance in moderate lesions and in a 38% reduction in severe lesions. This observation led to the conclusion that vasodilation of epicardial coronary stenoses is usually a significant component of the beneficial response to nitroglycerin (BROWN et al. 1981). In the presence of coronary stenoses involving primarily a single conduit vessel, downstream flow may be maintained through collateral channels arising from neighboring relatively normal coronary arteries. Both development of collaterals and dilation of the vessels from which collaterals arise increase collateral flow to ischemic myocardium in experimental models and in humans, improve contraction of ischemic segments, and limit the size of myocardial infarction (SCHAPER 1979). Thus, in the presence of coronary obstruction localized to a territory with collateral development, nitrates increase collateral flow through vasodilation of collateral vessels or by relaxation of normal smooth muscle tone at the site of the stenosis in the conduit vessel from which the collaterals arise (BROWN et al. 1981).

In contrast to the action of nitroglycerin or other smooth muscle relaxing drugs (i.e., calcium channel blockers), β-adrenergic blockade has been shown to produce a decrease in the severity of a fixed proximal coronary artery stenosis. Resistance to flow through the stenosis decreased significantly after β-blocker administration and remained below control values, even after atrial pacing (BUCK et al. 1981). This effect, however, is not due to an increase in stenosis area, but the result of reduced perfusion demand, i.e., lower stenosis flow resistance with unchanged stenosis geometry.

Summarizing these observations, we are dealing with essentially two types of stenoses, first, the so-called fixed calcified stenoses with no geometrical change of the stenosis itself and second, with the type of dynamic stenosis which often appears noncalcified and eccentric in shape with the capacity to dilate and contract the nondiseased part of the smooth muscle wall in the stenotic segment (SCHWARTZ et al. 1981; LOGAN 1975).

GOULD suggested four different mechanisms for altered severity of coronary artery stenosis during changing vasomotor states of the distal vascular bed:

1. Arterial smooth muscle relaxation and vasodilation of the stenotic segment itself.
2. Vasodilation of the coronary artery adjacent to the stenotic segment.
3. The appearance of fully developed turbulence in the stenotic segment.
4. Narrowing of the stenotic segment owing to decreasing intraluminal pressure caused by arteriolar vasodilation and decreasing distending pressure (SANTAMORE and WALINSKY 1980; SCHWARTZ et al. 1979).

In a similar way, expansion of a dynamic stenosis can be observed by increasing intraluminal pressure after arteriolar vasoconstriction. The latter mechanism is supported by the observation that agents such as isoproterenol and nitroglycerin which decrease distal coronary pressure, actually increase stenosis severity (SANTAMORE and WALINSKY 1980). However, vasoconstricting drugs such as methoxamine and vasopressin, which increase distal pressure, can decrease stenosis resistance and severity when the stenosis diameter is maintained with intraluminal plastic tubing; thus, decreased distal coronary pressure does not influence stenosis resistance, probably because the artery is now incapable of passive narrowing.

These experimental results can only be explained by dynamic changes in stenosis geometry secondary to changes in intraluminal pressure and distal coronary artery tone. In chronically instrumented dogs, dynamic increases in hemodynamic severity of coronary artery stenoses are observed with distal coronary vasodilation (GOULD 1978 b). Increasing stenotic resistance after coronary dilation is explained by relaxation of the epicardial artery segment adjacent to the fixed stenosis (i. e., increased percentage of stenosis) and not by a larger stenosis exit angle since the variation of this angle from 10° to 90° does not affect the pressure gradient across this stenosis (LIPSCOMB and HOOTEN 1978).

In human coronary arteries with eccentric lesions, LOGAN (1975) was the first to show that the resistance to flow is dependent upon perfusion pressure. With lower perfusion pressures stenosis resistance increases, whereas at higher perfusion pressures resistance decreases. Dipyridamole and hydralazine, both potent vasodilators have been associated with worsening angina in certain patients with coronary stenoses. Both drugs dilate distal resistance vessels rather than conductance vessels. By the mechanism described, both drugs can critically impair subendocardial perfusion since human coronary lesions are not simply fixed impediments to flow, but dynamic compliant wall segments with the capacity to dilate and to constrict; severe stenoses even demonstrate passive collapse in response to reduced intraluminal pressure. Based on these principles, the ideal agent for therapy of ischemic heart disease would dilate the coronary conductance vessels and

reduce distal myocardial perfusion demand by decreasing heart rate, myocardial contractility, diastolic preload, and systolic afterload. In practice, the combination of β-receptor antagonists and long-acting nitrates realizes this therapeutic concept. A marked reduction in coronary perfusion pressure, however, can be deleterious since partial collapse of a stenosis with reduced distending pressure can critically decrease transstenotic flow.

The attempt to visualize the vasodilating action of drugs with antianginal potency by quantitative evaluation of coronary arteriograms is difficult, since relief of angina is based on several mechanisms. Patients receiving sublingual nitroglycerin reveal a 14% mean reduction in coronary sinus flow as a reflection of reduced myocardial oxygen demand. However, the same study demonstrates a direct dilating effect of nitroglycerin on coronary smooth muscle, despite a simultaneous reduction in systemic arterial pressure (BROWN et al. 1981). Predicted flow resistance in severe coronary stenosis (65%–85% diameter reduction) falls 38% after sublingual administration of nitroglycerin owing to angiographically demonstrated increase in stenotic cross-sectional area. Thus, dilation of compliant stenoses is considered one of the greatest of the potentially beneficial effects of nitroglycerin.

IV. Coronary Artery Spasm

1. Mechanisms of Coronary Artery Spasm

Contraction of intramural smooth muscle fibers in the coronary arterial wall may temporarily narrow the vessel lumen and subsequently reduce coronary blood flow (RICCI et al. 1978; MONTZ et al. 1981; WATERS et al. 1979) with the result of myocardial ischemia (CONTI 1980; HILLIS and BRAUNWALD 1978) and sometimes even infarction (MADIAS 1979; MASERI et al. 1978).

The sensitivity of coronary artery smooth muscle to a variety of different extrinsic triggering stimuli seems to be enhanced in patients with coronary spasm; different etiologic theories are currently under discussion (HILLIS and BRAUNWALD 1978; GINSBURY et al. 1980; HEUPLER 1976; SHUBROOKS 1979). Vasoactive agents such as histamine, catecholamines, and prostaglandins have been shown to produce coronary artery constriction in animal models and isolated human coronary segments (GINSBURY et al. 1980; KELLEY and FEIGL 1978) and in certain subsets of patients (FIGUERAS et al. 1979; BERGER et al. 1977; MÜLLER et al. 1982; MASERI et al. 1979).

One important vasoconstrictor is the prostaglandin thromboxane A_2, whose release during platelet activation may locally stimulate coronary artery spasm (MASERI et al. 1978 b; CHIERCHIA et al. 1982). The most frequent clinical manifestation of coronary spasm is the syndrome of variant or Prinzmetal's angina (OLIVA et al. 1973; MASERI et al. 1978 b; PRINZMETAL et al. 1959) which is characterized by anginal chest pain at rest accompanied by transient ST-T segment elevation similar to those in acute transmural infarction, but usually without subsequent myocardial necrosis (Fig. 12; SHUBROOKS 1979; OLIVA et al. 1973; PRINZMETAL et al. 1959).

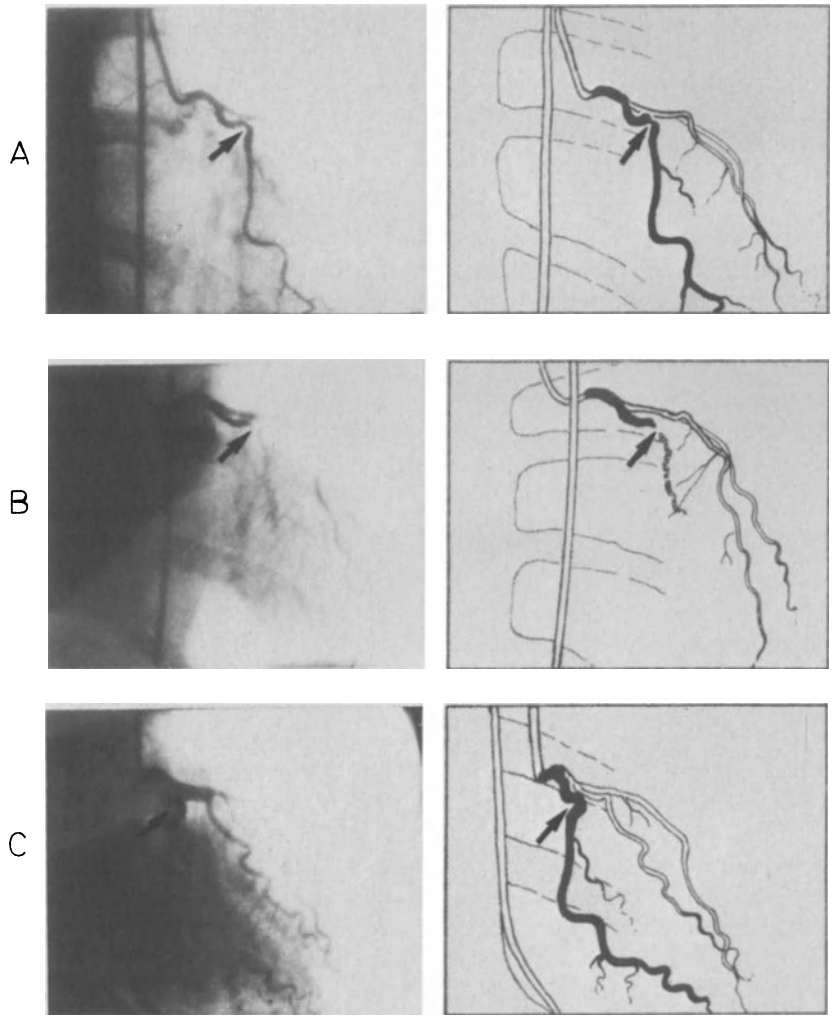

Fig. 12a. Coronary artery spasm in the proximal left circumflex coronary artery shown by contrast injections before (*A*) and during (*B*) an episode of spontaneous chest pain in a 39-year-old woman with a history of variant angina. After intracoronary injection of nitroglycerin (*C*), angina and spasm disappeared.

2. Provocation of Coronary Artery Spasm

Patients with this condition may have coronary arteries that appear normal at the time of angiography, but coronary spasm may be demonstrated following intravenous administration of ergonovine (WATERS et al. 1980; CURRY et al. 1977; OLIVA et al. 1973). Ergonovine may be most useful in patients with a characteristic pain pattern, but in whom electrocardiograms have not been recorded during pain. The ergonovine provocative test is also useful to evaluate the effect of ther-

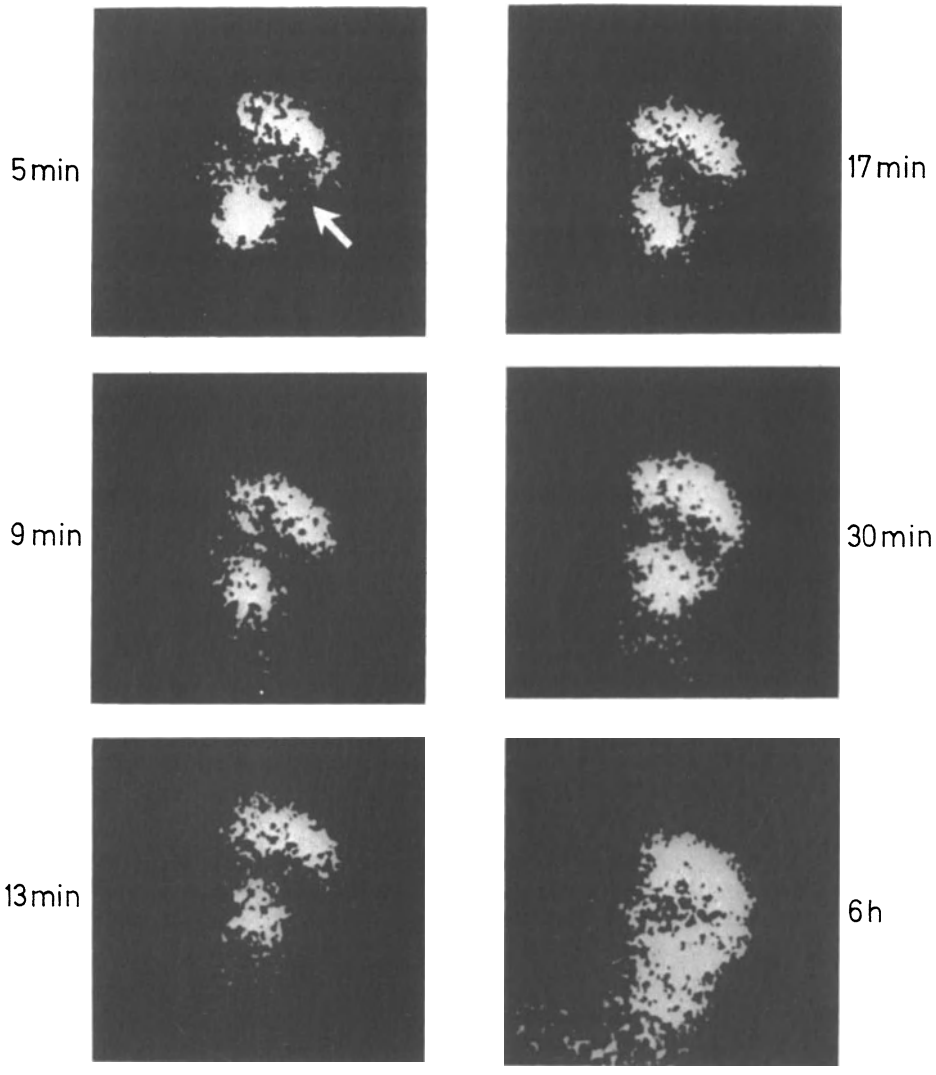

Fig. 12b. ^{201}Tl perfusion images during spasm-induced myocardial ischemia. Note the marked perfusion defect and the late phase of complete redistribution

apeutic agents. Failure to induce spasm with intravenous ergonovine injection in a patient on therapy, i.e., slow calcium channel blockers, especially nifedipine (MULLER and GUNTHER 1978) with recent evidence of coronary spasm, is indicative of efficient treatment. Although ergonovine tests are generally safe, there is a risk of producing nitrate-resistant spasm and even subsequent infarction. Vasodilating agents should be immediately available to reverse the spasm by intracoronary injection if sublingual nitroglycerin initially fails. It is recommended that ergonovine is only used in the catheterization laboratory.

V. Cardiac Metabolism in Ischemia

1. Metabolic Evidence of Myocardial Ischemia

The main method of evaluating myocardial metabolism in patients has been the measurement of certain metabolic products occurring in the coronary sinus blood during ischemia (SHELL and SOBEL 1976). In the clinical setting, the measurement of coronary blood flow and metabolites including oxygen, lactate, pyruvate, free fatty acids, adenosine and some other substances, is employed to evaluate myocardial metabolism in a state of ischemia (PANDLE and TUBBS 1979; NEELY and MORGAN 1974).

2. Coronary Blood Flow

Coronary blood flow is measured by the washout from the myocardium of indicators that are offered to the heart by intravenous injection, by direct intracoronary injection, or after inhalation of a reference gas. Thermal dilution measurements of cold solution injected into the coronary sinus can also be used (GANZ and SWAN 1972). Whereas in patients with ischemic heart disease at rest, only inconsistent abnormalities in coronary blood flow are found, some other studies have clearly shown diminished perfusion in areas distal to a stenosed vessel when flow demand is increased (KLOCKE 1976; KRASNOW and GORLIN 1963).

3. Metabolic Studies in Ischemia

A common technique to assess myocardial ischemia in humans is currently the determination of lactate extraction/production across the myocardium. Lactate is normally taken up by the heart (extraction). Lactate production or even decreased extraction was thought to be indicative of myocardial ischemia (KLOCKE 1976; KRASNOW and GORLIN 1963; OLSON 1963). Studies by GERTZ et al. (1980) have shown that in humans with no clinical evidence of coronary artery disease, lactate extraction during rapid atrial pacing falls below 10%, but in no case is lactate produced. Thus, myocardial production of lactate is probably diagnostic of ischemia in the human heart. Lactate metabolism is also affected by a variety of other factors, particularly free fatty acid metabolism by the heart and the level of circulating catecholamines.

Other metabolites released from the myocardium during ischemia include potassium, phosphate, adenosine, inosine, and hypoxanthine. Although there are some papers in the literature reporting the use of these metabolites for detection of ischemia, none has proven to be more sensitive for detection of ischemia than lactate alone. However, coronary sinus sampling raises some problems since the sinus drains the venous blood from the left ventricle. In right coronary artery disease, ischemia might not be detected in coronary sinus drainage since the dilution with blood from the normal left coronary artery bed is too high. Detection of ischemia in the area perfused by the left anterior descending coronary artery is more accurate. The heterogeneous distribution of ischemia has been demonstrated by regional sampling of the effluent with catheters inserted into different areas of the coronary venous system (Fig. 13; HERMAN et al. 1967). At the present time, the coronary sinus technique for measuring myocardial blood flow and metabolism

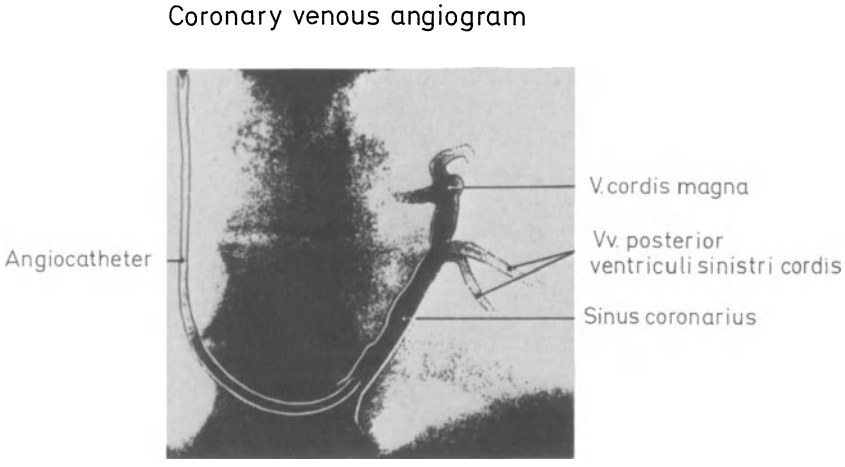

Fig. 13. Coronary venous angiogram with sampling catheter in the coronary sinus. The sinus drains venous blood from the entire left ventricle, whereas the vena cordis magna is known to drain the left ventricular anterior wall. Ischemia originating from the right coronary artery cannot be detected by sampling metabolites in the coronary sinus

is not in routine clinical use, but has proven to be efficient in demonstrating ischemia under conditions of increased oxygen demand.

D. Invasive Techniques in Therapy

I. Intracoronary Thrombolysis in Acute Coronary Thrombosis

1. Coronary Thrombosis as a Cause of Myocardial Infarction

Despite a long history of conflicting opinions on the pathophysiology of acute myocardial infarction, in the last two decades it has become very clear that acute coronary thrombosis is a major cause of sudden obstruction of myocardial blood flow with subsequent development of myocardial necrosis. Dramatic cineangiograms obtained in the last 5 years have clearly visualized mechanically or pharmacologically lysed blood clots, sometimes breaking off an intracoronary apposition thrombus and moving distally. In addition, direct observation of intracoronary thrombotic material has become possible with the increasing number of emergency coronary artery bypass grafting operations in a state of impending or evolving myocardial infarction. The major role of thrombosis as a cause of myocardial infarction has also been proven by a series of pathological papers (MITCHELL 1969; CHANDLER et al. 1974). In patients with acute myocardial infarction, the prevalence of thrombotic coronary artery occlusion reached about 95% in recent studies (MITCHELL 1969). A lower prevalence of thrombotic coronary artery occlusion as presented in earlier reports results from inclusion of patients with old infarctions and spontaneously recanalized infarct-related vessels as well as from nontransmural infarctions and patients who died suddenly owing to severe dysrhythmias.

Further evidence for coronary thrombosis as the main cause of infarction was provided by reports of FLETCHER et al. in 1965, showing that thrombolytic agents like urokinase could be safely administered to human beings and produce a thrombolytic state with lysis of thrombus. In 1966, the first major therapeutic trial for thrombolysis was completed in Germany, examining the value of streptokinase therapy for acute myocardial infarction (SCHMUTZLER et al. 1966). As a result of this trial, the 40-day mortality was significantly lower (14.1%) in the streptokinase group as compared with a control group receiving oral anticoagulants (21%).

2. The Concept of Intracoronary Thrombolysis

Based on experimental evidence in the 1970s, the concept of salvage of ischemic myocardium and a subsequent reduction of the infarct size attracted lots of interest. The underlying philosophy was that the size of myocardial necrosis after coronary occlusion, which correlates inversely with long-term prognosis (SOBEL et al. 1972; BLEIFELD et al. 1977), can be reduced by influencing a variety of factors determining the infarct size (MAROKO et al. 1971; BRAUNWALD et al. 1969; SCHAPER and PASYK 1976; NIENABER et al. 1983). Among several determinants, the restoration of myocardial blood flow seemed to be the most significant intervention and attracted experimental as well as clinical interest (SCHAPER and PASYK 1976; NIENABER et al. 1983; RIVAS et al. 1976; HIRZEL et al. 1976). In histochemical and hemodynamic studies by NIENABER et al. (1983), the extent and duration of the perfusion deficit in ischemic myocardium are clearly shown to determine the ultimate infarct size. It is obvious that extreme reduction in oxygen demand and early reperfusion is the most promising approach for salvage of ischemic heart muscle.

Acceptance of the concept of limitation of infarct size, the advanced technology of coronary angiography, and the availability of high quality thrombolytic agents led several investigators to infuse streptokinase or urokinase directly into an obstructed human coronary artery in the state of evolving infarction. CHAZOW et al. (1976), RENTROP et al. (1979a, b, 1981) and MATHEY et al. (1980, 1981b) clearly demonstrated that coronary recanalization was possible with this method. In the meantime, many centers report similar results and there is some evidence that early recanalization will be of value to some patients in limiting the extent of necrosis, but probably not of value to all patients (MATHEY et al. 1981).

Reperfusion may have no advantage and may even be dangerous if ischemic damage is irreversible and the progression of infarction is complete (SCHACHENMAYR and HAFERKAMP 1972; LIE et al. 1978). Severe dysrhythmia (KUCK et al. 1982), transmural hemorrhagic myocardial infarction, and severe bleeding may occur (MATHEY et al. 1982). The value of the procedure in patients with acute myocardial infarction seems to depend on the extent and the duration of compromised myocardial perfusion (NIENABER et al. 1982b, 1983). Under conditions of complete coronary artery obstruction with no development of collaterals, the maximal infarct extension seems to be reached 3 h after the onset of pain (LEINBACH and GOLD 1981; DEWOOD et al. 1980). At the moment, several randomized

studies are under way to determine the value of intracoronary thrombolysis on infarct size, cardiac function, rate of reinfarction, and mortality.

3. The Technical Procedure of Intracoronary Thrombolysis

In our department, nonoperative recanalization of an obstructive coronary artery in patients with evidence of acute myocardial infarction is performed on a 24-h basis. Patients arriving at the emergency room with symptoms and ECG evidence of acute myocardial infarction are considered for selective thrombolytic therapy if they meet certain inclusion criteria: (a) no basic conventional contraindication to aggressive thrombolytic therapy such as extensive cerebrovascular disease; (b) recovery from recent operations with suspicion of and ongoing healing process; (c) no known bleeding disorders; (d) and usually not more than 70 years old. After obtaining written consent, catheterization is performed according to the Judkins technique if the duration of chest pain has been no longer than 3 h.

After standard heparinization, the particular coronary artery judged to be occluded by distribution of ST-T segment elevation is identified by hand injections of contrast medium through the Judkins catheter. As soon as the occlusion is localized, nitroglycerin is slowly injected into the occluded vessel to exclude coronary spasm which could be associated with the acute occlusion. Then recanalization of the infarct-related vessel is attempted by either mechanical means, i.e., passing a 0.08-cm guide wire with a movable core through the occlusion or by direct infusion of streptokinase into the occluded coronary artery (Fig. 14). The conventional dosage is 2.000–4.000 IU/min selectively into the occluded coronary artery. The effect of the streptokinase infusion is evaluated angiographically at 15-min intervals. The streptokinase infusion is continued until the artery is maximally patent. Then a complete coronary angiogram and biplane ventriculogram are obtained from which global and segmental left ventricular ejection fraction is calculated according to the arealength method (DODGE et al. 1966). In a subgroup of the patients with successful streptokinase-induced recanalization in evolving infarction, acute coronary artery bypass grafting was performed on the day of recanalization or up to 5 days later. Another subgroup of patients reveived elective coronary artery bypass grafting after 60 ± 28 days. According to the results of MATHEY et al. (1981), early postrecanalization aortocoronary bypass grafting is not associated with an increased number of perioperative deaths or a decreased graft patency rate. Neither did the late postoperative death rate differ between the group with early emergency bypass grafting and that of elective operation.

4. The Possible Benefit from Coronary Thrombolysis

In contrast to standard management of acute myocardial infarction, this modern recanalizing approach is directed toward abolishing the principal factor involved in acute myocardial infarction, i.e., the acute thrombotic coronary occlusion, and tends to reestablish myocardial perfusion in order to salvage ischemic myocardium and reduce the potential extent of the infarct size. Moreover, recent data pro-

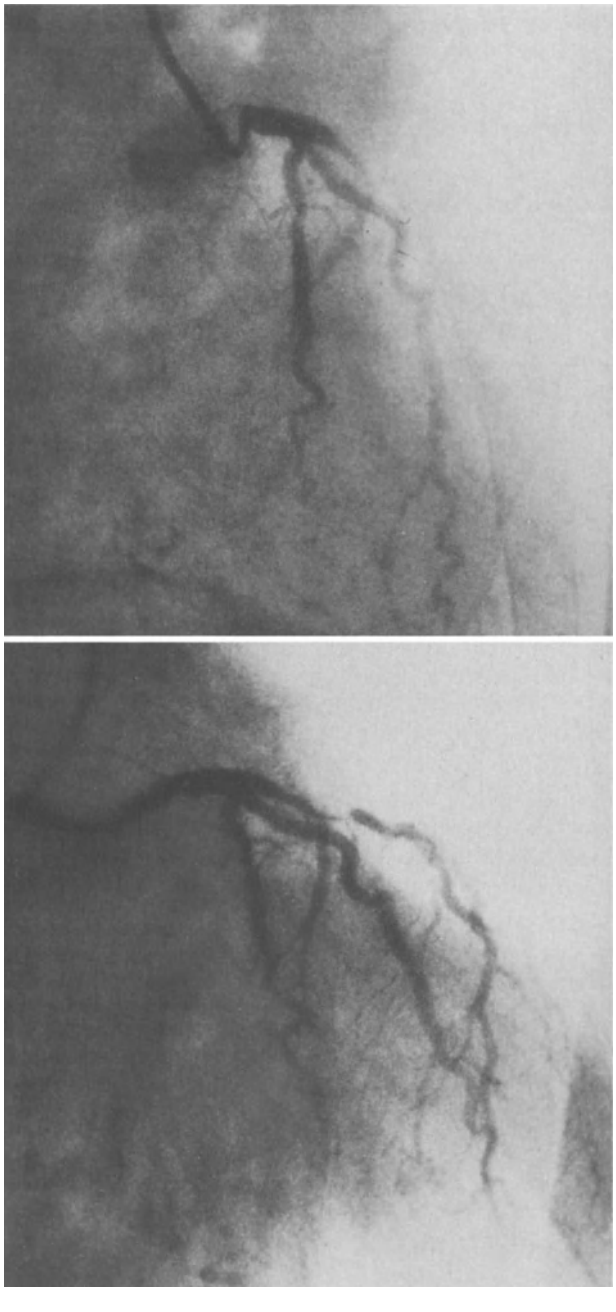

Fig. 14. **a** Complete occlusion of the proximal left anterior descending coronary artery in a 52-year-old man with evidence of anterior wall infarction 2 h after onset of pain. **b** After 15 min of intracoronary streptokinase administration, successful thrombolysis with distal run off of contrast medium and a remaining high degree stenosis at the site of the previous occlusion

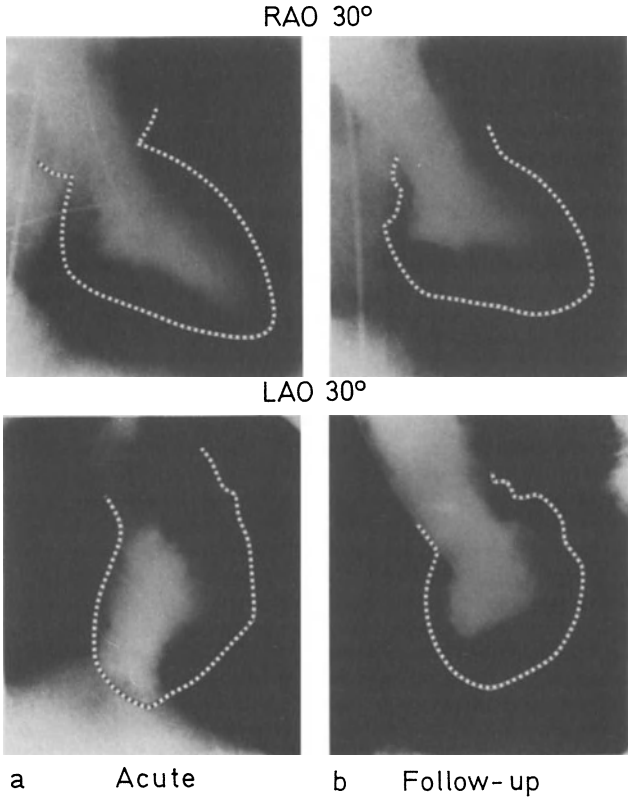

Fig. 15. a Acute angiogram in end-systole showing left ventricular anterior wall akinesis immediately following successful streptokinase-induced recanalization of the left anterior descending coronary artery. The *dotted line* is the end-diastolic contour. **b** Normal angiogram of the same patient 6 months after acute thrombolysis and subsequent coronary artery bypass grafting. SCHOFER et al. (1982)

vide evidence of substantial and consistent improvement of regional wall motion of a previously ischemic segment supplied by a coronary artery, which had been successfully recanalized. With reperfusion, such wall motion improved from 14% to 40% (MATHEY et al. 1981), which strongly suggests that early streptokinase-induced reperfusion converted ischemic nonfunctioning myocardium into non-ischemic functioning heart muscle (Fig. 15). This improvement of left ventricular function was even independent of patency of the bypass graft circumventing the residual fixed stenosis. This indicates that the early reperfusion achieved by thrombolytic recanalization alone is sufficient to restore considerable myocardial function in evolving myocardial infarction.

Further experience and careful examination of the continuously increasing data is required to recommend the intracoronary or intravenous thrombolytic approach as a routine procedure. In this regard, the principle of restoring precursors of elementary metabolites which have been degraded and washed off with reperfusion seems to be worth intensive study (NIENABER et al. 1982a).

II. Percutaneous Transluminal Coronary Angioplasty

1. The Principle of Dilating Arterial Stenoses

Dilatation of peripheral atherosclerotic lesions by use of an intravasal catheter device was first introduced by DOTTER and JUDKINS in 1964. The working principle of the Dotter catheter has been adapted by GRÜNTZIG (1976) who developed a double-lumen catheter system equipped with an inelastic inflatable balloon at its tip for dilatation of peripheral and renal artery stenoses. This principle has been modified for coronary angioplasty, first performed by GRÜNTZIG (1977). GRÜNTZIG et al. (1979) reported on 50 patients with an initial success rate of 64%. With increasing experience, however, this success rate has been reported to be more than 90% with a very low number of severe complications such as myocardial infarction of death (KRAYENBÜHL et al. 1980). Data collected up to 1981 show a clear relationship between the initial success rate and the experience of the performing team.

Dilatation of an atherosclerotic lesion is possible since the atheroma obstructing the inner lumen is composed of low density compressible fatty material. The inflated intraluminal balloon squeezes the atheroma mass, leading sometimes to intimal dissection. With reestablished normal blood flow, organization and fibrosis of this material results in smoothing of the vessel wall treated by angioplasty (LEU and GRÜNTZIG 1978). The healing process of this controlled injury is extensively demonstrated by angiographic and histologic studies after dilatation of peripheral artery stenoses.

2. Indications

When percutaneous transluminal coronary angioplasty (PTCA) was introduced into clinical use, te majority of patients had one-vessel disease, recent-onset angina, which would make them candidates for coronary bypass surgery (GRÜNTZIG et al. 1979). Angiographic findings are short subtotal noncalcified lesions in the proximal portions of the left anterior descending, the left circumflex or the right coronary artery (Fig. 16). Starting only with patients having one-vessel-disease, technical development of the catheter device as well as increasing skills of the operator have extended the indication to patients with two-vessel and three-vessel disease with similarly good results. Even patients with left main coronary artery disease have undergone successful PTCA, although this location is usually not accepted as an indication by most investigators (DORROS et al. 1983).

When successful, the procedure results in an immediate increase in coronary blood flow both at rest and during stress testing. Hospitalization and surgical costs are reduced dramatically and the patients can usually be discharged after 3 days. If angioplasty is unsuccessful, immediate or elective coronary bypass surgery should be available. During the procedure, a coronary surgery team should be on call in case of the need for emergency coronary bypass grafting (WILLIAMS

Fig. 16. a Concentric subtotal stenosis in the proximal right coronary artery in LAO view suitable for PTCA. **b** Inflated dilatation catheter at the site of the stenosis. The balloon of the angioplasty catheter is filled with contrast medium. **c** Successful PTCA with marked increase in luminal diameter

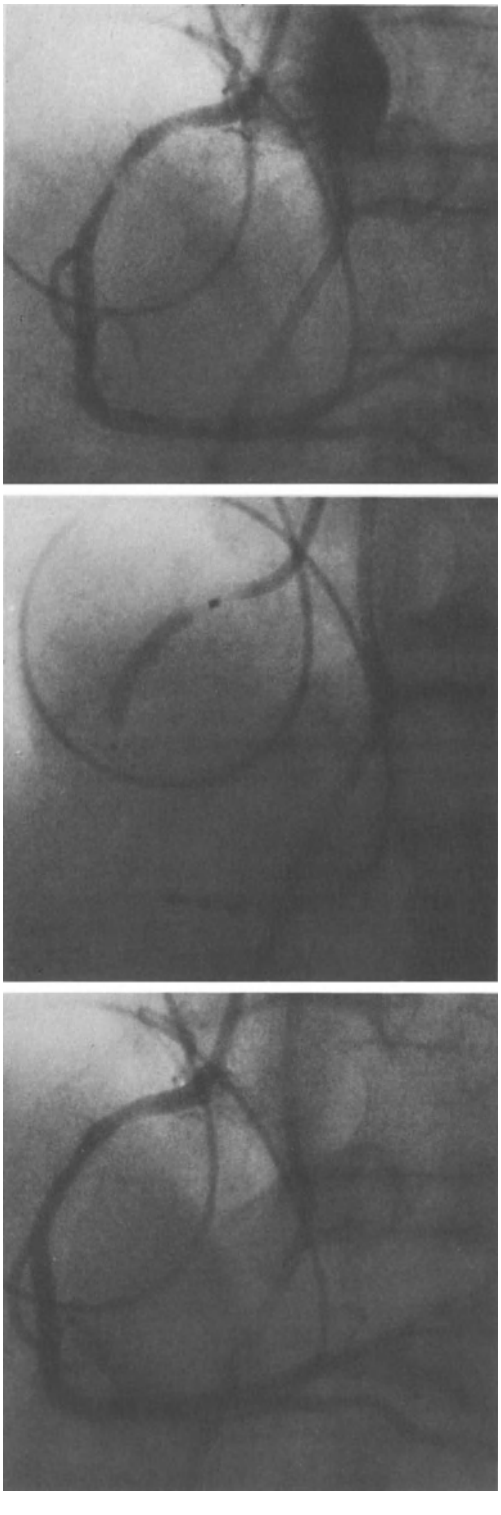

Fig. 16 a–c

et al. 1982). In successful cases, patency of the dilated artery seems to be maintained in the following period. When restenosis occurs, angioplasty can be repeated. Restenosis after more than 60 months is very unlikely to occur.

3. The Catheter System

The basic equipment consists of two catheters: the guiding catheter which has an outer diameter of 9 Fr., and the dilatation catheter. The guiding catheter is introduced into the femoral artery using the Seldinger technique for the Judkins procedure. It is advanced retrograde into the ascending aorta and positioned into the orifice of the coronary artery to be dilated. This catheter guides, the second catheter, the double-lumen dilatation catheter, into the stenotic arterial branch. At the proximal end of the guiding catheter is a Y-connector to allow simultaneous pressure measurements from the tip of the guiding catheter.

For the Sones technique, slight modification of the guiding catheter is necessary. The dilatation catheter has an outer diameter of 0.5 mm at the distal portion and a soft short wire tip in order to direct the catheter into the artery with no injury to the arterial wall. At the end of the dilatation catheter is a side hole connected to the main lumen of the dilatation catheter, which is connected to a manifold and used for pressure recording and injections of radiographic contrast material. The balloon itself is filled with a mixture of saline solution and contrast material via the second lumen of the dilatation catheter. The inflatable balloon keeps its predetermined outer diameter and shape constant up to a balloon pressure of more than 10 atm (see Fig. 16). The balloon segment is available with a maximal outer diameter of 3.0 or 3.7 mm, similar to the inner lumen of the left anterior descending, circumflex, and right coronary arteries. The inflation and deflation of the balloon is controlled by calibrated pressure pump.

4. Technical Aspects

The guiding catheter is introduced through the femoral artery and positioned at the orifice of the appropriate coronary artery or at the orifice of a bypass graft without obstructing it. After giving heparin 150 IU/kg and sufficient dosage of sublingual nitroglycerin and nifedipine to avoid coronary spasm during the procedure, a single coronary angiogram of the diseased segment is obtained in a projection most suitable to display the lesion. The guide catheter has to be filmed to assess stenosis severity in absolute dimensions. A complete coronary angiogram is now obtained, including hemiaxial views to visualize lesions of the proximal third of the left anterior descending artery, preferably with no overlap of branches and accentuation of eccentric stenoses. If the guiding catheter is positioned at the orifice or the coronary artery, it is disconnected from the manifold and connected to the Y-connector. The manifold is then connected to the main lumen of the dilatation catheter, while the second lumen of the dilatation catheter (i.e., for inflation) is connected to the pressure pump. Then the dilatation catheter is inserted into the Y-connector and advanced through the guiding catheter into a coronary artery with the balloon deflated.

The coronary pressure is monitored through the tip of the dilatation catheter and the aortic pressure through the tip of the guiding catheter (WILLIAMS et al.

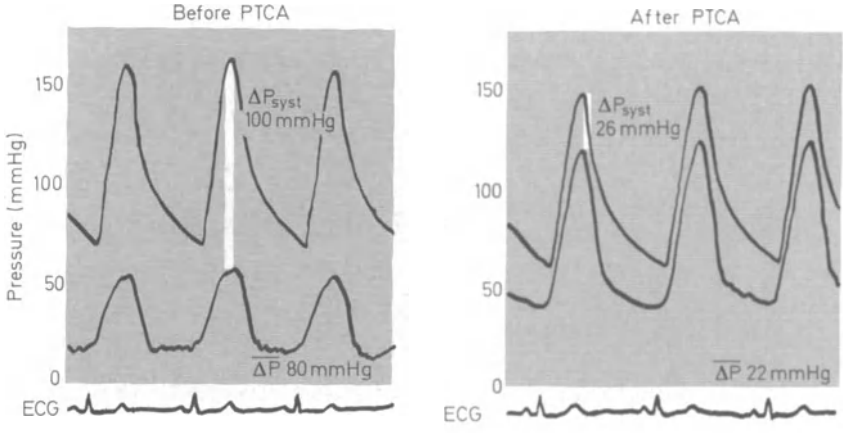

Fig. 17. Original records of a PTCA procedure with pressures measured proximal and distal to a severe bypass graft stenosis. After three inflations of the balloon, a decrease in mean transstenotic pressure gradient from 80 to 22 mmHg was observed with excellent morphological results

1982). If the region is too hard and its lumen too small, passage through the stenosis is not possible; backward displacement of the dilatation catheter into the aortic root indicates this. However, if a lesion is soft, a lumen smaller than the catheter diameter may allow passage of the deflated balloon. After successful passage across the stenosis, a drop in pressure occurs, although the phasic wave will persist (Fig. 17). Once the angioplasty catheter is properly positioned, the balloon is immediately inflated to a pressure of 4–6 atm. The inflation of the balloon is documented on film. The balloon is then deflated and the postdilatation and pullback pressures are continuously recorded. Sometimes, several inflations with increasing balloon pressure are required to achieve an acceptable morphological and hemodynamic result. The duration of each inflation ranges from 20 to 30 s.

The pressure gradient across the stenosis measured through the dilatation catheter gives only a rough idea of the stenosis severity, since the catheter itself contributes to the stenosis. Therefore, the distal pressure is more or less a wedge pressure, representing the actual collateral pressure. This is even more pronounced if the balloon is inflated. However, a decline and transstenotic gradient with stable hemodynamic conditions probably represents a reduction in stenosis severity since the size of the catheter is unchanged. Depending upon the response and the symptoms of the patient, the procedure can be repeated several times under continuous recording of ECG and pressures. The dilatation catheter is finally withdrawn and at least four coronary arteriograms in various oblique and hemiaxial projections are performed through the guiding catheter to assess the geometrical effect of the dilatation. The procedure is then terminated, heparinization is maintained for another 24 h and then replaced by platelet aggregation inhibitors.

The geometrical result of the angioplasty procedure is calculated from at least two orthogonal views before and after percutaneous transluminal coronary

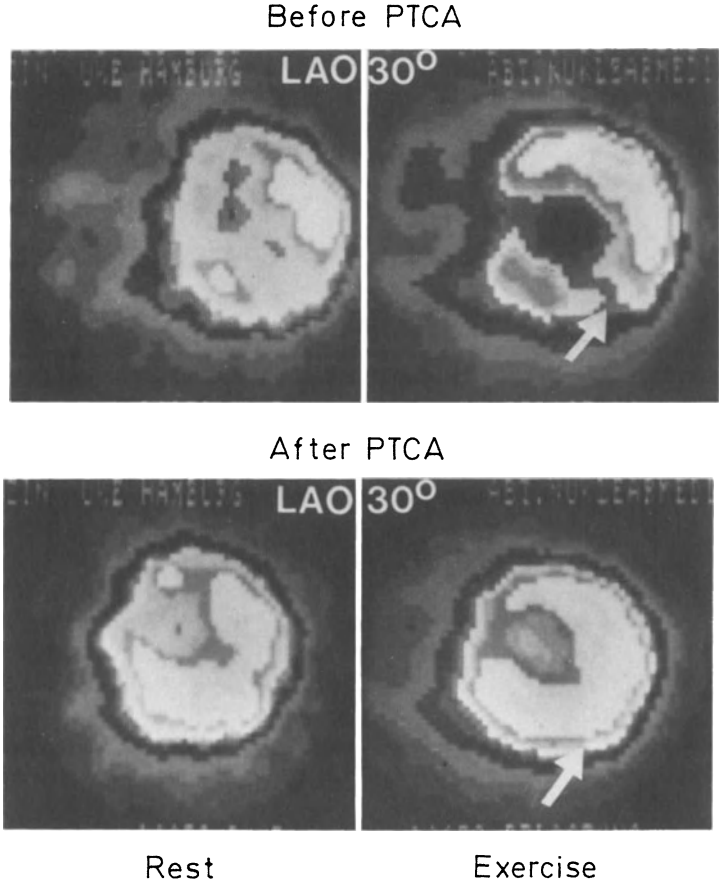

Fig. 18. ^{201}Tl scintigrams of exercise-induced hypoperfusion indicative of transient ischemia in the inferior left ventricular wall. After successful PTCA, normal perfusion pattern was restored at rest and during exercise

angioplasty. The hemodynamic success is estimated by the decrease in pressure gradient as calculated from the geometrical change or the stenosis shape, from proximal and distal coronary artery pressure, and from clinical parameters such as exercise tolerance, ECG stress tests and biphasic ^{201}Tl scintigraphy (Fig. 18).

5. Results and Future Application

In summary, selection of appropriate patients for PTCA is based on the information of a previous coronary angiogram and discussed from a medical and surgical point of view. The first criterion to be met by the patient is evidence of angina pectoris heavily compromising the quality of life. Second, the history of pain should be less than 1 year, since a recent-onset angina correlates well with soft compressible atheroma, especially in the left anterior descending artery. A patient with single-vessel disease is the most appropriate one. In addition, the anatomy

of the artery and the stenosis has to be clearly visualized, should be proximal, discrete, hourglass-shaped, and not located close to an acute bend. Regarding these indications, 3%–10% of patients undergoing diagnostic coronary angiography may be suitable candidates for PTCA. Refined catheter technology including the use of steerable guide wires and the growing skill of operators have resulted in a primary success rate of 90% (KRAYENBÜHL et al. 1980).

These results justify enthusiasm and more aggressive patient selection in terms of coronary anatomy (i.e., two- and three-vessel disease), but do not necessarily imply an extension of clinical indication, which was based on the patient's need for coronary surgery. In fact, from recent reports in the literature, successful PTCA has been performed in acute evolving myocardial infarction with evidence of complete thrombotic obstruction (MEYER et al. 1982), in a subset of patients with variant angina as well as in patients with unstable angina due to subtotal occlusion of a coronary artery (DAVID et al. 1982). In contrast, preventive dilatation of a coronary artery with less than 60% diameter stenosis should not be performed since the incidence of complications is higher and the recurrence rate reaches almost 30% with potential disease acceleration in the previously compressed lesion (ISCHINGER et al. 1983).

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Types of Antianginal Drugs

CHAPTER 10

Organic Nitrates*

U. ABSHAGEN

A. Introduction

The following should be understood as a supplement to the excellent review of organic nitrates in Vol. 40 of this handbook which was edited in 1975 by P. NEEDLEMAN. For this reason, literature older than 1974 which has already been covered by that volume is only used here when necessary. In the same way, topics such as historical background, chemistry and physicochemical properties or side effects of organic nitrates, which naturally have remained constant since then, are not referred to. Although some progress has been achieved in the difficult field of bioanalysis of organic nitrates in recent years, limited space does not allow discussion of this important matter. Sect. B in particular should be read in the context of the earlier chapter on biotransformation of organic nitrates by NEEDLEMAN (1975). Generally, special attention has been given to topics where the experimental evidence accumulated in the meantime has not confirmed the previous views of the authors of Vol. 40, such as enteral activity of organic nitrates, therapeutic value of so-called long-acting nitrates; or where our knowledge has been extended, for instance, the relation between pharmacokinetics and effect, some aspects of the mechanism of action and the development of isosorbide-5-mononitrate for the prophylactic treatment of angina pectoris. Because of the recently revived discussion of nitrate tolerance, a special section has been devoted to this problem, although some redundancy within the later sections on clinical usage was unavoidable. However, new indications for organic nitrates other than angina pectoris have had to be omitted in accordance with the topic of the present volume and the limited space available.

B. Pharmacokinetics of Organic Nitrates

I. Trinitroglycerin

1. Absorption

According to experiments in rats with ^{14}C-labelled trinitroglycerine (glyceryl trinitrate, GTN), almost complete absorption of GTN from the gastrointestinal tract can be assumed (HODGSON and LEE 1975). Systemic availability, however, is thought to be very low after oral administration since GTN undergoes an extensive first-pass metabolism (NEEDLEMAN 1975). In humans, only scanty data are available on the bioavailability of GTN after sublingual, oral or transdermal ad-

* Dedicated with gratitude to Professor Dr. HELMUT KEWITZ on the occasion of his 65th birthday

ministration. This is mainly due to the fact that bioanalytical methods that are sensitive enough have become available only during the last few years. BLUMENTHAL et al. (1977) reported maximum plasma levels of GTN after a sublingual dose of 0.3 mg amounting to 1 ng/ml 3 min after administration, whereas at 16 min concentration had dropped below 0.1 ng/ml. In good agreement with this, P. W. ARMSTRONG et al. (1979) found maximum plasma concentrations of 2.3 ng/ml which were reached 2 min after sublingual administration of 0.6 mg and declined with an apparent half-life of 4.4 min. BLUMENTHAL et al. (1977) had also measured the plasma concentrations after oral administration of 6.5 mg GTN in the same study. If one estimates graphically the areas under the curves (AUC) from the published figures after both routes of administration, one gets an approximate 10% relative bioavailability for the oral formulation, if dose-linear kinetics can be assumed. Although the respective data were poorly documented, I have also tried to compare the AUC after sublingual administration according to the data of BLUMENTHAL et al. (1977) with that after intravenous infusion, given by MCNIFF et al. (1981). This reveals approximately 80% absolute bioavailability for the sublingual administration and thus roughly 8% for the oral formulation.

The order of magnitude of this very rough estimation is, however, in good agreement with the determination of enteral activity as performed by PORCHET and BIRCHER (1982). These authors compared the pharmacodynamic activity as measured by digital plethysmography – a method accepted by the U.S. Food and Drug Administration for determination of bioavailability of organic nitrates – after intravenous infusion and oral administration of GTN, and determined an oral bioavailability of GTN of $2\% \pm 4\%$ in normal volunteers. The obvious difference between the bioavailability after oral and sublingual administration already points to an intensive hepatic first-pass metabolism of GTN. In addition to the sublingual administration, the hepatic first-pass effect can also be avoided by cutaneous administration. Thus, several studies showed that after administration of GTN ointment, sufficient amounts of GTN reach the systemic circulation (BLUMENTHAL et al. 1977). Plasma levels of about 3 and 8.9 ng/ml were reached after 2–5 cm and 10 cm, respectively, of a 2% ointment (P. W. ARMSTRONG et al. 1980 b). These levels could be maintained for 240 min in patients with congestive heart failure for whom the therapeutic threshold concentrations are said to be in the range of 1 ng/ml (P. W. ARMSTRONG et al. 1980 a). These studies have also shown a linear relationship between the dose administered and the resulting plasma concentrations. Using the recently developed transdermal systems, P. MÜLLER et al. (1982) observed in a similar manner, dose-dependent and nearly constant plasma levels of 0.13–0.27 ng/ml after one patch, up to 0.5–1.5 ng/ml after four patches, which could be maintained over 24 h.

2. Distribution

The apparent volume of distribution of GTN seems to be very high. The most reliable estimate is based upon experiments by MCNIFF et al. (1981) who infused 0.58 ± 0.06 mg within 32 min to nine normal volunteers and obtained a mean value of 3.3 l/kg. Thus, GTN cannot be evenly distributed within the body, but must be highly concentrated in certain compartments. According to distribution experiments by HODGSON and LEE (1975), the concentrations of total radioactiv-

ity are 4.4 and 7.8 times higher in the liver and 2.4 and 2.8 times higher in the kidney than in plasma at 4 and 24 h after oral administration of GTN ^{14}C in rats. Binding to plasma proteins accounts for only 60% (DiCarlo 1975) and the radioactivity content of rat blood cells averaged 40% and 70% of the plasma concentrations at 4 and 24 h after administration (Hodgson and Lee 1975).

These results of animal experiments cannot therefore sufficiently explain the high apparent volume of distribution when calculated from the plasma levels in humans. Recent experiments by Fung et al. (1981 b, 1984) point to a considerable accumulation of GTN in its pharmacological target, the blood vessels. According to observations by Brymer et al. (1977) and J. A. Armstrong et al. (1980 a), this accumulation is higher in the venous than in the arterial bed. Although it cannot be quantified at present, this high affinity and accumulation in the vessels may explain the uneven distribution and the consequently high distribution volume of GTN.

3. Elimination

The biological half-life of GTN in humans is very short. P. W. Armstrong et al. (1979) estimated it as 4.4 min after sublingual administration, whereas after intravenous infusion, a half-life of 1.9 min was found by the same group (P. W. Armstrong et al. 1980 a), and McNiff et al. (1981) reported 2.8 min. Since the apparent volume of distribution is relatively high, this implies unusually high values for total body clearance. Thus, McNiff et al. (1981) determined values of 29.8–78.3 l/min after intravenous infusion and P. W. Armstrong et al. (1979) reported 28 l/min after sublingual administration in normal subjects. In patients with congestive heart failure, somewhat lower figures were observed (P. W. Armstrong et al. 1980 a). The more advanced the venous congestion the lower the total body clearance proved to be. In the less severe cases, however, it still amounted to 13.8 ± 5.8 l/min. GTN is almost entirely cleared from the body by metabolic degradation (for older literature see Needleman 1975; Hodgson and Lee 1975).

In rats given GTN ^{14}C orally, most of the absorbed radioactivity was excreted in the expired air and in the urine. The pattern of metabolites excreted in urine showed that GTN is degraded by two pathways which seem to be common for all organic nitrates. First, the stepwise denitration to di- and mononitrates and to glycerol, which is finally oxidised to CO_2 and, second, conjugation with glucuronic acid. Since after administration of monoglycerol itself, no monoglycerol glucuronides could be detected (Hodgson et al. 1977) the monoglycerol glucuronide which is found after administration of GTN in the urine of rats must be formed by denitration of the respective dinitroglycerol glucuronides. Similar results have been reported with respect to the glucuronides of pentaerythrityl trinitrate (Melgar et al. 1974; Leinweber et al. 1974). The terminal half-lives of the dinitroglycerols (GDN) are obviously longer than that of their parent compound. In dogs, they were recently found to amount to 40.6 min for 1,2-GDN and 48.5 min for 1,3-GDN (Miyazaki et al. 1982).

It has been known for some time that the predominant site of metabolic breakdown of GTN is the liver where high concentrations of glutathione-*S*-transferase are present (see Needleman 1975). It has been shown that livers from vari-

ous species metabolised GTN in a qualitatively similar way to 1,3-GDN and 1,2-GDN, but there were some quantitative differences. Human liver showed a somewhat lower activity than, for instance, monkey, rabbit, and mouse livers and remarkably less activity than rat liver (SHORT et al. 1977). The liver exhibited the highest activity of glutathione-*S*-transferase within several organs examined, and no activity at all could be found in small intestine, lung and skin by MAIER et al. (1980). Other authors (PINKUS et al. 1977; GUTHENBERG and MANNERVIK 1979; POSADAS 1973 cited according to STEIN et al. 1980), however, were able to show glutathion-*S*-transferase activity in lung and intestinal mucosa too. Since the pharmacokinetics of GTN are characterised by remarkably high interindividual variations, MAIER et al. (1980) tried to correlate the individual in vitro activities of hepatic organic nitrate reductase to the previously determined AUC of GTN plasma concentrations and revealed a very good correlation ($r = 0.84$). This again confirms the role of the liver as the main organ for GTN metabolism.

Moreover, recent experiments in humans with impaired hepatic function have very impressively underlined the role of the liver in GTN pharmacokinetics. PORCHET and BIRCHER (1982) had determined only 2% absolute bioavailability of GTN in healthy volunteers by means of digital plethysmography. However, in seven patients with cirrhosis of the liver and after an end-to-side portocaval shunt operation, the bioavailability was increased to $94\% \pm 18\%$ and in three patients with distal splenorenal shunt to $57\% \pm 11\%$. In ten other patients with portal hypertension and spontaneous shunts, the bioavailability varied between 15% and 85% and showed a close correlation to the respective shunt volumes. In addition, the findings of P. W. ARMSTRONG et al. (1980a) that the total body clearance of GTN in patients with severe congestive right heart failure was only 3.6 ± 1.8 l/min in comparison with 13.8 l/min in less severely ill patients can be interpreted in a similar way as a haemodynamically impaired liver flow and function.

Although these experiments have most impressively underlined the role of the liver and, at the same time, indicated the difficulty of adequate GTN dosing in patients with impaired liver flow and function, they cannot explain the unusually high clearance values of GTN – far higher than the hepatic blood flow and even the cardiac output. In the search for possible pitfalls in the calculation of clearance, an incorrect determination of the infused dose could be definitely ruled out as a source of error in the paper of MCNIFF et al. (1981), as well as inconsistencies in determination of the serum concentrations. A rapid degradation of GTN in red blood cells has, however, to be considered (J. A. ARMSTRONG et al. 1980b; NOONAN and BENET 1982). J. A. ARMSTRONG et al. (1980b) reported a half-life of only 6.2 min for GTN when incubated with human blood at 37 °C. This could be ascribed to the glutathione-*S*-transferase which has been isolated from human red cells (MARCUS et al. 1978). Although of less activity than the glutathione-*S*-transferase of the liver (HABIG et al. 1976), this enzyme has a high enough capacity to metabolise the tiny amounts of GTN present in plasma. However, taking into account a blood volume of 69 ml/kg, this gives a clearance of approximately 8 ml/min^{-1} kg^{-1}, which only contributes about 1% of the total body clearance of GTN. This becomes easily understandable by considering the fact that only about 1.3% of GTN in the body is present in plasma (J. A. ARMSTRONG et al. 1980b). Thus, metabolism of GTN by red cells cannot explain the high clearance values

of GTN – provided, however, that care is taken for immediate separation of erythrocytes and plasma after drawing the blood samples. Another explanation is indicated by experiments which show a very rapid and effective accumulation of GTN in the vessels (FUNG et al. 1981b, 1984). MCNIFF et al. (1981) suggested that the vascular bed may function as a first-pass extraction tissue during intravenous infusion of GTN and suggest a "first-pass vessel uptake" as a possible cause of the high clearance values calculated. Further studies, however, are necessary to check this hypothesis.

4. Relationship Between Pharmacokinetics and Effects

Since the denitrated metabolites of GTN exhibit only a few percent of the pharmacodynamic activity of their parent compound (NEEDLEMAN 1975), it can be anticipated that at least in acute experiments a correlation between the pharmacokinetics of GTN and the elicited effect exists. Thus, P. W. ARMSTRONG et al. (1979) reported parallel changes in heart rate and systolic blood pressure after sublingual administration of 0.6 mg GTN in healthy volunteers. IMHOF et al. (1980) showed in normal volunteers after sublingual and cutaneous administra-

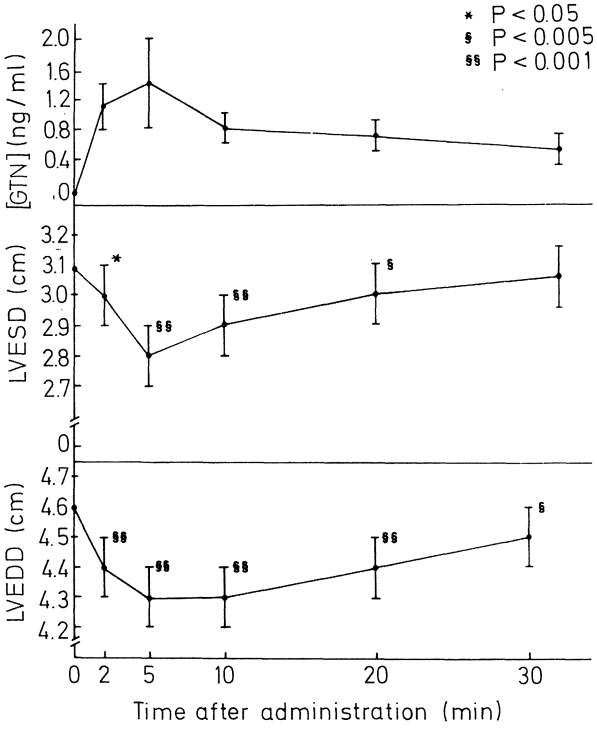

Fig. 1. Plasma GTN levels compared with echocardiographic left ventricular end-systolic (LVESD) and end-diastolic (LVEDD) dimensions. Statistical significance refers to the comparison by paired *t*-test of a value at each time point with its control. WEI and REID (1981)

tion of single doses a weak correlation between the GTN plasma concentrations and the change in the a/b quotient from digital pulse curves, which should be indicative of the action of the nitrate on the arterial bed, whereas no definite correlation could be established for venous parameters. More conclusive data have been provided by WEI and REID (1981), who showed concomitant time courses of plasma concentrations and changes in heart rate, echocardiographically measured left ventricular diastolic and systolic dimensions as well as ventricular velocity of circumferential fibre shortening and systolic blood pressure in normal volunteers (Fig. 1).

All these experiments, however, were carried out after single acute administrations in healthy volunteers. During chronic treatment, however, this convincing relationship may be interfered with by the accumulation of the dinitrates, which (although less active) exhibit a longer half-life. Furthermore, in patients with coronary artery disease or congestive heart failure, high variations in individual response to the same GTN plasma concentration (P. W. ARMSTRONG et al. 1980a, b) add to the inherently high variations in GTN plasma concentrations due to pharmacokinetic factors (IMHOF et al. 1982). From the few published data, one can only conclude that for prophylactic treatment of angina pectoris, GTN plasma concentrations less than 1 ng/ml might be sufficient for the majority of patients with stable angina (P. MÜLLER et al. 1982), whereas for acute termination of an anginal attack and for the treatment of congestive heart failure, levels that are higher, sometimes far higher than 1 ng/ml, are needed (P. W. ARMSTRONG et al. 1979, 1980a, b).

II. Isosorbide Dinitrate

1. Absorption and Bioavailability

After oral administration of isosorbide dinitrate (ISDN), complete absorption occurs from the gastrointestinal tract of experimental animals (REED et al. 1977) and of humans (DOWN et al. 1974; CHASSEAUD et al. 1975). Up to 99% of the administered radioactivity could be recovered in urine within 5 days after oral administration of ^{14}C-labelled drug to normal volunteers and only traces (0.8%) were excreted in the faeces. According to the results of NEEDLEMAN (1975), however, essentially none of the orally administered ISDN should reach the systemic circulation intact and it has been claimed that all the substance absorbed is degraded to metabolites thought to be inactive during the first passage through the liver. This complete first-pass inactivation of ISDN, as well as of a number of other organic nitrates, is thought to be the reason that, in contrast to the prompt fall of systolic blood pressure after intravenous injection, no pharmacodynamic activity at all could be seen after intraportal injection in anaesthetised rats (NEEDLEMAN et al. 1972).

However, subsequent studies by several groups (COMMARATO et al. 1973; WASTILA et al. 1976; DIETMANN et al. 1981) could not reproduce these results. Thus, a pronounced decrease of the systolic blood pressure after intraportal infusion or intraduodenal administration of GTN, ISDN and pentaerythrityl trini-

trate could be shown in anaesthetised as well as in chronically instrumented conscious dogs, cats and rats. Moreover, pharmacokinetic studies in rats (REED et al. 1977) and in humans (CHASSEAUD et al. 1975; for further references see Table 1) convincingly demonstrated that, although ISDN undergoes an intensive first-pass metabolism, considerable amounts of unchanged substance reach the systemic circulation even after oral administration. In addition, the denitrated metabolites of ISDN, which are of less absolute potency but reach higher blood levels, contribute to the pharmacodynamic activity seen after ISDN administration. Thus, it can be stated that the repeatedly claimed ineffectiveness of orally administered organic nitrates (NEEDLEMAN 1975; ARONOW 1975, 1976) has been disproved for ever. Even low oral doses of ISDN (10–20 mg) exhibit an absolute bioavailability in terms of the unchanged substance of 19%–29% according to very recent independent investigations (Table 1). The absolute bioavailability after sublingual administration amounts to about twice this percentage (30%–58.8%) but is still far from being complete (FRYDMAN et al. 1982; TAYLOR et al. 1982; ABSHAGEN et al. 1985; MORRISON et al. 1983a), suggesting that either the majority of sublingually administered drug is in reality swallowed or that ISDN undergoes presystemic degradation other than the hepatic after sublingual administration. The relative bioavailability after administration of sustained-release formulations varies considerably between formulations of different manufacturers and amounts to 20%–77% of the nonretarded oral formulations (ASSINDER et al. 1977b; GLADIGAU et al. 1981; GEIGENBERGER et al. 1982; ABSHAGEN et al. 1985). Although the extent of absorption of ISDN is incomplete owing to intensive first-pass metabolism, its absorption occurs very rapidly. Peak levels are already reached on average 30 min after oral and 15 min after sublingual administration of the conventionally formulated preparations (Table 1). After single administration of sustained-release formulations, irregular time courses of concentrations were sometimes observed (CHASSEAUD and TAYLOR 1980) and peak levels naturally occur later in these cases (Table 1).

2. Distribution

DOYLE and CHASSEAUD (1981) recently determined the volumes of distribution V_{Dss} after intravenous injection of ISDN to be 273%, 168% and 84% of the body weight of rhesus monkeys, cynomolgus monkeys and baboons, respectively. In humans, even higher apparent volumes of distribution of ISDN have been established (Table 1). Studies on the distribution of ^{14}C-labelled ISDN in rats (REED et al. 1977) showed generally higher concentrations of radioactivity in heart, lungs, kidney und liver as compared with whole blood only after oral administration, whereas after intravenous injection this applied to the heart only. In both cases, however, the drug concentration in the vasculature exceeded by far the whole blood concentration (50 and 20 times after oral and intravenous administration, respectively) which might explain the high volumes of distribution calculated. Only small amounts of ISDN are bound to plasma proteins, so that 72% $\pm$ 12% of the drug is present in unbound form in humans (FUNG et al. 1981a).

Table 1. Pharmacokinetic parameters of isosorbide dinitrate

Reference	Number	Dose (mg)	Route of administration	t_{max} (min)	c_{max} (ng/ml)	$t_{1/2}$ (min)	Total body clearance (l/min)	VD (l)	Bioavailability (%)
Frydman et al. (1982)	11	12.5	i.v.			64.8±30.5	3.8±1.48	318 ±117	
Platzer et al. (1982)	2	18							
	3	3	i.v.			67.3± 4.9	1.6±0.38	83.6± 8.4	
	4	100 s.r.	p.o.					(V_{Dss})	22 a.b.
Taylor et al. (1982)	6	10	i.v.		19.8 ± 3.8	79.0±26.0	4.1±0.7	473 ± 69	
	6	10	p.o.	34±15	7.5 ± 3.0	34.0±11.0			23 a.b.
Abshagen et al. (1985)	6	14.1	i.v.		23.42± 2.0	54.5±10.7	3.7±0.23	298.5± 73.4	
Morrison et al. (1982, 1983a, b)	11	2	i.v.	15	25.0	18.0± 7.0; 20.3	3.4±1.4	101 ± 67	
	6	5	s.l.	10		64.0			58.8
Spörl-Radun et al. (1980)	18	5	s.l.	10± 1.8	17.9 ± 3.1	28.5± 7.8			
Bogaert et al. (1981)	5	10	p.o.			22.2± 0.12			
Halkin et al. (1979)	6	20	p.o.	30	29.0 ± 8.3	25.5			
Assinder et al. (1977a)	10	5	p.o.	36	6.4	48.0			
	10	20 s.r.	p.o.	234	4.3				76 r.b.
Assinder et al. (1977b)	6	5	s.l.	15	8.9 ± 3.1	30.0			
	6	5	p.o.	30	3.1 ± 0.7	40.0			58 r.b.
	6	20 s.r.	p.o.	40	1.4 ± 1.2				47 r.b.
Chasseaud and Taylor (1980)	?	5	s.l.	30	15.9 ± 7.0	48.0			
		5	p.o.	30	5.8 ± 2.8	48.0			
		20 s.r.	p.o.	300	4.5 ± 3.3				
Taylor et al. (1980)	2	12.5	p.o.	10; 20	13.0; 27.0	25; 27			
Laufen et al. (1978)	8	5	s.l.	16	17.3	30.1			

Abbreviations: t_{max} time of maximum concentration after oral administration; c_{max} maximum concentration (the respectice data after intravenous administration are not comparable since different authors used different infusion times); $t_{1/2}$ half-life of elimination; VD distribution volume; a.b. absolute bioavailability; r.b. relative bioavailability; i.v. intravenous; p.o. oral; s.l. sublingual; s.r. sustained-release; V_{Dss} distribution volume at steady state

3. Elimination

ISDN is eliminated from plasma with a short half-life which, however, is considerably longer than the extremely short half-life of GTN. In most of the studies after oral or sublingual administration, half-lives in the range of 30 min were reported (Table 1). Only FUNG et al. (1981 a) observed in one of his normal volunteers a biphasic decline of ISDN concentrations with half-lives of approximately 1.5 and 4 h for the α- and β-phases, respectively after administration of 60 mg. Very recent investigations of the elimination rate of ISDN after intravenous infusion yielded values between 18 and 79 min (weighted mean value 51.72 min) by various independent laboratories (Table 1) which therefore can be regarded as the most reliable figures after single dosing. The latest data of FUNG and PARKER (1983) according to which ISDN should exhibit a slow terminal half-life of elimination of 7.7 ± 2.6 h after chronic oral dosing of 60 mg q.i.d., remain to be confirmed.

Although in the rhesus monkey (DOYLE and CHASSEAUD 1981) the total body clearance of ISDN equalled the hepatic blood flow, the respective data for humans clearly exceed the hepatic flow rate (Table 1). Recently, MORRISON et al. (1983 b) showed a mean hepatic extraction ratio of 0.71 in four subjects in whom ISDN concentrations could be simultaneously measured in the abdominal aorta and the hepatic veins. This fits very well to the data on absolute oral bioavailability and at the same time points to a considerable degree of extrahepatic elimination of ISDN. In this respect, metabolism by erythrocytes or other tissues and "first-vessel uptake" (MCNIFF et al. 1981) must be considered, since almost no unchanged ISDN is excreted in the urine (DOWN et al. 1974).

The metabolic degradation of ISDN by denitration and glucuronidation is similar to that of GTN. In accordance with the different affinities for organonitrate reductase (NEDDLEMAN 1975), the rate of denitration is by far the highest in the case of ISDN, followed by isosorbide-2-mononitrate (IS-2-MN) with the nitro group in the *exo* position, and lowest in the case of isosorbide-5-mononitrate (IS-5-MN), where the nitro group occupies the sterically protected *endo* position. In accordance with these in vitro activities and the preferential cleavage of the 2-*exo* nitro group, the biological half-lives increase from approximately 1 h for ISDN to approximately 2 h for IS-2-MN and to 4–5 h for IS-5-MN in humans (SPÖRL-RADUN et al. 1980; ABSHAGEN and SPÖRL-RADUN 1980; ABSHAGEN et al. 1981 a, b; BOGAERT et al. 1981; CHASSEAUD and TAYLOR 1981). Thus, IS-5-MN appears to be the main metabolite of ISDN both in experimental animals and in humans. According to studies using ^{14}C-labelled ISDN, approximately 60% of the metabolism of ISDN after oral administration proceeds via IS-5-MN, and about 25% via IS-2-MN (DOWN et al. 1974). Approximately the same percentages are obtained if one calculates the amounts which actually pass through the body during the metabolic degradation of ISDN from the areas under the concentration curves for IS-2-MN and IS-5-MN after oral or sublingual administration of ISDN and the known clearance values of these two metabolites. (ABSHAGEN et al. 1985). The 10%–20% of the dose that is missing must have been metabolised by simultaneous denitration of ISDN at the *exo* and *endo* positions to give isosorbide, since ISDN is completely absorbed and also completely metabolised at the other.

4. Relationship Between Dose and Plasma Concentrations

Several groups were able to show dose-linear kinetics for ISDN after single oral doses in the range of 15–120 mg (TAYLOR et al. 1978; BOGAERT and ROSSEEL 1980; FUNG et al. 1981 a). Considerable interindividual differences in plasma concentrations were unanimously reported during these and other pharmacokinetic studies with ISDN so that the coefficients of variation for the mean concentrations range from 39% to 76% (ASSINDER et al. 1977 a, b; SHANE et al. 1978; MANSEL-JONES et al. 1978; CHASSEAUD and TAYLOR 1980; FRYDMAN et al. 1982). Moreover, whereas dose-linear kinetics apply for single doses of ISDN this seems not to be the case during long-term treatment. The first indications of a deviation from linear kinetics after multiple dosing were given by SHANE et al. (1978) who observed after chronic high oral dosages (up to a total of 720 mg ISDN q. i. d.) unexpectedly high plasma levels of ISDN, which in some cases persisted till the next dose 6 h later. FUNG et al. (1981 a) showed in a carefully conducted study in 12 patients with coronary artery disease a clear deviation from dose linearity on chronic treatment with doses higher than 15 mg ISDN q. i. d. In a similar way, BRUYNEEL et al. (1982) reported a gradual increase of ISDN and IS-5-MN concentrations during a 19-day treatment with either 5 or 20 and 40 mg ISDN t. i. d. This deviation from linearity during multiple dosing might be due to a possible product inhibition of the ISDN disposition by the generated mononitrates, in particular IS-5-MN (MORRISON et al., 1983 b). On the other hand, SCHNEIDER et al. (1982) have recently demonstrated dose-linear behaviour of the concentrations of ISDN and its mononitrates in plasma of patients who had been treated with 5, 20, 40, and 80 mg every 4 h for 7 days. However, since the concentrations were measured only 1 and 4 h after the last administration on the 7th day and thus cannot be compared with the conditions after the first administration, these results cannot rule out deviation from linearity under chronic treatment.

5. Relationship Between Pharmacokinetics and Effects

SPÖRL-RADUN et al. (1980) were not able to correlate the effects of sublingual ISDN on the finger volume pulse with either the time course of the unchanged ISDN or that of the pharmacologically active moiety as generated by a superposition of the weighted curves of ISDN, IS-2-MN and IS-5-MN. However, JOHNSON et al. (1981) reported a satisfactory correlation in the same experimental procedure using weighting factors for pharmacological activity of 1:0.1:0.025 for ISDN:IS-2-MN:IS-5-MN. In patients with coronary artery disease, THADANI et al. (1980 a–c) found that although peak response and maximum drug concentration in plasma usually occurred at the same time, the rate of decline of ISDN concentrations was more rapid than those exhibited by the pharmacological effects. FUNG et al. (1981 a) could only establish a weak correlation ($r = 0.42$) when the logarithms of the doses were correlated with the AUC of changes in heart rate or standing systolic blood pressure in patients with stable angina. Most interestingly, however, is their observation during a double-blind, placebo-controlled, crossover study that those patients who exhibited serious adverse reactions, such as severe hypotension during dose titration, exhibited clearance values for ISDN that were only half the respective values of the other patients who tolerated ISDN

well. These data suggest that adverse reactions to ISDN may be related to a decreased metabolic capacity of the individuals concerned. Recently, SCHNEIDER et al. (1982) reported fairly good correlations between the daily dosage of orally administered ISDN (30–480 mg) and the reduction of exercise-induced ST depressions in patients with coronary artery disease. Thus, the results concerning dose-response relationships are at present controversial for ISDN.

III. Isosorbide-5-mononitrate

Because of the preferential cleavage of the 2-*exo* positioned nitro group of ISDN, IS-5-MN represents the main metabolite of ISDN (see Sect. B. II. 3). The pharmacological activity, however, diminishes in the same order as the denitration rate from ISDN via IS-2-MN to IS-5-MN. According to perfusion experiments by BOGAERT and ROSSEEL (1972) on isolated perfused canine femoral arteries, the potency of IS-5-MN should be only 1/60 of that of ISDN. Similar experiments in isolated perfused left coronary arteries gave a relative potency of 1/10 (WENDT 1972). It was probably because of these results that IS-5-MN was not considered for some years to be suitable for therapy, although its principal nitrate pharmacodynamics had already been shown in patients with coronary artery disease after intravenous injection by STAUCH et al. (1975) and MICHEL (1976). Reevaluation of the relative potency of IS-5-MN in chronically instrumented conscious dogs, however, showed a higher potency in an experimental setting, which is without doubt more relevant to the therapeutic situation than experiments on isolated perfused vessels (DIETMANN et al. 1981). These findings, together with the hypothesis that the first-pass metabolism of ISDN, IS-2-MN and IS-5-MN would decrease in the sequence of the respective denitration rates and consequently be least in the case of IS-5-MN, prompted detailed pharmacokinetic studies of IS-5-MN.

1. Absorption

In contrast to ISDN, the pharmacodynamic activity of IS-5-MN given either orally or by intraportal infusion was the same as that found after intravenous infusion of identical dose levels in chronically instrumented dogs. In accordance with these findings, the pharmacokinetically determined biovailability of IS-5-MN proved to be about 100% in these animals (DIETMANN et al. 1981). This applies to humans as well (ABSHAGEN and SPÖRL-RADUN 1980; ABSHAGEN et al. 1981 a; TAYLOR et al. 1981). Thus, IS-5-MN is at present the only therapeutically used organic nitrate which is not subject to any first-pass metabolism and therefore exhibits complete bioavailability after oral administration. In addition, the absorption from the gastrointestinal tract takes place rapidly and maximum concentrations are reached within 1 h of oral administration (ABSHAGEN and SPÖRL-RADUN 1981; ABSHAGEN et al. 1981 a, b).

2. Distribution

Because of its markedly higher polarity in comparison with ISDN, IS-5-MN distributes within a considerably smaller apparent volume of distribution, which is in the range of total body water. Distribution coefficients of about 0.6 l/kg have

been more or less uniformly found by independent groups in human volunteers (ABSHAGEN et al. 1981 a; TAYLOR et al. 1981). Binding to plasma proteins is negligible (U. ABSHAGEN 1982 unpublished work).

3. Elimination

The elimination half-life of IS-5-MN after a single oral and intravenous administration is in the range of 4–5 h in healthy young subjects (ABSHAGEN et al. 1981 a; ABSHAGEN and SPÖRL-RADUN 1981; BOGAERT et al. 1981; TAYLOR et al. 1981). In patients with advanced renal failure, the half-life averaged 4.95 ± 0.4 h after a single oral administration (KÖSTERS et al. 1981). MANNEBACH et al. (1981) determined the pharmacokinetics of IS-5-MN in patients with coronary artery disease at steady state using a t.i.d. regimen. Although the elimination half-life of IS-5-MN from serum was slightly longer (5.69 ± 0.2 h) than that reported after a single administration in healthy young volunteers, the AUC within one dosage interval at steady state did not differ from the corresponding total AUC after a single dose in healthy subjects. The total body clearance of IS-5-MN was therefore the same in patients with a mean age of 52.6 years after multiple dosing as after a single administration in young volunteers, which has been reported to amount to 115 ± 6.4 ml/min (ABSHAGEN et al. 1981 a) or 132 ml/min (18% coefficient of variation) (TAYLOR et al. 1981). Straight dose-linear kinetics of IS-5-MN were also demonstrated by experiments using single oral doses in the range 5–80 mg in healthy young volunteers, as well as in patients with ischaemic heart disease (ABSHAGEN and SPÖRL-RADUN 1981; REIFART et al. 1981 b; BÖDIGHEIMER et al. 1981).

In accordance with the rapid and complete absorption without any first-pass metabolism, considerable lower coefficients of variation of the pharmacokinetic parameters have been observed after administration of IS-5-MN in comparison with the respective data after ISDN administration. Coefficients of variation of mean concentrations in serum, or of related parameters, amounted to not more than 18% (TAYLOR et al. 1981), 19% (MANNEBACH et al. 1981) or 25% (ABSHAGEN et al. 1981 a) after administration of IS-5-MN, whereas up to 62% was found in the case of ISDN (TAYLOR et al. 1981) and 39%–76% in another study (CHASSEAUD and TAYLOR 1980). IS-5-MN is cleared from the body almost exclusively by metabolism, since only traces of unchanged IS-5-MN were excreted in the urine. Up to 20% of the administered dose is conjugated with glucuronic acid, whereas the remainder is slowly denitrated to isosorbide, which forms the main metabolic end product and which is further metabolised to a lesser degree to sorbitol (ABSHAGEN et al. 1985). Since IS-5-MN is only partially denitrated at a far slower rate than ISDN during its metabolic breakdown, free reactive nitrite ions are generated at a rate that is less than 1/10 of that observed after ISDN. The toxicological differences between ISDN and IS-5-MN can be explained by these different rates of nitrite ion formation (STREIN et al. 1982, 1984). This might be of clinical relevance in those rare cases where, under high doses of organic nitrates and an underlying genetic or acquired enzyme deficiency of red cells, severe methaemoglobinaemia and even toxic haemolytic anaemia can occur (FIBUCH et al. 1979; HORNE et al. 1979; MARSHALL and ECKLUND 1980; ROMERIL and CON-

CANNON 1981; SHESSER et al. 1980; STEINER and MANOGUERRA 1980; GIBSON et al. 1982; ARSURA et al. 1982). This danger should be far less in the case of IS-5-MN because of the aforementioned metabolic differences.

4. Relationship Between Pharmacokinetics and Effects

Since, in contrast to other organic nitrates, only one pharmacodynamically active substance is present in the body after administration of IS-5-MN, a good correlation between pharmacokinetics and effects can be anticipated. Accordingly, DIETMANN et al. (1981) and SPONER et al. (1984b) showed a nice correlation between the maximum decrease of systolic blood pressure and the logarithm of the maximum concentration of IS-5-MN in serum of chronically instrumented conscious dogs. The threshold concentration of 90 ng/ml determined in dogs was, interestingly, in the same range as that estimated in normal volunteers for an alteration of the digital volume pulse (ABSHAGEN and SPÖRL-RADUN 1981). In patients with ischaemic heart disease, REIFART et al. (1981 b) were able to establish a good correlation of the time course of the IS-5-MN concentrations in serum and the simultaneously measured drug-induced changes in pulmonary capillary wedge pressure (Fig. 2). Similar results were obtained by BÖDIGHEIMER et al. (1981) for several parameters of central and peripheral haemodynamics and the respective serum concentrations of IS-5-MN in patients suffering from congestive heart failure. Thus, a clear correlation between the orally administered dose and both the resulting concentrations in serum and the pharmacodynamic activity can be taken for granted in the case of IS-5-MN.

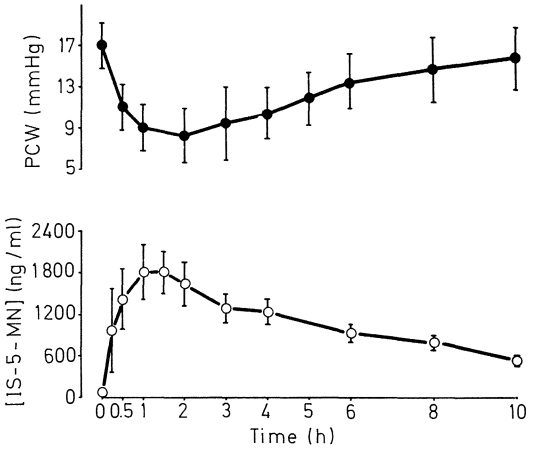

Fig. 2. Kinetics of drug action – decrease of pulmonary capillary wedge pressure (PCW) – and kinetics of serum concentrations of IS-5-MN after oral administration of 80 mg IS-5-MN to patients with acute myocardial infarction. Mean ± standard error. REIFART et al. (1981 b)

IV. Pentaerythrityl Tetranitrate

Pentaerythrityl tetranitrate (PETN) is a highly lipophilic, almost water-insoluble organic nitrate. Because of this physicochemical property, its absorption from the gastrointestinal tract is rather slow and incomplete. After oral administration of 20 mg PETN ^{14}C, 60.3% ± 3.6% of the dose could be recovered in the urine of ten test subjects within 48 h and 31.5% ± 4.8% in the faeces (72 h). Whereas no intact PETN could be detected in serum or urine, up to 31% of the faecally excreted radioactivity consisted of unchanged PETN (DAVIDSON et al. 1970). This can be taken as evidence of an incomplete absorption of this organic nitrate. In addition, since after oral administration of pentaerythrityl trinitrate (PETriN), which undergoes the same metabolic breakdown as PETN once the first nitro group of the latter is removed, only 2% of the administered dose is excreted in faeces (DAVIDSON et al. 1971 a), the conclusion seems justified that almost all of the radioactivity found in faeces after oral administration of PETN represents nonabsorbed drug. Thus PETN seems to be absorbed by only 50%–60% and maximum concentrations in plasma are reached 4–6 h after oral administration (DAVIDSON et al. 1971 b).

The elimination of PETN from plasma occurs exclusively by metabolism since no intact PETN is found in urine. As in the case of the other organic nitrates, the metabolic disposal occurs via stepwise denitration and glucuronidation. The rate of denitration is obviously highest in the case of PETN and PETriN, which could not be detected in plasma or urine within the limits of the bioanalytical method (DAVIDSON et al. 1970, 1971 a, b). Whereas the concentrations of pentaerythritol are twice as high as those of pentaerythrityl mononitrate in serum, approximately the same amount of pentaerythrityl mononitrate (52%-53%) is present in the 48-h urine as compared with pentaerythritol (47%–49%) after oral administration of 20 mg PETN. After administration of 40 mg, as much as three times higher amounts of pentaerythrityl mononitrate than of pentaerythritol are found in urine. Thus, the renal clearance of pentaerythrityl mononitrate is obviously higher than that of pentaerythritol. In addition, the denitration capacity of humans seems to be limited, since doubling the dose leads to a decrease in the excretion of pentaerythritol and a corresponding increase in pentaerithritol mononitrate. Only traces of pentaerythrityl dinitrate could be detected in serum and urine. The half-lives of the urinary excretion rate of total radioactivity as well as of pentaerythritol and pentaerythrityl mononitrate were in the range of 7–10 h (DAVIDSON et al. 1971 a).

Recently, HANNEMANN et al. (1981) investigated the bioavailability of 10 mg PETN given sublingually, orally or as chewable tablets in comparison with 0.3 mg sublingual GTN in a randomised, placebo-controlled, crossover trial by means of digital plethysmography. Maximum response occurred 6 min after sublingual GTN, but 12 min after chewable PETN, 18 min after sublingual and 13 min after oral PETN. Whereas this rapid onset and early peak response might be ascribed to the short-lived PETN and PETriN, the proven duration of action of 120 min after sublingual and 360 min (HANNEMANN et al. 1981) or 240 min (DE-LAPAZ et al. 1979) after oral administration might be due to the pentaerythrityl mononitrate or (more likely) to a reconversion of glucuronides into the respective

active nitrate, in particular PETriN in peripheral tissues as suggested by DiCarlo et al. (1977).

V. Pentaerythrityl Trinitrate

Since PETtriN has a higher coronary vasodilator activity than PETN when tested after intrajugular administration in anaesthetised dogs, PETN can be regarded as a prodrug of the intrinsically active moiety PETriN (Parker et al. 1975). Removal of one nitro group of PETN increases the water solubility of the resulting molecule. Consequently, PETriN shows a considerably enhanced absorption from the gastrointestinal tract. After oral administration of PETriN ^{14}C, 92% of the administered radioactivity could be found in urine within 48 h and only 2% in faeces, thus showing complete absorption (Davidson et al. 1971 a; DiCarlo et al. 1977). Maximum concentrations of total radioactivity in the plasma were reached within 1 h. PETriN disappeared rapidly with a half-life of 10 min and could not be detected in the plasma after 2 h. The drug, however, was excreted in urine in small quantities up to 48 h with an estimated terminal half-life of 11.4 h. This observation, together with the duration of action which exceeds by far the presence of PETriN in plasma, leads to the hypothesis that the slowly eliminated glucuronide of PETriN might be reconverted to the pharmacologically active free nitrate in peripheral tissues and/or via enterohepatic recirculation (Crew et al. 1975), thus acting as a reservoir of active substance which could explain the long duration of drug activity (DiCarlo et al. 1977).

In urine, pentaerythrityl mononitrate contributed $53.04\% \pm 2.4\%$ of the excreted radioactivity, whereas $14.29\% \pm 1.13\%$ was attributable to pentaerythritol, 0.91% to pentaerythrityl dinitrate and only 0.081% to PETriN. Nearly 23% of the dose was excreted as glucuronides – 8.4% as the PETriN glucuronide and 12.6% as the glucuronide of pentaerythrityl dinitrate (DiCarlo et al. 1977). Thus the metabolism of PETriN is similar to that of PETN. No significant differences in the metabolic pattern could be observed after oral and sublingual administration of PETriN (Davidson et al. 1971 a). This need not to be due to a negligible hepatic first-pass metabolism of PETriN, but is most probably due to the fact that the drug is scarcely absorbed from the oral mucosa and is absorbed only after having been swallowed. The fact that maximum concentrations in plasma were reached only 78 min after sublingual, but as early as 34 min after oral administration is support for this assumption. On the whole, PETriN can be regarded as the active moiety of PETN, differing from the latter in its better absorption.

C. Mechanism of Action at the Molecular Level

I. Influence on Electrolytes

The role of free cytoplasmic calcium as a regulator of smooth muscle tension and contraction can be regarded as generally accepted. It therefore seems reasonable to suggest that free cytoplasmic calcium might also act as the terminal effector of the relaxant activity of organic nitrates on smooth muscle. In fact, Fleckenstein et al. (1975) claimed that GTN should exert its vasodilating action by inhib-

iting calcium influx, since they observed a partial recovery of contractile tension in GTN-relaxed strips when the external calcium concentration was increased. In a similar way, KREYE et al. (1975) showed that sodium nitroprusside (SNP) inhibited the contractile response of calcium-depleted depolarised rat aorta to extracellular calcium. In addition, SNP inhibited the increment in ^{45}Ca uptake of rabbit aorta elicited by potassium in a manner comparable to that of the calcium channel blocker verapamil. The findings of BIAMINO and NÖRING (1977) provided further evidence for the hypothesis of calcium influx inhibition. These authors reported nearly identical effects of GTN, ISDN and SNP on helical strips of rat aorta in comparison with verapamil. The nitro compounds relaxed strips depolarised with potassium chloride (30 m*M*) in a concentration-dependent manner, which indicates an inhibition of calcium influx. In addition, the decrease in tension induced seemed to be due to a fall in the frequency of the spontaneous potentials and a deterioration of the conductance, whereas the amplitude of the induced contractions increased. This decrease of spontaneous activity can, however, be interpreted as a further indicator of a calcium influx blocking activity of the nitro compounds investigated. Another piece of evidence was provided by HARDER et al. (1979) who showed that GTN completely blocked the calcium current that had been induced with tetraethylammonium on electrical stimulation of dog coronary arteries.

In spite of these suggestive experimental results, there has accumulated in recent years a considerable body of evidence that the action of nitro compounds on calcium movements differs from the mode of action of the other calcium channel blockers such as nifedipine or verapamil. Thus, experiments of KREYE et al. (1975) had already shown that SNP reduces the rapid contraction phase in response to noradrenaline after calcium influx into rabbit aorta had been prevented by pretreatment with lanthanum. This result can be interpreted as an inhibition of intracellular activation of calcium by SNP rather than inhibition of calcium influx. Subsequent observations of KREYE and LÜTH (1976), FERMUM et al. (1976) and HÄUSLER and THORENS (1976) showed that SNP obviously has no effect on the transmembrane flux of calcium. MIKKELSEN et al. (1978) studied the effects of verapamil and GTN on contractile responses to potassium and noradrenaline in isolated human peripheral veins. In contrast to verapamil, GTN induced a further decrease in the response to noradrenaline when the response had already been decreased with a calcium-free medium. In addition, the contractile responses to both potassium and noradrenaline were restored almost to normal by increasing the external calcium concentration from 0 to 4 m*M* despite the presence of GTN. In contrast, verapamil effectively antagonised the contraction-inducing effect of increasing external calcium concentrations. Such differences in behaviour of verapamil and GTN towards changes in external calcium were also seen by GAGNON et al. (1980) in strips of rabbit renal artery moderately contracted with noradrenaline.

Similar observations were made by GROSS et al. (1981) who reported that, in contrast to nifedipine and another dihydropyridine calcium antagonist (FR 7534), GTN elicited no reversal of the effect induced by raising external calcium in potassium-depolarised canine, bovine and porcine large coronary arteries. Furthermore, the GTN-induced relaxation of potassium-depolarised strips

differed from that induced by the other calcium antagonists with respect to extent and kinetics. Further evidence that the vasodilating activity of organic nitrates cannot be ascribed – or at least not exclusively – to an inhibition of calcium influx, stems from experiments by KARASHIMA (1980) and ITO et al. (1980). KARASHIMA (1980) showed that GTN consistently suppressed mechanical activities in the portal veins of rats as well as of guinea-pigs. Whereas GTN induced in strips from guinea-pigs a short transient hyperpolarisation followed by depolarisation, the drug had no effect at all on the membrane activity of the rat portal vein. In particular, GTN did not suppress the spontaneous activity and phasic contraction of rat portal vein, as it did in guinea-pigs during the transient phase of hyperpolarisation. But even in guinea-pigs the membrane activity was consistently increased and the mechanical activity was suppressed during the following phase of depolarisation. Since the spontaneous activities and phasic contractions of veins are thought to be due to calcium influx, the relaxant action of GTN cannot be solely the result of an inhibition of calcium influx. ITO et al. (1980) demonstrated that GTN (2.8×10^{-10}–$10^{-8} M$) did not modify the membrane properties of porcine coronary smooth muscle cells, although the mechanical response was suppressed. From interaction experiments with acetylcholine, KCl, Ca and GTN they concluded that GTN produces a nonselective suppression of the calcium mobilisation from intracellular stores rather than an inhibition of calcium influx. The same conclusion was drawn by IMAI and KITAGAWA (1981) from a comparison of the differential effects of GTN, nifedipine and papaverine on lanthanum-induced contractures in coronary and intestinal smooth muscle.

Another possible effect of nitro compounds on calcium balance has been indicated by experiments of ZSOTER et al. (1977) who reported that SNP promoted ^{45}Ca efflux in rabbit mesenteric vein and in rat aorta in a concentration-dependent manner. Finally, organic nitrates may exert an indirect influence on other ionic movements across the cell membrane and within the cell by stimulation of the chloride efflux leading to a hyperpolarisation, as has been shown for SPN and GTN in rabbit aortal strips (KREYE et al. 1977; KREYE 1978, 1981).

On the whole, it seems to be obvious that organic nitrates elicit their pharmacological effects by interfering either directly or indirectly with influx, primarily, however, with intracellular binding or efflux of calcium in vascular smooth muscle. Although at present the precise mechanism of action cannot be given and needs further elucidation, the molecular mode of action of organic nitrates seems to differ in many respects from that of the calcium channel blockers.

II. Influence on Cyclic Nucleotides

Whereas the terminal step by which smooth muscle relaxation is brought about by organic nitrates still remains to be elucidated, more agreement prevails about the penultimate step of organic nitrate action. This is ascribed to an increase in intracellular cyclic guanosine monophosphate (cGMP) with subsequent activation of a GMP-dependent protein kinase, which in some way interferes with Ca^{2+} metabolism. Although some years ago cGMP was regarded as being involved in smooth muscle contraction (DUNHAM et al. 1974) and as acting as a comediator with calcium to promote contraction (ANDERSSON et al. 1975), there has accumu-

lated an overwhelming body of experimental evidence which argues against this original concept. The hypothesis of K.-D. SCHULTZ et al. (1977) and KATSUKI et al. (1977b) that the increase in cGMP seen concomitantly with ACh-induced smooth muscle contraction represents a negative feedback signal to limit or reverse the contractile effects of ACh in smooth muscle has been confirmed very recently by conclusive experiments by KUKOVETZ et al. (1982). It thus seems generally accepted at present that cGMP is an essential mediator of smooth muscle relaxation. The concept that organic nitrates exert their vasodilating action by increasing smooth muscle cGMP stems from the following experimental evidence.

1. A broad spectrum of different nitro compounds: GTN, glyceryl dinitrate (GDN), ethyleneglycol dinitrate (EGDN), ISDN, PETN, SNP, $NaNO_2$, relaxed in a concentration-dependent manner vascular smooth muscle or smooth muscle of other tissues in close association with pronounced increases of cGMP levels (KATSUKI et al. 1977a, b; KUKOVETZ et al. 1979; JANIS and DIAMOND 1979; C. A. GRUETTER et al. 1981a, b,; AXELSSON et al. 1979, 1981). For example, KUKOVETZ et al. (1979) found a statistically highly significant positive correlation between the logarithm of the increase of cGMP and the percentage relaxation induced by nitro compounds. The ED_{50} for the relaxant effect of GTN was in the range of $2.7 \times 10^{-8} M$ (AXELSSON et al. 1979) and $4.4 \times 10^{-8} M$ (KUKOVETZ et al. 1979), which is in the range of therapeutic concentrations. This correlation between the physiological response to organic nitrates and the simultaneously determined cGMP content of the target organ could also be established in vivo. KOBAYASHI and OGAWA (1979) and KOBAYASHI et al. (1980) were able to demonstrate a significant correlation between the increase in coronary blood flow induced by intravenous injection of 0.02 μg/kg) GTN in anaesthetised dogs and the increase of cGMP concentration in the coronary artery, the cyclic nucleotide content of which was preserved by rapid heat inactivation using microwave irradition. In contrast to cGMP, the cAMP content was not affected by organic nitrates, neither in vitro nor in vivo.

2. The nitrate-induced increases in cGMP content clearly precede the mechanical response. Thus, the cGMP content was already significantly increased 30–60 s after addition of the respective nitro compounds, whereas relaxation just began to develop (KUKOVETZ et al. 1979, 1982; AXELSSON et al. 1979; Keith et al. 1982).

3. Inhibition of the activation of coronary arterial guanylate cyclase by methylene blue at a concentration which itself did not alter arterial tone abolished both the increase in cGMP content and the relaxation induced by GTN, amyl nitrite and $NaNO_2$ (C. A. GRUETTER et al. 1981b). This action of methylene blue, which is supposed to be due to its electrophilic properties leading to competition with the enzyme for electrons necessary for activation, seems to be highly specific. Thus, methylene blue did not inhibit relaxation of the strips due to noradrenaline, which is believed to be mediated by an increase of cAMP.

4. The relaxant effects of GTN, SNP and $NaNO_2$ were significantly potentiated by a selective inhibition of cGMP hydrolysis showing hyperadditive synergism. Thus, the concentration response curves of GTN and SNP were markedly shifted to the left under the influence of the azapurinone derivative M & B 22.948

at a concentration that increased cGMP in coronary arteries 2.8-fold, while cAMP was not affected (KUKOVETZ et al. 1979).

5. Exogenously applied cGMP was able to relax bovine coronary arteries, although relatively high concentrations were needed (10^{-4}–10^{-2} *M*). The more lipophilic derivative 8-Br-cGMP, which probably penetrates the cells more easily, however, was much more effective in causing relaxation of the strips and thus to mimic the action of organic nitrates. As with the latter compounds, its activity could by potentiated by selective phosphodiesterase inhibition (KUKOVETZ et al. 1979). Similar results were obtained with cGMP and analogues by NAPOLI et al. (1980) and G. SCHULTZ et al. (1978).

On the whole, there seems to be convincing pharmacological evidence that organic nitrates and nitrites bring about their vasodilating action by increasing smooth muscle cGMP content. This increase is the result of an activation of guanylate cyclase by nitro compounds and therefore of an enhanced cGMP formation. Whereas GTN, NaN_3, SNP and hydroxylamine directly increased guanylate cylcase activity in crude preparations of particulate and/or soluble preparations of various tissues (BÖHME et al. 1978; KATZUKI et al. 1977 a), this did not apply in the same way to partially purified enzyme preparations. In the case of GTN, enzyme activation occurred only in the presence of added cysteine (IGNARRO and GRUETTER 1980; C. A. GRUETTER et al. 1981 a, b; D. Y. GRUETTER et al. 1980) and the activation of guanylate cyclase by nitric oxide (NO), $NaNO_2$, amyl nitrite and SNP was markedly enhanced by addition of thiols (C. A. GRUETTER et al. 1979, 1980 b, 1981 b). Further experiments revealed that organic nitrates obviously do not directly activate guanylate cyclase, but release NO by an intermediate reaction which subsequently reacts with a variety of thiols to form unstable, *S*-nitrosothiols, which finally are thought to act as potent activators of guanylate cyclase (IGNARRO and GRUETTER 1980; IGNARRO et al. 1980 a, b, 1981 a, b; C. A. GRUETTER et al. 1980 a, 1981 a). Experimental evidence to support this hypothesis of active, unstable nitrosothiols as essential mediators of nitrate-induced smooth muscle relaxation via an activation of guanylate cyclase has been accumulated by IGNARRO et al. (1981 c). These authors showed that:

1. The activation of partially purified coronary arterial guanylate cyclase by GTN, ISDN, PETN, $NaNO_2$, amyl nitrite and SNP required the addition of cysteine or other triols.

2. The vasodilators reacted with cysteine to form *S*-nitrosocysteine.

3. *S*-Nitrosocysteine and other *S*-nitrosothiols activated guanylate cyclase, increased tissue cGMP levels and relaxed coronary arterial strips without further additions.

4. Methylene blue, which is known to inhibit both nitrate-induced cGMP elevation and smooth muscle relaxation C. A. GRUETTER et al. 1981 b), inhibited in the same way the activation of guanylate cyclase by *S*-nitrosothiols.

5. Intravenous administration of four different *S*-nitrosothiols in a wide range of doses decreased systemic arterial pressure in anaesthetised cats.

6. The respective dose-response curves for the four nitrosothiols paralleled each other and those of GTN and SNP.

7. Both the quality and time course of haemodynamic changes elicited by intravenous injection of *S*-nitrosothiols closely resembled that observed after intravenous injection of GTN or SNP.

8. The hypotensive effect of *S*-nitrosothiols, SNP and GTN was in no case affected by pretreatment with propranolol.

The mechanism by which cGMP is activated obviously involves oxidation of haeme, which serves as the prosthetic group of the enzyme (CRAVEN and DERUBERTIS 1978; GERZER et al. 1981, 1982). Thus a paramagnetic nitrosyl-haeme complex plays a key role in the nitrate-induced activation of cGMP. This hypothesis has been confirmed by conclusive experiments by OHLSTEIN et al. (1982) on haemodeficient soluble guanylate cyclase.

1. Concept of Organic Nitrates Vasodilating Mechanism of Action

Whereas the final mechanism of guanylate cyclase activation, i.e. the formation of the highly reactive, unstable *S*-nitrosothiols from NO and tissue thiols is common for SNP, amyl nitrite, $NaNO_2$ and the other organic nitrates like GTN, ISDN or PETN, there are differences in the formation of NO among these substances. Whereas the former group spontaneously releases NO at neutral or slightly acidic pH, the latter group does not. Thus organic nitrates are thought to react first with tissue SH groups, such as cysteine, to form NO_2, which subsequently reacts with H^+ to form NO. This concept is now compatible with the original hypothesis of NEEDLEMAN et al. (1973) that organic nitrates act first through a "nitrate-specific receptor" which is characterised by SH groups and subsequently via a "common intermediate vasodilator site" which also requires SH groups. In accordance with the earlier suggestion of NEEDLEMAN and JOHNSON (1973), the nitrate-specific receptor should possess sulphydryl-containing molecules and should be responsible for NO_2^- formation from organic nitrates according to the equation

$$RONO_2 + 2\,R'SH \rightarrow R'\text{–}SS\text{–}R' + R\text{–}OH + NO_2^- + H^+.$$

In the light of recent experimental evidence the common intermediate vasodilator site seems to be the subsequent reaction of nitric oxide formed via nitrous acid with tissue thiols to form the active *S*-nitrosothiols which activate guanylate cyclase. Thus, the following schematic diagram of proposed mechanisms by which nitrogen oxide-containing vasodilators relax vascular smooth muscle can be given (Fig. 3).

According to this theory, organic nitrates have to be denitrated within the smooth muscle cell in order to elicit their relaxant activity. However, ARMSTRONG et al. (1980a) were unable to detect denitrated metabolites in the incubation medium after maximum GTN-induced relaxation of isolated canine veins and arteries using a highly sensitive GC-EC assay. Since denitration occurs within the cell and the metabolites formed are more polar than their parent compound, their rediffusion into the incubation medium might have been impaired. In fact FUNG et al. (1984) showed very recently uptake of organic nitrates into vascular smooth

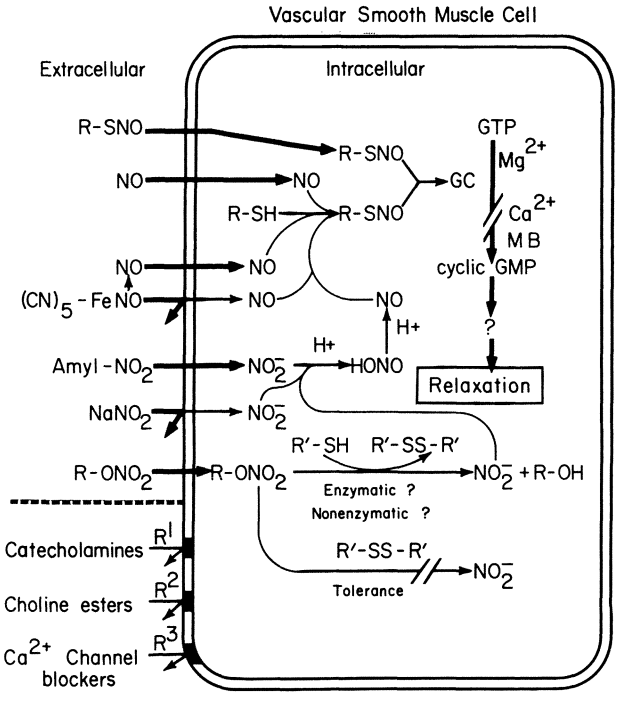

Fig. 3. Schematic diagram of proposed mechanisms by which nitrogen oxide-containing vasodilators relax vascular smooth muscle. Abbreviations: *R–SNO*, *S*-nitrosothiol; *NO*, nitric oxide; *HONO*, nitrous acid; $(CN)_5$–*FeNO*, nitroprusside; R–ONO_2, organic nitrate; *R–OH*, denitrated organic nitrate; *R–SH*, low or high molecular weight thiol; *R'–SH*, thiol that is distinct from *R–SH*; *GC*, guanylate cyclase; *MB*, methylene blue; R^1, R^2, R^3, extracellular specific receptors. IGNARRO et al. (1981 c)

muscle with subsequent vascular metabolism as the presumed prerequisite of the postulated mechanism of action of nitrates.

2. Concept of the Mechanism of Nitrate Tolerance

In the same way this concept sheds light on the problem of nitrate tolerance. According to the original proposal by NEEDLEMAN and JOHNSON (1973), nitrate tolerance is thought to stem from oxidation of critical sulphydryl groups in the nitrate-specific receptor with subsequent formation of disulphide bridges. This is accompanied by a loss, or at least a considerable decrease, of affinity for the drug. This hypothesis has been validated by a reversal of both in vitro and in vivo induced tolerance of arterial strips towards organic nitrates by addition of the disulphide reducing agent dithiothreitol, as well as by the pH dependence of the disulphide formation, which correlated with the respective development of tolerance. The current concept the molecular mechanism of action of organic nitrates makes it easy to understand why organic nitrates are able to induce cross-tolerance among themselves, but not to inorganic nitrite or SNP (NEEDLEMAN and JOHNSON 1973; KEITH et al. 1982). Whereas organic nitrates require first the reac-

tion with the specific receptor to form NO_2 this does not apply to $NaNO_2$ and SNP. Thus $NaNO_2$, amyl nitrite and SNP bypass the reaction that gives rise to the development of tolerance when the availability of reactive SH groups drops below a critical point. At the same time it becomes obvious that the development of tolerance towards organic nitrates must be dependent on the dose and the dosing interval, which govern the actual concentration at the specific receptor site and thus the availability of free, reactive SH groups.

Finally, results on nitrate tolerance by KEITH et al. (1982) confirmed and extended the hypothesis of the mechanism described of vasodilation mediated by cGMP. The occurrence of an in vitro induced tolerance towards GTN in helical rat aortic strips was accompanied by an inability to generate cGMP. The same applied to vascular tissue derived from animals made GTN tolerant in vivo. In a similar way, inhibition of GTN or SNP relaxation by methylene blue corresponded to an impaired cGMP formation. On the other hand, 8-Br-cGMP relaxed vascular smooth muscle irrespective of whether it had been previously made GTN tolerant or pretreated with methylene blue. This suggests that the subsequent action of cGMP, once formed, is not impaired by these manoeuvres. The results of KEITH et al. (1982), which were confirmed independently by similar results of AXELSSON et al. (1982), strongly support the concept presented that cGMP generation is causally involved in the molecular mechanism of action of nitro compounds. Contrary results of BRAUGHLER (1981), showing a lack of correspondence between tolerance and the inability to generate cGMP, are probably due to methodological inadequacies.

III. Influence on Prostaglandin Metabolism

It has recently been claimed that the antianginal efficacy of organic nitrates might be due to their ability to shift the prostaglandin endoperoxide metabolism from the thromboxane site to that of prostacyclin (PGI_2). The typical vasodilating activity of organic nitrates could be explained by this mechanism in addition to an inhibition of platelet aggregation, which should be beneficial, considering the pathogenetic role of platelets in myocardial ischaemia (SCHAFER and HANDIN 1979).

1. In Vitro Studies

Experiments by SCHAFER et al. (1980) proved that GTN, ISDN and $NaNO_2$ inhibited platelet aggregation induced by collagen, adrenaline, arachidonate, ionophore and ADP. The effect of GTN, which was studied in detail, was reversible and not dependent on external calcium concentration. However, the concentrations of organic nitrates needed for platelet inhibition were several orders of magnitude higher (80–800 μM GTN; 8 mM ISDN) than those attainable under therapeutic conditions. This direct action of organic nitrates on platelet aggregation is therefore certainly of no relevance to the therapeutic action of these drugs.

Nevertheless, LEVIN et al. (1981) and SCHRÖR et al. (1981 a) showed independently that GTN in nanomolar concentrations (therapeutic range) stimulated PGI_2 synthesis in human endothelial cells and in bovine coronary arteries and thus indirectly inhibited platelet aggregation by this mechanism. The stimulation

of PGI_2 synthesis could be prevented in a typical manner by several inhibitors of cyclooxygenase or prostacyclin synthetase. In addition, SCHRÖR demonstrated that the GTN-induced PGI_2 release in coronary arteries inhibited the formation of "rabbit aortic contracting substance". These findings give rise to the question whether the vasodilating efficacy of organic nitrates is in fact due to their action on prostaglandin metabolism.

2. In Vivo Studies

The only experimental result which might be indicative of a mediation of nitrate-induced vasodilation by this mechanism has been reported by MORCILLO et al. (1980). They observed in anaesthetised open-chest dogs that the haemodynamic response towards a GTN infusion was accompanied by an increase in prostaglandin E and both were attenuated by pretreatment with indomethacin. In contrast, the same author reported subsequently (MORCILLO 1980) that indomethacin in doses that completely inhibit the response to arachidonic acid tended to enhance rather than decrease the dilator response towards GTN in the canine hindlimb. Similar results were obtained with mesenteric and hindquarter vascular resistance of the cat by LIPPTON et al. (1981). Previous experiments by FEIGEN et al. (1978) had already shown that pretreatment with indomethacin or meclofenamic acid was unable to prevent canine renal artery vasodilation induced by GTN. Furthermore, FÖRSTER (1980 a) could not detect an increase of PGI_2 in the coronary effluent of isolated perfused rat or guinea-pig hearts during a GTN-induced increase in the coronary blood flow. In addition, the same group (RETTKOWSKI et al. 1982) reported that GTN did not influence the synthesis of prostaglandins and thromboxanes in organs and microsomal fractions of rats, pigs or rabbits. Finally, recent experiments by BARTSCH et al. (1983) failed to show any effect of acetylsalicylic acid or indomethacin on the relaxing effect of IS-5-MN, the main metabolite of ISDN, on canine venous helical strips. In addition, the typical haemodynamic response after intravenous administration of this nitrate could not be influenced by pretreatment with the cyclooxygenase inhibitors in chronically instrumented conscious dogs. In the same way THADANI and KELLERMAN (1983) showed that indomethacin did not modify the circulatory effects of TGN at rest or during exercise and had no influence on the exercise tolerance under TGN in coronary patients. Also SIMONETTI et al. (1983) reported that acetylsalicylic acid did not prevent the relative vasodilation induced by ISDN in patients who had undergone coronary angiography.

Thus, is seems highly unlikely that the typical effects of organic nitrates on peripheral and central haemodynamics, which are thought to be essential for their antianginal efficacy, would be mediated by prostaglandins. This conclusion is confirmed by the observation (SCHRÖR et al. 1981 c) that although PGI_2 relaxes arterial strips, no relaxation of venous strips occurs and at higher concentrations they even contract. Venous pooling, however, is generally regarded as being essential for the antianginal activity of organic nitrates.

Nevertheless, the stimulation of PGI_2 at low, therapeutically attainable nitrate concentrations might be of importance for the beneficial action of these drugs on coronary arterial microcirculation in myocardial ischaemia (FÖRSTER

1980 b). This possibility stems from the recently accumulated knowledge of the role of prostaglandins in the pathophysiology of coronary circulation on the one hand (NEEDLEMAN and KALEY 1978; HIRSCH et al. 1981; FRIEDMAN et al. 1981) and the beneficial effects of PGI_2 in acute myocardial ischaemia in animal experiments (LEFER et al. 1978; OGLETREE et al. 1979; OHLENDORF et al. 1980; SCHRÖR et al. 1981 b) as well as the salutary effects of PGI_2 infusion in patients with coronary artery disease on the other (BERGMANN et al. 1981).

D. Mechanism of Acute Antianginal Efficacy

I. Peripheral Haemodynamic Effects

Both the peripheral and central haemodynamic effect have been extensively studied over the last two generations. For this reason, only a brief summary of the results is given here in the course of which some recent literature will be discussed. For the literature before 1974 the reader is referred to Vol. 40 of this handbook.

The basic mechanism of nitrate action on haemodynamics consists of its vasodilating potency on both venous and arterial smooth muscle. The typical haemodynamic response to organic nitrates results from differences in the sensitivity of the various vascular regions to these drugs. Thus, it has been demonstrated in experimental animals (BASSENGE et al. 1981), as well as in normal human volunteers (IMHOF et al. 1980) and in patients with coronary artery disease (MILLER et al. 1976; GERSON et al. 1982), that the venous capacity vessels obviously have the highest sensitivity towards organic nitrates, since a reduction in preload predominates at low concentrations. This might be due to a genuine higher sensitivity of venous vessels as compared with arterial vessels towards organic nitrates (MACKENZIE and PARRAT 1977; J. A. ARMSTRONG et al. 1980 a; KADOWITZ et al. 1981; HEEG and LANGER 1981; KREYE and STIEFEL 1983). In addition, however, it might be the consequence of the fact that, at least after sublingual and oral administration, the concentrations of nitrates at the postcapillary venous capacity vessels of the pulmonary and the mesenteric bed respectively are naturally higher than those on the arterial side. Thus, the pulmonary (FERRER et al. 1966; KOBER et al. 1981; KOBER and STROHM 1982) and the splanchnic circulation (CHEN et al. 1979, 1981; HEINZOW and ZIEGLER 1981; STROHM et al. 1983) have been suggested as the major sites of nitrate-induced venous pooling.

The arteriolar resistance vessels are dilated only at high concentrations of organic nitrates (BASSENGE et al. 1981). In the usual therapeutic range, however, the systemic arterial resistance remains largely unaffected by these drugs (STRAUER and SCHERPE 1978; KOPMAN et al. 1978; WILLE et al. 1980; KOBER et al. 1981). The diastolic aortic pressure, which is decisive for coronary perfusion, therefore shows little change under the influence of nitrates (MARTIN et al. 1976). Thus, the well-documented nitrate-induced decrease of the afterload must be ascribed either to an increased aortic compliance (MARTIN et al. 1976) or to an increase of the capacity of the Windkessel without alteration of aortic distensibility, as was demonstrated by WILLE et al. (1980). This action is responsible for the decrease in sys-

tolic aortic pressure which is regularly seen after administration of nitrates (MARTIN et al. 1976; JANSEN et al. 1980).

In the intact body, the primary vasodilating effects of organic nitrates on the venous and arterial side are modified by secondary reflex responses mediated by low and high pressure baroreceptors which lead to a biphasic behaviour of regional blood flow (VATNER et al. 1978) and increases in heart rate and in contractility (see Sects. D. IV and D. V)

II. Effects on Central Haemodynamics and Myocardial Oxygen Consumption

As a consequence of the reduced venous return from the peripheral vascular regions and of the increased capacity of the pulmonary bed, the filling pressures of the right and left ventricles decrease under the influence of organic nitrates. Right atrial pressure as well as left ventricular end-diastolic pressure are regularly diminished (LICHTLEN et al. 1974; MARTIN et al. 1976; VATNER et al. 1978; WILLE et al. 1980; KOBER et al. 1981). This directly leads to a diminution of left ventricular diameter, size and volume (GREENBERG et al. 1975; Battock et al. 1976; VATNER et al. 1978). Such a change in left ventricular geometry implies a decrease in wall tension (GREENBERG et al. 1975; HARDARSON and WRIGHT 1976), one of the major determinants of internal cardiac work and myocardial oxygen consumption. At the same time, the decrease in wall tension leads to a decrease of the extravascular component of coronary resistance, in particular within the inner, subendocardial layers of the myocardium. On the other hand, the reduced impedance to left ventricular ejection, as shown by the decrease of systolic aortic pressure (JANSEN et al. 1980), diminishes the left ventricular peak systolic pressure (LICHTELEN et al. 1974; GREENBERG et al. 1975; VATNER et al. 1978) and thus the external cardiac work.

At the same time, this decrease in afterload and preload leads to changes in stroke volume and in association with simultaneous changes in heart rate to alterations in cardiac index. The behaviour of cardiac index is furthermore dependent on the state of left ventricular function before administration of the nitrate (FRANCIOSA et al. 1978 a). In patients with normal or near normal filling pressures prior to nitrate administration, a decrease of cardiac index can be anticipated (LICHTLEN et al. 1974; BATTOCK et al. 1976; BUSSMANN et al. 1977), whereas no change or even an increase can be observed in patients with initially elevated filling pressures due to congestive heart failure (BUSSMANN et al. 1977; CYRAN 1980). The oxygen-sparing effect of the nitrate-induced diminution in internal and external cardiac work, which is caused by the primary effects of organic nitrates on peripheral and central haemodynamics, is partly counteracted by the reflex increase of sympathetic drive in response to the decreased systolic and mean arterial pressure, which leads to an increase of heart rate and contractility (LICHTLEN et al. 1974; GREENBERG et al. 1975; BATTOCK et al. 1976; VATNER et al. 1978; JANSEN et al. 1980). The net balance of these opposing effects, however, results in a decrease of myocardial oxygen consumption under nitrates both at rest (GREENBERG et al. 1975; CARTHEUSER and KOMAREK 1979) and during exercise (JANSEN et al.

1980, 1981) or during pacing-induced angina (GANZ and MARKUS 1973), which is thought to constitute the main mechanism of the nitrate's antianginal efficacy.

Although there are some experimental indications that organic nitrates might exert a direct oxygen-sparing effect (GROSS and HARDMAN 1975) by interfering with cardiac metabolism or by preventing the impairment of the efficiency of oxidative phosphorylation produced by increased ion transport during ischaemia (SZEKERES et al. 1978), such a direct effect seems to play only a minor role, if at all, in the light of recent studies. Using a myothermal technique which permits direct estimation of myocardial energetics, BOROW et al. (1981) showed that GTN (0.12 mg/l) did not affect cardiac oxidative metabolism since no change in the calorific equivalent of oxygen could be observed. At the same time, anaerobic metabolism remained unchanged. Thus, the well-known oxygen-sparing effect of organic nitrates seems at present to be the result of the actions of these drugs on peripheral and central haemodynamics as well as on myocardial blood flow.

III. Effects on Myocardial Blood Flow

1. Total Myocardial Blood Flow

a) Animal Data

Since the vasodilating activity of GTN was first described by VOEGTLIN and MACHT (1913/1914) in isolated coronary arteries, the extent and time course as well as the definitive importance of coronary vasodilation for the antianginal activity of organic nitrates has been a matter of dispute and the subject of numerous publications. In the older literature (for reviews see CARR 1975; PITT 1975; VATNER and HEYNDRICKX 1975) there are many inconsistencies as to whether organic nitrates increase, decrease or do not alter total myocardial blood flow depending on dosage, route of administration or time of observation. With respect to the time course of alterations of the coronary flow after administration of organic nitrates, REES et al. (1966) and WINBURY et al. (1969) have observed a biphasic response with a short-lived, pronounced increase of flow followed by a longer-lasting decrease of flow as a consequence of an increase of total coronary resistance. Although VATNER and HEYNDRICKX still stated in 1975 that this biphasic effect of organic nitrates has never observed when the drug was administered to conscious animals and therefore ascribed the second phase to the effects of anaesthesia on arterial pressure and reflex responses, the same group (VATNER et al. 1978) were able to demonstrate this biphasic overall effect of GTN on the coronary flow in chronically instrumented conscious dogs.

In these carefully conducted experiments, systemic, coronary and regional haemodynamics, as well as left ventricular dimensions, pressures and myocardial contractility, were directly and continuously measured using Doppler ultrasonic and electromagnetic flow transducers and miniature pressure transducers. Intravenous infusion (8 and 32 $\mu g\,kg^{-1}\,min^{-1}$) and sublingual administration (1.2 mg) of GTN led to a dose-dependent increase of late diastolic flow up to a maximum of 75% of the control flow for the time of infusion (7 min) or 3 min after sublingual dosing, respectively. Subsequently, a decrease occurred below control values until the end of the observation period of 37 min. In the same way,

the flows in the mesenteric, renal and iliac beds resembled this biphasic reaction. However, after denervation (bilateral cervical section of carotid sinus and aortic nerves and vagi), this biphasic reaction to GTN was abolished and only a decrease of resistance could be observed. Thus, prior results on the effect of organic nitrates on coronary blood flow, while seemingly inconsistent, can be reconciled by considering the kinetics of response to organic nitrates. It is believed that the first phase represents the effects of the drug primarily on vascular smooth muscle, whereas the later effects are largely due to vasoconstriction mediated by high and low pressure baroreflexes which have been stimulated by reductions in intercardiac and arterial pressures and also to the effects of GTN on the venous system which has resulted in a reduction of the preload and consequently in the metabolic requirements of the heart. This biphasic alteration of coronary flow under the influence of organic nitrates could be demonstrated by WILKES et al. (1975) who also continuously measured, apart from the flow, the arteriovenous oxygen difference and myocardial oxygen consumption after administration of PETriN and GTN. These values were consistently decreased. This indicates that, after the first transient rise of blood flow, the subsequent decrease is mainly due to the autoregulatory response by the coronary bed to the reduced oxygen requirement. Similar results showing biphasic behaviour of coronary flow were obtained by OEI et al. (1978) after intravenous administration of GTN in anaesthetised dogs. It is interesting to note that the myocardial oxygen arteriovenous difference during both phases of coronary blood flow alterations decreased below its control value, which means that the coronary blood flow first increased more than the oxygen consumption and subsequentely decreased less than the oxygen consumption under the influence of GTN.

b) Human Data

In accordance with the previously cited haemodynamic data in dogs, the myocardial blood flow and myocardial oxygen consumption in patients with coronary artery disease show only a short-lived increased (COWAN et al. 1969), whereas the main alteration seen under the influence of organic nitrates is a decrease of these parameters both at rest (OPHERK et al. 1977; BEHRENBECK et al. 1976; LICHTLEN 1974; JANSEN et al. 1980) and during pacing-induced angina (KUPPER and BLEIFELD 1980). The decrease of myocardial blood flow is thought to occur as a consequence of the diminished myocardial oxygen requirements owing to the systemic effects of organic nitrates, which were regarded as the main or even the only antianginal mechanisms. These data on global myocardial blood flow, however, cannot positively rule out any possible beneficial effects of organic nitrates on regional transmural perfusion.

2. Regional Myocardial Blood Flow

The total coronary resistance consists of the resistance of the large epicardial and transmural conductive arteries on the one hand and of the small arterioles on the other. Under normal conditions, the total resistance is primarily (about 95%) governed by the small arterioles which adapt their diameter in an autoregulatory manner to the metabolic demands of the myocardium, whereas the large arteries

play a negligible role. In the case of critical stenoses of large coronary arteries with subsequent poststenotic ischaemia, however, the resistance of the poststenotic small arterioles may be decreased to such an extent that the resistance of the large epicardial and conductive vessels which are not subject to the autoregulatory processes contribute up to more than 20% of the total coronary resistance and may therefore become the flow-limiting factor in coronary insufficiency (WINBURY et al. 1969).

Since the work of FAM and MCGREGOR (1964) and of WINBURY (1964) ist has been claimed that organic nitrates produce a favourable redistribution of blood to the ischaemic area by their different action on large and small arteries, although the total coronary blood flow may not be altered or even be decreased (for a review of the literature up to 1974 see VATNER and HEYNDRICKX 1975). Alterations of regional myocardial flow by organic nitrates in favour of the subendocardial layers which were first underperfused during ischaemia have been reported by many authors using different methods. Thus HOWE et al. (1975) measured the regional blood flow and O_2 consumption in epicardial and endocardial layers of anaesthetised dogs under the influence of intravenous PETriN (80 μg/kg) and GTN (20 μg/kg). Basal endocardial metabolism was 20%–30% higher than epicardial metabolism. Both nitrates reduced metabolism in each region. Since the absolute decrease in oxygen consumption was greater in the subendocardium, a more favourable balance between perfusion and oxygen requirements occurred in that region. NAKAMURA et al. (1978) studied the effect of intravenous GTN on the ratio of subendocardial to subepicardial perfusion of anaesthetised dogs in which underperfusion of the left circumflex coronary artery had been induced. Using tracer microspheres, they showed a significant increase in subendocardial perfusion in this model, thus confirming similar results of other groups (GROSS and WALTIER 1977; BACHE 1978; COHEN et al. 1976; for literature before 1974 see VATNER and HEYNDRICKX 1975). Thus, the fact that organic nitrates after sublingual or intravenous administration alter the regional myocardial blood flow in favour of the ischaemic regions can be taken for granted. Until the present day, however, there has been considerable discussion whether this beneficial effect results from the aforementioned postulated direct effect of organic nitrates on coronary circulation or whether it is partly or even exclusively due to the decrease in extravascular resistance, which follows the systemic haemodynamic alterations provoked by organic nitrates. This question was investigated with different approaches both in animals and in humans.

a) Animal Data

α) *Studies with Isolated Coronary Vessels or Vessels In Situ.* In 1979, HARDER et al. confirmed and extended results from previous publications on differential effects of GTN on large (1.0 mm) and small (500 μm) coronary arteries of the dog. Using intracellular microelectrodes, they showed that GTN ($10^{-5}M$) blocked the action potential and the Ca^{2+} inward current in the large coronary arteries, but not in the small arteries, whereas adenosine ($10^{-5}M$), which might be an essential mediator of autoregulatory flow increase, elicited the inverse pattern of response. Recently, TILLMANNS et al. (1981) performed in vivo microscopic studies of large (85–328 μm) and small (15–62 μm) rat and cat coronary arteries, together with si-

multaneous determinations of intraluminal pressures by micropuncture after intravenous and intracoronary administration of 30 μg/kg and 0.2 μg GTN, respectively. With these dosages they observed a considerable (19%) dilatation of large coronary arteries and only a slight dilatation of the small arterioles. After intravenous administration, the decrease in pressure in small arterioles was less pronounced than in the aorta and large coronary arteries. In addition, a slight, but statistically highly significant decrease in intercapillary distances was observed, which means additional improvement of coronary oxygen supply. In a similar way, MACHO and VATNER (1981) showed a preferential vasodilating action of GTN on large coronary arteries in conscious dogs. In another study (BASSENGE et al. 1981) on chronically instrumented conscious dogs, the coronary artery diameter was measured continuously by the ultrasonic transit time technique. With this method, the effects of an infusion of GTN (0.2–200 $\mu g/kg^{-1}\ min^{-1}$) into the pulmonary artery on the coronary vasculature were measured in addition to the systemic haemodynamic effects of the drug. This revealed that in healthy dogs two ranges of GTN dosages with a different pattern of effects exist: a low range (below 5 $\mu g\ kg^{-1}\ min^{-1}$) causing venous pooling and coronary conductance artery dilation and a higher range causing additional systemic arteriolar dilation. Coronary resistance vessels were not affected directly with dosages below 200 $\mu g\ kg^{-1}\ min^{-1}$. Thus, there exists at least a 40-fold difference in the sensivity of large and small coronary arteries according to these results. This difference in sensitivity might be due to the fact, that organic nitrates exhibit a direct smooth muscle relaxation only and show no additional socalled flow dependent, endothelium mediated dilator activity, which in contrast is the only mechanism by which dipyridamole and chromonar exhibit their action (HOLTZ et al. 1983).

β) Studies on Regional Myocardial Perfusion Without Systemic Haemodynamic Alterations by Organic Nitrates. Another way to differentiate between direct and indirect effects of organic nitrates on regional myocardial perfusion is to try keeping the systemic haemodynamic parameters constant during the observation period. CAPURRO et al. (1976) studied the retrograde flow and peripheral coronary perfusion in open-chest dogs 2–4 weeks after ligation of the left anterior descending (LAD) artery after intracoronary and intravenous administration of 0.3–100 μg/min GTN for 90 s and 10–300 μg/min for 3 min, respectively. The mean aortic pressure was kept constant during the experimental period. After intravenous administration, a dose-dependent increase in both retrograde flow and peripheral coronary perfusion pressure occurred, whereas intracoronary administration led to a rise in retrograde flow, too, but not to changes in peripheral perfusion pressure. Thus, GTN had obviously increased collateral flow in both cases, but only after intracoronary administration had it additionally effected the resistance vessels.

JETT et al. (1978) investigated the influence of ISDN on regional myocardial blood flow during acute coronary occlusion in dogs. Cardiac output was kept constant by isotonic fluid infusion; mean aortic pressure and heart rate were maintained by adequate constriction of the descending aorta and atrial pacing, respectively. Under these conditions, ISDN given either prior to or after LAD ligation increased collateral blood flow to ischaemic myocardium significantly and

the effect continued for at least 45 min after treatment. Direct measurements of collateral flow were performed by ERTL et al. (1979). They determined the retrograde flow within a main coronary branch after its proximal ligation and subsequent microembolisation of its peripheral bed. Using this model, they could clearly demonstrate an increase of collateral flow of 18% after intracoronary GTN administration of 7 $\mu g\ kg^{-1}\ min^{-1}$ with a concomitant decrease of the collateral resistance. Factors of the extravascular component of coronary resistance, i.e. left ventricular peak pressure, left ventricular end-diastolic pressure, dP/dt and heart rate did not change significantly during the experimental period. In contrast to GTN, adenosine and verapamil had no direct influence on collateral resistance.

Another approach was tried by BACHE et al. (1975) who studied the effect of 0.15 mg/kg GTN infused over 60 min on the extent of reactive hyperaemia after 5 s occlusion of the left circumflex artery with subsequent restricted flow in chronically instrumented conscious dogs. In this model, which resembles the pathophysiological conditions of angina pectoris, GTN reduced the extent of reactive hyperaemia to the value which was observed after occlusion without further restricted inflow. At the same time the regional pattern of perfusion was altered in favour of the subendocardial layers. These alterations occurred without changes in mean arterial pressure, myocardial oxygen consumption, myocardial arteriovenous oxygen extraction or coronary venous oxygen content. These results were recently reproduced and extended by BACHE and TOCKMAN (1982) confirming that GTN alleviates the subendocardial hypoperfusion and ischaemia which occur in the presence of a proximal flow-limiting coronary stenosis.

The strongest evidence that organic nitrates were able to influence directly the coronary circulation in a favourable manner can be derived from continuous measurements of coronary artery dimensions with ultrasonic dimension gauges and coronary blood flow and pressure in conscious dogs (VATNER et al. 1980). An intravenous bolus of 25 μg/kg GTN induced, after a short initial decrease in coronary dimensions, a sustained dilation and a fall in the large vessel coronary resistance, while the determinants of myocardial oxygen demand (preload, afterload, heart rate and contractility) were at or near control levels. Regional myocardial blood flow during transient ischaemia was also investigated in chronically instrumented conscious dogs under the influence of 0.5 mg intravenous GTN by SWAIN et al. (1979). Measurements were carried out in periods when neither total flow to the ischaemic region nor haemodynamic parameters and heart size, all of which were continuously monitored, varied from conditions that existed before drug administration. Under these conditions, a significant increase of the ratio of subendocardial to subepicardial flow was registered, which must be due to a selective dilation of large collateral vessels.

γ) *Comparative Studies with Other Vasoactive Substances.* Further attempts to elucidate the mode of a possible direct effect of organic nitrates on regional myocardial perfusion have been directed to comparative analyses of various vasoactive substances with different targets within the arterial coronary tree. GORMAN and SPARKS (1980) showed that GTN (2.3 $\mu g\ kg^{-1}\ min^{-1}$), when infused into the LAD, which had been ligated 1 h before, decreased the ischaemic

bed resistance and increased the subendocardial flow, while adenosine (2 μg kg^{-1} min^{-1}) did not. They concluded that systemically administered GTN raises the blood flow of ischaemic myocardium by decreasing the resistance of the collateral pathway and the resistance within the ischaemic bed. In a similar way, ERTL et al. (1979) could demonstrate that after acute occlusion of the left circumflex artery and the LAD, adenosine (9 μg/min), in contrast to GTN did not affect the collateral resistance and retrograde flow. With higher doses of adenosine (37 μg/min), even a slight decrease of retrograde flow was seen. Apart from comparisons with adenosine, many other authors analysed the different effects of organic nitrates in comparison with other dilators which act predominantly at the terminal level of the coronary bed, such as dipyridamole (NAKAMURA et al. 1978; LACROIX et al. 1978; BECKER 1978), chromonar (GROSS and WALTIER 1977; LACROIX et al. 1978) or SNP (MACHO and VATNER 1981). In all these studies with different experimental designs both in anaesthetised and conscious dogs, a selective effect of organic nitrates on large coronary vessels could be demonstrated which differed from the response seen after administration of the other agents.

Thus, the overwhelming bulk of experimental results in animals provides evidence that organic nitrates exert favourable direct effects on the regional myocardial blood flow, which might be of importance for their antianginal efficacy. The only contradictory results in the recent literature were reported by MALINDZAK et al. (1978). These authors infused GTN in doses of 0.15, 0.30 and 0.60 mg/ml until maximum alterations of coronary blood flow occurred, which meant a pronounced decrease of the coronary perfusion pressure down to 55% of control values. Under these conditions, the large coronary end-diastolic resistance was raised to 180%–220% and the small coronary resistance was decreased to about 60% of control values. As was shown by pretreatment with phenoxybenzamine, the increase of the large coronary resistance under GTN alone had to ascribed to a reflex α-stimulation in response to the severe systemic hypotensive effect of GTN. Thus, the observed dilating action of GTN on small coronary vessels seems to result from an overdose and is of no significance for the therapeutic mechanism of action of organic nitrates.

b) Human Data

Regional myocardial blood flow cannot, for obvious reasons, be determined with the same precision in humans as is possible in animal experiments. Indirect evidence that organic nitrates predominantly dilate large coronary arteries was drawn by LICHTLEN et al. (1974) from studies in which the myocardial blood flow was measured using the xenon residue detection technique in patients with coronary artery disease at rest and during exercise. Since the exercise-induced reduction of total coronary resistance remained unchanged after sublingual administration of 5 mg ISDN, it was concluded that ISDN does not affect the arteriolar resistance vessels, but rather the large conductive arteries only. COHN et al. (1977) investigated regional myocardial specific blood flow in 31 patients at rest. In the subset of patients with coronary artery disease and angiographically proven collateral vessels, the decrease of regional flow induced by sublingually administered GTN was significantly less when compared with the corresponding values in the subset with normal coronary arteriograms. In five patients whose collateral

vessels showed large diameters and arose from nonstenosed coronary arteries, a mean increase in regional myocardial blood flow was even observed.

Similar results were reported by MANN et al. (1978) who evaluated the effect of SNP (25–100 μg/min; mean 40 μg/min) on regional myocardial specific blood flow in 25 patients with coronary artery disease and compared the data with those obtained after 0.5 mg GTN given sublingually to another 31 patients with the same ^{133}Xe washout technique. GTN decreased the regional flow markedly in normal subjects, but increased it in patients with coronary artery disease and high grade collaterals. In contrast, SNP did not alter the regional flow in normal subjects and decreased it significantly in patients. Although the ^{133}Xe clearance cannot differentiate between subendocardial and subepicardial flow, the opposite effects of the two drugs suggest that SNP primarily affects the resistance vessels whereas GTN dilates specifically the large coronary vessels and collateral vessels. This conclusion is supported by the fact that the systemic haemodynamic effects of sodium nitroprusside and GTN were comparable. ENGEL and LICHTLEN (1981) used the ^{133}Xe washout at rest and during pacing-induced ischaemia in order to measure myocardial blood flow in normal and poststenotic areas of patients with isolated coronary stenoses. In 12 patients, the sublingual administration of 0.8 mg GTN prevented pacing-induced ischaemia, although flow in both poststenotic and normal areas was less than that during pacing under control conditions. This finding of reduced myocardial blood flow after GTN administration is limited by the inability of the xenon washout technique to detect transmural flow differences. Thus it cannot be decided from these findings whether, or to what extent, the observed antianginal effect is due to a reduction in myocardial oxygen requirements as a consequence of the systemic effects of GTN or to a direct effect on coronary circulation.

Better insight into the question whether organic nitrates were at all able to dilate preferentially the large coronary arteries in patients with coronary artery disease is provided by studies using high resolution photospot film coronary angiography. FELDMAN et al. (1979) investigated 13 patients with coronary artery disease after cumulative sublingual doses of GTN (75–450 μg). Small doses (75 or 150 μg) without effects on aortic pressure and heart rate led to a dose-dependent increase of the diameter of the LAD (10% or 20%) of the left circumflex artery (9%, 22%), as well as of collaterally filled vessels (18%, 28%). The highest dose, which provoked a decrease of blood pressure of 11 mm HG, produced only a modest additional increase in coronary arterial diameter. These results indicate a selective dilation of large coronary vessels and collaterals, which might contribute to the antianginal effect as long as the coronary perfusion pressure does not drop below critical values. RAFFLENBEUL et al. (1980) confirmed these data with quantitative angiometric investigations (accuracy 0.05 mm) in 20 patients with coronary artery disease in comparison with 18 patients with normal coronaries. A dose of 5 mg ISDN given sublingually dilated all the normal epicardial arteries (mean 21%). Approximately one third of the large stenosed arteries showed a substantial increase of stenotic diameter, whereas very little change was observed in the other 18 stenoses. Studies by FELDMAN et al. (1981) using quantitative magnification coronary angiography in 34 patients yielded the apparently surprising result that the extent of GTN induced (0.4 mg sublingually) coronary vasodila-

tion was inversely related to the size and diameter of the arteries. Coronary arteries with the smallest control diameter showed the greatest magnitude of vasodilation. The size of the "small" arteries (0.3–1.0 mm), however, was more than the diameter of those human arterioles (0.03–0.1 mm) to which the principle control of resistance is ascribed (SHERF et al. 1977). The authors discuss their results in the light of the previous concept of WINBURY et al. (1969), according to which organic nitrates should lead to a preferential redistribution of blood from the subepicardial regions via dilation of the transmural tributary conductance arteries, which might be of the size of the "small" arteries in the present study.

A further approach to the investigation of possible direct effects of organic nitrates on the coronary circulation uses direct measurements of anterograde flows in saphenous vein bypass grafts during or after aortocoronary bypass surgery under the influence of nitrates. KLEIN et al. (1981) assessed the action of an intravenous GTN infusion of 32 μg/min on graft flow intraoperatively in 24 patients. GTN was infused for approximately 5 min until a decline in arterial blood pressure of 10 mm Hg occurred. At this point, arterial pressure and pulmonary wedge pressure were returned to control levels by blood infusion in order to keep the systemic determinants of coronary blood flow and myocardial oxygen consumption stable during the following determinations of graft flow and haemodynamics. Patients with 50%–90% stenoses of the native vessel and without detectable collaterals responded to GTN with a considerable decrease of graft flow, which was attributed by the authors to a GTN-induced dilation of the native vessel with resultant increased anterograde flow through this stenotic vessel. Patients with stenoses greater than 90% and well-developed collateral vessels showed a lesser decrease of graft flow under GTN. Here, graft flow was thought to decline because of increased flow through these auxiliary channels. Patients with stenoses greater than 90% and without detectable collaterals, however, responded with an increase of graft flow under GTN, since increased flow through the severely damaged native vessel was not possible and collaterals were absent. The authors conclude that GTN is able to dilate less severe stenotic coronary arteries and collateral vessels, thus leading to a favourable redistribution of myocardial blood flow. Although KLEIN et al. (1981) tried to achieve constant haemodynamic conditions during their measurements, their results and interpretations may be criticised since it seems very difficult to exclude all other influencing factors immediately after bypass and during anaesthesia. DONALDSON and RICKARDS (1981), however, were able to confirm the results of KLEIN et al. (1981) by graft flow measurements in conscious, haemodynamically stable patients without inotropic support who were given 0.5 mg GTN or 5 mg ISDN sublingually 2–3 days after surgery. In another study (SIMON et al. 1981) it was found that 0.8 mg GTN sublingually exerted dilating effects on proximal epicardial arteries without changes in coronary resistance. SIMON et al. (1981) performed direct measurements of diameters, flow and blood flow velocities in single coronary arteries as well as in aortocoronary bypass grafts using X-ray videodensitometry. In contrast to intracoronary administration, flow decreased in the LAD in the majority of patients and decreased significantly in the entire group of bypass grafts after sublingual administration.

On the whole, there is convincing evidence from both animal experiments and observations in patients with coronary artery disease that organic nitrates exert

a direct effect on the coronary arterial tree with preferential dilation of the coronary arteries before the arterioles. This selective action might result in a redistribution of blood flow in favour of the ischaemic areas. Such a redistribution to the subendocardial layers is without doubt also favoured by the systemic haemodynamic actions of organic nitrates by which the extravascular component of coronary resistance is decreased predominantly in the subendocardial layers (HOFFMANN and BUCHBERG 1976). The crucial question, however: which mechanism prevails and is the decisive one for the antianginal efficacy, still remains unanswered. The findings of GANZ and MARCUS (1972) that intracoronary administration of GTN was not able to alleviate pacing-induced angina whereas intravenous administration promptly relieved it in patients with coronary artery disease cannot be used as strong evidence against the participation of a direct action of GTN on the coronary bed in the antianginal effect. In these investigations, the intracoronary bolus of 0.075 mg GTN had resulted in almost doubling of coronary sinus blood flow, which means that this dose mut have been clearly above the threshold (BASSENGE et al. 1981) for the coronary resistance vessels. Thus, the potentially beneficial effect of GTN which would result from selective dilation of the large coronary arteries was counteracted by effects on the autoregulatory processes at this dose level. This interpretation is confirmed by the findings of a dose-dependent decrease of total coronary resistance (ERTL et al. 1979), of a lack of increase of peripheral coronary pressure as compared with intravenous administration (CAPURRO et al. 1977) and of a decrease in subendocardial perfusion (GROSS and WALTIER 1977) after intracoronary administration of GTN in animal experiments.

Direct evidence for the validity of this interpretation comes from the results of BROWN et al. (1981) which were obtained in 46 patients with coronary artery disease and sublingual administration of different doses of GTN and in a further 17 patients after low dose (50 μg over 2–3 min) intravenous, administration of GTN using bling, computer-assisted analysis of quantitative angiography. In this context, the data from a subset of 11 patients after intracoronary low dose administration are of special importance. In these, intracoronary GTN had no effect on the systemic arterial pressure or on the right atrial pressure and cardiac index, whereas the elevated pulmonary capillary wedge pressure fell from 20 to 11 mm Hg. The luminal calibre dilated in normal and diseased arterial segments with an average 40% reduction of predicted stenotic flow resistance and was accompanied by improvements of both the abnormal compliance and left ventricular function. The authors therefore concluded that vasodilation of epicardial coronary stenoses is usually a major component of the beneficial response to GTN.

The seemingly contradictory results of other authors (GANZ and MARCUS 1972; HOOD et al. 1980) are explained by the higher dosages that were given as bolus injections by these investigators which must have led transiently to up to 200 times higher GTN concentrations in the vessels and this could cause dilation of the peripheral resistance vessels, too. Although the paper by BROWN et al. (1981) was criticised for some minor inconsistencies (FELDMAN and CONTI 1981), it is a challenge to further investigations of this problem. More recently, FELDMAN et al. (1982) confirmed at least that coronary artery dilation occurs at as little as 5 μg intracoronary GTN without important changes in heart rate or systemic hae-

modynamics. The crucial question remaining, however, is whether low dose intracoronary infusion of GTN is able to alleviate pacing- or exercise-induced angina.

Since most authors agree that organic nitrates are able to alter the regional coronary perfusion selectively in addition to their systemic effects in a similar dose range (BASSENGE et al. 1981), it is reasonable to assume that the long-lasting direct effects on coronary circulation (JETT et al. 1978; MACHO and VATNER 1981) contribute to the antianginal efficacy of these drugs. Furthermore, there is no doubt at all that in cases of vasospastic angina the therapeutic efficacy of organic nitrates is predominantly due to this direct vasodilating effect on large coronary arteries (ENGEL and LICHTLEN 1981; HILLS and BRAUNWALD 1978; FALLEN et al. 1978; for further references see Sect. F. II).

IV. Influence of Organic Nitrates on Contractility and Left Ventricular Performance

1. Animal Data

In the older literature there are many inconsistencies regarding a direct effect of organic nitrates on the contractility of the heart. Whereas the general opinion prevailed that organic nitrates exerted little direct inotropic effect, some authors reported a decrease and others an increase of contractility (for review up to 1974 see VATNER and HENDRICKX 1975). STRAUER (1975) demonstrated a short-lasting increase of isotonic shortening velocity by 14% and 13% after 0.2–0.5 μg/ml GTN in right ventricular and left ventricular human papillary muscle under conditions of constant preload, afterload and rate of contraction. Using higher concentrations he observed a decrease of contractility. In a similar manner, HIMORI et al. (1977) reported a 24% increase in tension developed by injection of 100 μg GTN into the septal artery of a cross-circulated canine papillary muscle preparation. In addition, KAVERINA and CHUMBURIDZE (1979) showed an increase of contractility in isolated guinea-pig atria with 10^{-6}g/ml GTN. In a similar way, BONORON-ADELE et al. (1981) reported a positive inotropic effect of $10^{-6}M$ GTN in isolated cat papillary muscles during hypoxia and subsequent reoxygenation which was ascribed to increased cellular calcium movements since the inotropic effect could be abolished by calcium channel blockers.

On the other hand, MATHES (1975) was not able to show a positive inotropic effect of GTN in right ventricular cat papillary muscle. In contrast he observed a decrease of shortening velocity under 10 μg GTN and ISDN respectively per millilitre bath fluid. This finding of a slight negative inotropic effect of organic nitrates was confirmed by recent experiments of BOROW et al. (1981) on the isolated beating rabbit heart. 0.12 mg/l GTN caused a 14% fall in mechanical performance at the apex of the Frank-Starling curve. Previous experiments in isolated rat hearts by GMEINER (1974), however, had failed to show any alteration of the contractility indices under GTN (1 μg/ml) under aerobic and hypoxic conditions when rate, preload and afterload were kept constant. KORTH (1975), however, appeared to reconcile the seemingly contradictory results by demonstrating a biphasic response of guinea-pig papillary muscles to incubation with 2×10^{-4}–5×10^{-4} M GTN. Of 26 papillary muscles, 15 showed a transitory (3–5 min) increase of the force of contraction, which was followed by a marked negative ino-

tropic effect. Since the GTN-induced increase in contractile force could be prevented by β-adrenoceptor blockade or pretreatment with reserpine, KORTH concluded that it was due to a liberation of noradrenaline and possibly, in addition, to an inhibitory on monoamine oxidase by GTN.

In all these experiments, however, concentrations of GTN or ISDN were used which are far above those that are relevant for therapeutic conditions. Thus, the significance of these results for the therapeutic mechanism of action of organic nitrates is seriously questioned.

In extension of the in vitro experiments cited, KUMADA et al. (1980) investigated regional segment length and dynamic wall thickness in addition to central haemodynamics in chronically instrumented conscious dogs after oral administration of 30 and 60 mg ISDN using sonomicrometry. Chronic obstruction of the left circumflex artery was performed by an ameroid constrictor, allowing collaterals to develop. At 1 h after administration of ISDN, the percentage wall thickening and segment shortening did not deteriorate in the ischaemic zone during exercise as was the case during control runs without ISDN. In the normally perfused zones, the percentage shortening remained unchanged during exercise after ISDN administration whereas it even improved in the ischaemic zones. This different behaviour, therefore, argues against a direct positive inotropic effect of ISDN as the underlying mechanism of increased contractility in the ischaemic zones. Since in all dogs the only sources of blood supply to the ischaemic regions were the collaterals, it seems very likely that ISDN improved flow to the ischaemic zones and thereby enhanced contractility by acting on the intercoronary collateral vessels in addition to reducing the global metabolic demand owing to decreased peak systolic pressure and left ventricular end-diastolic pressure.

2. Human Data

The assessment of a possible direct inotropic action of organic nitrates in the intact human body is very difficult since these drugs affect, either directly or indirectly, in a complex, rapidly fluctuating manner, preload, afterload, heart rate and coronary flow, all of which influence the contractile state of the heart. There is ample evidence that organic nitrates are capable of increasing left ventricular performance in patients with coronary artery disease. Thus, BATTOCK et al. (1976) found a significant increase of the radiocardiographically determined ejection fraction in 27 patients with coronary artery disease after administration of both 5 mg sublingual or 20 mg oral ISDN and after administration of 0.4 mg sublingual GTN. Since at the same time the stroke volume was decreased and the heart rate increased, it cannot be stated whether this was due to a primary action of the nitrate or merely due to a reflex increase of contractility. In other studies, an increase in the contractile state after sublingual administration of GTN was proven by an increase of circumferential fibre shortening and ejection fraction accompanied by a consistent reduction in left ventricular end-diastolic volume in patients with coronary artery disease (DUMESNIL et al. 1975; GREENBERG et al. 1975; MCANULTY et al. 1975). The accompanying increase in heart rate was too small to account for the change in the contractile state (GREENBERG et al. 1975). In one study (MCANULTY et al. 1975), the ejection fraction was only improved

in two patients whose wall motion abnormalities were ameliorated at the same time. This fits well with the observation of DUMNESNIL et al. (1975) that the peak rate of wall thickening during systole, which can be regarded as an index of regional left ventricular functional status, increased to a significantly greater extent in segments with abnormally low initial peak rate values (5 cm/s) than in normal areas, which change only slightly. Although these data allow no definite conclusion regarding the underlying mechanism of this effect, the differences in regional response and the fact that in two normal subjects no significant change in peak rate after GTN administration could be seen argue against a direct influence of GTN on myocardial contractility. The radiocineangiographically determined data of BORER et al. (1978) in 47 patients with coronary artery disease and in 25 patients without coronary stenoses may be interpreted in a similar way. These authors found that 0.4 mg sublingual GTN increased ejection fraction in normal subjects at rest, but not during exercise. In contrast, ejection fraction rose significantly in patients with coronary artery disease during exercise from 36% to 48% after GTN administration.

This differential response between normal subjects and patients with coronary artery disease points to an additional mechanism of organic nitrates apart from the lowering of impedance to left ventricular ejection, which was presumed to be comparable in both groups. In accordance with these data on left ventricular performance during exercise, GTN (mean dose 0.88 mg sublingually) shifted global and regional left ventricular function towards the normal state during spontaneous angina pectoris (SHARMA et al. 1980). An enhancement of systolic ejection velocity parameters could also clearly be demonstrated by SIMON et al. (1980) in both normal subjects and coronary patients after 0.8 mg GTN sublingually. Since the maximal velocity of shortening of the contractile elements, which may be taken as an estimate of the inotropic state if intraindividual comparisons are made, remained unaltered in either group after GTN administration, any direct influence of the drug on contractility seemed to be unlikely. The enhanced systolic shortening velocity was therefore interpreted by these authors primarily as a result of a lowered arterial impedance to systolic ejection fraction.

Another indirect approach to the differentiation between direct and indirect effects of organic nitrates on contractility under clinical conditions was tried by AMENDE et al. (1981) who compared the effects of GTN on systolic and diastolic left ventricular function after intracoronary (0.15 mg) and sublingual (0.8 mg) administration. Whereas after sublingual administration the left ventricular end-diastolic pressure, left ventricular end-diastolic volume index and left ventricular systolic volume index fell as expected, the mean velocity of circumferential fibre shortening and the mean systolic ejection rate increased significantly. After intracoronary administration, however, no change in either of these parameters occurred. A slight but significant and sustained increase of dP/dt_{max} could be explained in part by a stretch phenomenon due to GTN-induced myocardial thickening and in part by an increase in heart rate. Neither muscle stiffness nor volume stiffness was altered by intracoronary GTN in contrast to sublingual GTN. Thus, the largely negative results with intracoronary GTN in contrast to the significant effects of sublingual GTN on systolic and diastolic left ventricular function and geometry suggest that the major cardiac actions of the drug are in-

direct rather than direct. Although RUTSCH and SCHMUTZLER (1981) reported somewhat different results on comparing the effects of intracoronary and intravenously administered ISDN, they agree that during systemic administration of nitrates, direct cardiac effects may be of little or no significance.

Thus, on the basis of more or less indirect evidence, most investigators assume that the positive effect of organic nitrates on left ventricular performance in angina pectoris is the consequence of the beneficial action of these drugs on the balance of oxygen supply and demand with a consequent increase in inotropy. In this respect the balance may be influenced by a reduction in afterload and wall tension, which means decreased oxygen demand, and by a decrease of the preload and extravascular resistance in the subendocardial layers in addition to a direct action on regional myocardial perfusion, which means increased oxygen supply to the underperfused areas.

In contrast to the investigations cited, however, STRAUER and SCHERPE (1978) tried to differentiate between direct and indirect effects of organic nitrates on the inotropic state of the heart in patients with coronary artery disease. They compared left ventricular dynamics and coronary haemodynamics under control conditions, under intravenous infusion of GTN and under continued infusion of GTN, while arterial and pulmonary artery pressure were restored to control levels by infusion of dextran. The heart rate was kept constant during all three observation periods by pacing. During infusion of 62 μg/min GTN alone, a decrease of left ventricular systolic pressure (20%), left ventricular end-diastolic pressure (43%), dP/dt_{max}(13%), cardiac index (16%), stroke volume index (15%), stroke work index (30%) and pulmonary vascular resistance (29%) occurred, which are in accordance with numerous other publications. However, after infusion of dextran, which restored the control conditions with respect to preload and afterload, an increase of dP/dt_{max}(12%), cardiac index (13%), stroke volume index (14%) and stroke work index (10%) was observed. From these increases in left ventricular contractility indices at constant preload, afterload and heart rate, the authors postulate a moderate but significant direct inotropic effect of GTN. Coronary blood flow (28%) and myocardial oxygen consumption (21%) were increased under the experimental conditions in parallel to the enhancement of ventricular performance. Since the coronary arteriovenous oxygen difference was almost unchanged, the authors felt that the increased flow should be due rather to increased metabolic demand resulting from the increase in inotropy than to coronary vasodilation. This assumption, however, does not take into account a possible selective action of organic nitrates on the large tributary coronary arteries (as discussed in Sect. D. III) with a favourable redistribution of blood to relatively hypoperfused areas, which could result in an increased contractile force.

In this respect experiments by MEHTA and PEPINE (1978) are of interest. They report that in patients with coronary artery disease there are poststenotic areas with some degree of ischaemia even at rest without angina. Sublingual administration of GTN (0.3–0.6 mg) was able to improve the flow to these regions without significant changes in total coronary flow. Under the experimental conditions of STRAUER and SCHERPE (1978), the total coronary blood flow might have been increased by the fact that, in spite of coronary dilation, the fall in coronary perfusion pressure was prevented by infusion of dextran. The possibility cannot

therefore be ruled out that this increased flow, together with a more favourable transmural distribution, may have resulted in the observed increase in inotropy. Furthermore it seems doubtful whether it is possible at all to control all the systemic effects of organic nitrates influencing the inotropic state in vivo in order to prove the direct inotropic action in question.

Whereas in the past most of the investigations on left ventricular function dealt with systolic function, the influence of organic nitrates on diastolic function has been studied only very recently. Sublingual as well as intracoronary administration of TGN and oral administration of IS-5-MN decrease the speed of isovolumic pressure decay and enhance left ventricular relaxation. Thus, the organic nitrate-accelerated decrease of left ventricular pressure may enhance myocardial perfusion early in the diastole and via this mechanism contribute to the antianginal action of these drugs (AMENDE et al. 1983a, b; BRÜGGEMANN et al. 1983; HIRZEL et al. 1983).

On the whole, however, there is no doubt that organic nitrates are capable of increasing left ventricular performance in angina pectoris, which contributes to their beneficial effects on ventricle size. The question which has still not been unequivocally settled, whether this effect may be due partly to a direct inotropic action in addition to the undoubted indirect effects of nitrates that enhance left ventricular function, seems to be rather of academic than of practical importance.

V. Chronotropic and Antiarrhythmic Effects

1. Chronotropic Effects

Organic nitrates are not considered to possess any direct chronotropic effect. Injection of 0.03–100 μg GTN into the sinus node artery failed to produce any alteration of the heart rate of dogs (HIMORI et al. 1977). In a similar way, GTN did not influence the spontaneous rate in the isolated sinus node (SENGES et al. 1979). Thus, the changes in heart rate which occur after administration of organic nitrates to intact animals or humans are obviously reflexly mediated in response to the drug-induced haemodynamic effects.

a) Tachycardia

Administration of organic nitrates in doses which cause a hypotensive response by reduction in preload, stroke volume and arterial tone usually results in an increase in heart rate. This is thought to be mediated primarily by sympathetic efferent discharge from the carotid sinus and aortic arch baroreceptors in response to the decrease in systemic arterial pressure (PARMLEY and CHATTERJEE 1978). Since the tachycardia occurs in response to the induced hypotension, it can be readily understood why, for instance, patients with congestive heart failure and high filling pressures whose left ventricular function after administration of organic nitrates improves (whereas little or no reduction and sometimes even an increase in arterial blood pressure occurs), exhibit no, or only a slight, increase in heart rate after administration of organic nitrates. The extent of increase in heart rate after nitrate administration thus depends on the different primary reactions of the various patients to these drugs.

b) Bradycardia

In contrast to the typical reflex increase in heart rate, severe, sometimes life-threatening bradycardia and hypotension occur after sublingual or intravenous administration of organic nitrates. The first report on a patient with clinical shock associated with a very low and irregular pulse following GTN administration dates back to NOER (1887). Similar observations were made in patients with unstable angina (SPRAGUE and WHITE 1933) and in patients with and without cardiac disease after sublingual administration of usual doses of GTN (PRODGER and AYMAN 1932). Apart from these scarce early reports, there were, for approximately 40 years, no comparable cases documented with the syndrome of severe bradycardia and hypotension. In recent years, however, a number of reports have appeared independently, which might be due to the increased usage of organic nitrates (CHENG 1971; COME and PITT 1976; BOSSI et al. 1977; LAX et al. 1977; SPÖRL-RADUN et al. 1980; KHAN and CARLETON 1981; NEMEROVSKI and SHAH 1981). COME and PITT (1976) observed the syndrome in 7 of 54 patients, BOSSI et al. (1977) in 14 of 100 patients with acute myocardial infarction after sublingually administered GTN and we ourselves (SPÖRL-RADUN et al. 1980) in 3 of 18 normal subjects after 5 mg ISDN administered sublingually.

In the typical case, severe arterial hypotension develops suddenly within 5–10 min after sublingual administration and is accompanied by bradycardia, which ranges from sinus bradycardia to sinoatrial (SA) block and further to atrioventricular (AV) block of second and even third degree with and without short transient periods of previously increased heart rate. In nearly all reported cases this episode was rapidly reversible by increasing venous return (Trendelenburg position) and/or administration of atropine. The effectiveness of this treatment, together with the observation that the majority of the reported cases exhibited or can be presumed to have had normal or low normal filling pressures before administration of nitrates, points to the following interpretation. The nitrate-induced reduction in venous return might have resulted in a further pronounced diminution of the already low normal end-diastolic ventricular volume. The vigorous contraction of the relatively empty ventricles then leads to deformation of neural receptors, thereby eliciting vagal reflexes similar to the Bezold-Jarisch reflex (THOREN et al. 1976), which can also be observed during rapid, massive haemorrhage (OBERG and THOREN 1973). As our observations in normal volunteers (SPÖRL-RADUN et al. 1980) clearly demonstrate, this reaction can occur independently of existing and predisposing diseases of automaticity of conduction. One may thus assume that those subjects are at risk of experiencing such a syndrome who exhibit low normal filling pressures and a more vagotonic state prior to administration of nitrates. Extending the therapeutic indications of organic nitrates to patients other than those suffering from angina pectoris may possibly increase the incidence of this rare side effect.

2. Antiarrhythmic Effects

In experiments on open-chest dogs, KENT et al. (1974) showed that GTN enhanced the electrical stability of acutely ischaemic myocardium as assessed by the ventricular fibrillation threshold technique. In accordance with these animal ex-

periments, it could be demonstrated that sublingual or intravenous administration of GTN in usual doses reduced the frequency of premature ventricular beats in patients with acute myocardial infarction (KNOEBEL et al. 1975; BUSSMANN et al. 1980) or in patients with life-threatening ventricular arrhythmias in unstable angina (GAGNON et al. 1980) or even in patients with mitral valve prolapse (SENGES et al. 1979).

To elucidate the underlying mechanism of this antiarrhythmic effect of nitrates, several sets of experiments were performed in animals and in humans. LEVITES et al. (1975) showed that GTN enhanced the electrical stability of the acutely ischaemic myocardium by decreasing the difference between refractory periods of ischaemic and nonischaemic areas in the period immediately following coronary artery occlusion in dogs. DASHKOFF et al. (1976) reported that the fibrillation threshold in nonischaemic open-chest dogs was increased by infusion of GTN (75 μg/ml). This effect, however, seemed to be independent of the systemic effects of the nitrate, as shown in separate experiments with simultaneous administration of phenylephrine to prevent the nitrate-induced fall of arterial pressure. Furthermore, haemorrhage alone (to mimic nitrate action) was associated with a reduction rather than a rise in ventricular fibrillation threshold. In addition, MICHAELSON et al. (1979) suggested that the demonstrated antiarrhythmic effect of nitrates is also independent of possible beneficial effects of the drug on regional myocardial blood flow, which was not altered by GTN in their experiments. On the other hand, SENGES et al. (1979) showed in very carefully conducted experiments in isolated rabbit atria and canine ventricles under normoxic and hypoxic conditions that GTN exhibited no direct electrophysiological effect at all. The antiarrhythmic nitrate efficacy cannot therefore be related to direct membrane effects.

This latter observation in animal experiments corresponds to the observations of DURAIRAJ et al. (1979), who recorded His bundle electrograms in 12 normal subjects before and after sublingual administration of 0.5 mg GTN. In these studies, as well as in others performed in patients with coronary artery disease (GOULD et al. 1976, 1977), GTN increased sinus nodal automaticity and improved AV nodal conduction, as shown by a reduction in the atrio-His (AH) interval and the AV nodal functional and effective refractory periods, whereas no influence on the His-ventricular (HV) intervals could be seen. These effects, however, were most probably due to the reflex increase in sympathetic drive and decrease in vagal tone in response to the nitrate-induced hypotension. Using smaller doses (0.25–0.5 mg), HOELZER et al. (1981) noted in patients with and without coronary artery disease only a tendency of the AV nodal conduction towards improvement under GTN, whereas the ventricular echo zone and the number of echorepetitive ventricular response beats following ventricular stimulation decreased significantly. Finally, SENGES et al. (1979) were not able to demonstrate any influence of 0.5 mg sublingual GTN on intercardiac conduction and refractoriness in patients with mitral valve prolapse whose ventricular arrhythmias could be completely suppressed by the drug.

In the light of these findings it seems unlikely that organic nitrates exert a direct antiarrhythmic effect. Their antiarrhythmic properties must therefore be attributed to their primary actions on systemic and central haemodynamics, re-

gional prefusion and left ventricular performance, all of which obviously influence various arrhythmogenic determinants in a favourable manner.

E. Problems of Long-Term Treatment [1]

I. Nitrate Tolerance

Observations of diminishing efficacy of organic nitrates during long-term treatment of different cardiovascular diseases or in experimental studies have been reported since the first clinical reports on GTN in the last century. Since, however, this phenomenon could not be confirmed in some experimental and clinical investigations, tolerance to organic nitrates and its clinical relevance have been a subject of controversy up to the present time.

In order to avoid misunderstanding, some definitions will be given at the beginning of this section. Tolerance to a drug exists when, after repeated administration, increasing dosages are required to obtain a given pharmacological or therapeutic effect (JAFFE 1980). Tolerance disappears after cessation of the drug exposure. Cross-tolerance occurs with related compounds and means that more than one agent can incude tolerance to a given drug or, vice versa, one drug may induce tolerance to other similar ones. Dependence on a drug is defined by the appearance of psychological and/or physical symptoms when the drug is withdrawn. Although tolerance and physical dependence are combined in many cases, one may exist without the other.

1. Animal Data

Investigations of tolerance were performed using different in vitro and in vivo models. Tolerance was demonstrated, for example, by the shift of the dose–response curve for organic nitrates after pretreatment with high doses of these drugs (BOGAERT and DE SCHAEPDRYVER 1968; BOGAERT 1968; NEEDLEMAN 1970; RUSH et al. 1971). For instance, NEEDLEMAN (1970) demonstrated for GTN in anaesthetised rats a drop of blood pressure at intravenous doses of about 0.003–0.3 mg/kg, but the dose–response curves shifted markedly to the right after pretreatment by subcutaneous injection of GTN in doses of 10–100 mg/kg t.i.d. The degree of decreased responsiveness was found to be dependent on the dose and the duration of chronic administration of GTN.

However, the tolerance disappeared rapidly after cessation of nitrate administration. This observation has also been reported in experiments with rabbits (BOGAERT 1968) in which the acute GTN effects were examined after different schedules of GTN pretreatment. If the administration of 1 mg/kg GTN injected every 30 min for 3–5 days was stopped 12–16 h before the acute GTN test, a partial restitution of the response was obtained. Similarly, PARKER et al. (1975) observed in anaesthetised dogs that 20–60 min after withdrawal of nitrate administration the haemodynamic response was restored completely.

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1 This section was written in collaboration with Dr. G. SPONER, Experimental Pharmacology, Boehringer Mannheim

In vitro experiments demonstrate that aortic strips from rats made tolerant to GTN by chronic systemic administration of this drug show a desensitisation to challenge with GTN, whereas the uterus or ileum responded normally (HERMAN and BOGAERT 1971). However, aortic strips of untreated rats incubated with high concentrations of GTN were not desensitised. Tolerance by incubation was obtained in in vitro experiments only at the alkaline pH 9.1 (NEEDLEMAN and JOHNSON 1973). With this model, cross-tolerance of other organic nitrates to GTN could be demonstrated. Erythrityl tetranitrate was the strongest, ISDN was the weakest inducer. Recently, IS-5-MN has been assessed using Langendorff's preparation to induce less tolerance than ISDN or GTN (NOACK 1982).

Such differences have been found also in conscious dogs, in which the responsiveness to intravenous injection of 30 μg/kg GTN before, during and after intravenous infusion of different nitrates was investigated. Infusion of GTN or IS-5-MN over 6 h decreased the systolic blood pressure by about 25 mmHg to a new constant baseline. Remarkably, the acute response to GTN injection was attenuated during GTN infusion by 40%, but only by 15% during IS-5-MN infusion. The original acute effect of GTN injection was restored very rapidly after withdrawal of the GTN infusion, but more slowly in the IS-5-MN group, corresponding to 1–2 pharmacokinetic half-lives. Indeed, in complementary investigations in conscious dogs it was observed that intravenous injections of IS-5-MN at dose intervals of 1.3 half-lives (this is related the t.i.d. dosing schedule in humans) does not show any indication of tolerance (SPONER et al. 1984a). The mechanisms which might be involved in the development of tolerance to organic nitrates have been the subject of some experimental investigations.

NEEDLEMAN's group were able to rule out decreased availability of free drug, tissue exhaustion, increased biotransformation and counterregulation with increased sympathetic activity as causes. They proposed that the cellular mechanism of tolerance to GTN could be the result of nitrate-induced oxidation of sulphydryl groups which are related to the nitrate receptor site in vascular smooth muscle. Organic nitrates act on these receptor to produce vascular relaxation, whereby the sulphydryl groups are changed to the disulphide configuration. The disulphide receptor has, however, less affinity for GTN. This hypothesis was supported by the fact that the tolerance to GTN could be reversed by the disulphide reducing agent dithiothreitol (NEEDLEMAN and JOHNSON 1973; see also Sect. C.II.2).

The role of compensatory reflex mechanisms in the development of tolerance to organic nitrates has been investigated in dogs. Remarkably, acute tolerance on intravenous infusion of 1 mg/kg GTN has been shown to be prevented by pretreatment with guanethidine and anaesthesia. In contrast, chronic tolerance induced by subcutaneous injections of 1 mg/kg GTN 20 times daily over 4 days could not be influenced. From these results it can be concluded that compensatory reflex mechanisms triggered by the vasodilatation are involved only in the first phase of tolerance to GTN (RUSH et al. 1971). Data obtained from cats support the view that counterregulating reflex adjustments limit the instantaneous effect of GTN: cervical vagotomy and carotid sinus denervation potentiated the GTN-induced blood pressure response, but abolished the increase in heart rate (CHEN et al. 1979). On the other hand, ISDN does not enhance the plasma cat-

echolamines in dogs, whereas plasma renin activity is raised to a higher plateau if the dose interval is shorter than 3 h. This activation of the renin–angiotensin–aldosterone system induced by relatively high doses of 4 mg/kg ISDN may finally lead to Na^+ retention and volume expansion with the consequence that the haemodynamic responses to organic nitrates may be gradually attenuated (BENKE et al. 1980).

Summarising, the experimental studies indicate that tolerance to organic nitrates occurs, but the findings demonstrate likewise that the decreased responsiveness disappears rapidly if the treatment is discontinued (BOGAERT 1968; NEEDLEMAN 1970; SPONER et al. 1984a; PARKER et al. 1975). Even though tolerance to nitrates exists as a pharmacological phenomenon, it must kept in mind that it can be provoked in vitro as well as in vivo only under specific conditions which are not related to clinical use. In particular, the doses in experimental studies are unrealistically high. In some cases, doses 100–1,000 times those required for a haemodynamic response have been administered to demonstrate the development of tolerance (NEEDLEMAN 1970). Similarly, the extremely short dosing intervals in some investigations do not correspond to dosing schedules in humans (BOGAERT 1968). However, there is no doubt that the rate of development and extent of nitrate tolerance that develops depend upon the type of nitrate, the time of exposure, the dose (or the plasma concentration) and the dosing interval (e.g. in relation to the pharmacokinetic half-life) (BOGAERT and DE SCHAEPDRYVER 1968; NOACK 1982; SPONER et al. 1984a; PARKER et al. 1975). Taking into account these objections to previous investigations and considering the results of recent experimental studies, it seems unlikely that the clinical use of long-acting nitrates is regularly accompanied by a relevant decrease of responsiveness to these drugs and that nitrate tolerance is an important clinical problem (ABRAMS 1980).

2. Human Data

a) Evidence for the Occurrence of Tolerance

Organic nitrates, especially GTN, were initially used for the treatment of arterial hypertension. Indeed, some early reports provide evidence of reduced hypotensive efficacy and of the well-known disappearance of headaches during the chronic administration of these drugs (STEWART 1905; BERNSTEIN and IVY 1955). Surprisingly, headaches seem to disappear faster and easier than the blood pressure lowering effect (CRANDALL et al. 1931).

The classic report by SCHELLING and LASAGNA (1966) demonstrated a diminished, but not abolished, effect of sublingual GTN on blood pressure and heart rate during treatment with PETN over 4 weeks. Further evidence for haemodynamic tolerance or cross-tolerance to organic nitrates was provided by SCHLUP et al. (1980) and ZELIS and MASON (1975). The latter investigators studied in healthy volunteers the decrease in blood pressure as well as the arterial and venous dilatation induced by sublingual GTN before and 6–8 weeks after administration of 120 mg ISDN daily in slow-release preparations. Remarkably, the blood pressure and the arterial vascular resistance fell to the same extent in the control and in the ISDN period. In contrast, the small increase in venous volume induced by GTN was totally abolished in the ISDN period.

Cross-tolerance between ISDN and GTN was also observed by THADANI et al. (1980c). They compared in patients with coronary heart disease the dose–response curves for the nitrate-induced decrease in blood pressure after acute and sustained ISDN therapy (5 days, 15–60 mg q.i.d.). They found that after sustained treatment the blood pressure effect was smaller, shorter and nearly dose independent, indicating partial circulatory tolerance. In a second well-conducted and well-documented study with a similar protocol THADANI et al. (1982) investigated the antianginal effect of ISDN after acute and sustained therapy. In additon to other parameters, the walking time on a treadmill required to induce anginal pain was evaluated. With respect to the haemodynamic findings the results of this recent study confirmed those of the earlier one. With respect to the antianginal effect, the investigators found that ISDN enhanced the exercise capacity of the patients after both acute and chronic administration, but the improvement after any given dose of ISDN was greater during acute than during sustained therapy. Furthermore, during acute therapy the exercise capacity was improved over 8 h, whilst during sustained therapy the effect persisted for only 2 h. This study indicates partial tolerance to haemodynamic and antianginal effects of ISDN with the consequence of reduced and shortened effect during chronic therapy. However, the authors' recommendation to prescribe ISDN every 2–3 h rather than every 6 h does not take into account the fact that short dose intervals may further enhance the risk of tolerance.

Similar results are available from a placebo-controlled, double-blind investigation in patients with stable angina pectoris treated with ISDN in a sustained-release preparation (BLASINI et al. 1980). Besides haemodynamic effects, the antianginal effect of ISDN was assessed by determination of ST segment depression and exercise capacity during tests with a bicycle ergometer. These tests were performed after acute administration of 20–60 mg ISDN and 8 weeks after the start of chronic treatment with 20–40 mg ISDN t.i.d. At this time the rate of anginal attacks and nitrate consumption were evaluated. The haemodynamic and antianginal efficacy of ISDN, which was clearly present after acute administration in a dose-dependent manner, could no longer be observed after chronic treatment. Neither nitrate consumption nor the rate of anginal attacks nor the exercise capacity and ST segment depression differed significantly in the ISDN group from that in the placebo group. Although the data indicate tolerance it must be remembered that the exercise tests were carried out in the chronic phase 3 h after drug administration only. In addition, the results may have been influenced by the pharmaceutical preparation of ISDN as a sustained-release formulation. However, the fact that ISDN sublingually was effective in stopping the anginal attacks provides strong evidence that only partial tolerance has been developed.

The same investigators presented a report on patients with congestive heart failure, NYHA II, who took 40 mg ISDN orally every 6 h for 1 week (BLASINI et al. 1982). The investigators observed that the pulmonary arterial pressure responses to oral and sublingual ISDN became smaller from day to day. On day 7 the pressure was no longer affected, but on rechallenge after a 36-h nitrate-free interval the effect of ISDN was restored completely. The data support the hypothesis that organic nitrates might provoke tolerance towards some haemodynamic effects. These data, however, obtained in patients with moderate heart fail-

ure in the resting state, can hardly be extrapolated to the antianginal efficacy of organic nitrates. Furthermore, it should also be realised that the study demonstrates the rapid disappearance of tolerance. It can not be ruled out that rechallenge after shorter dose-free intervals (for example 8–12 h, which would be more related to clinical practice) would also obtain restoration of the initial effect. If so, a dose-free overnight period, which is the normal practice in the treatment of patients, could prevent the development of tolerance.

The influence of dosage and administration schedule has recently been demonstrated. RUDOLPH et al. (1983) reported the results of a study on two groups of patients with stable angina pectoris who where treated with various administration schedules of ISDN. Indications for development of tolerance were observed in patients treated with 40 mg ISDN q.i.d. whereas in the group treated with 20 mg ISDN b.i.d. the antianginal effect was maintained completely during the chronic phase of treatment. These findings fit the observations of JANSEN et al. (1982). They reported that the haemodynamic effect (e.g. decrease of pulmonary arterial pressure during physical exercise) and antianginal efficacy (exercise capacity) of IS-5-MN declined in patients with coronary artery disease who have been treated with this drug for 4 weeks at a dose of 50 mg t.i.d. Interestingly, the dose regimen of 20 mg t.i.d. provoked not only almost the same acute effects as the higher dose, but also the effect remained unchanged in the chronic phase without any indication that tolerance had developed.

b) Evidence that Nitrate Tolerance is Not of Major Clinical Relevance

There are many clinical studies that show the long-term efficacy of organic nitrates in the treatment of angina pectoris. However, STIPE and FINK (1973) have stated that the results and conclusions regarding the antianginal efficacy of drugs becomes more positive if the clinical experimental design is inappropriate. Therefore, only those clinical investigations will be discussed in the present chapter that provide data based on valid criteria for the assessment of the long-term antianginal effect (e.g. frequency of angina attacks, GTN consumption, excercise tests) and appropriate protocols including controls, placebo groups, crossover trials, etc. WINSOR and BERGER (1975) investigated GTN as a sustained-release preparation in excellently documented studies on patients with stable angina pectoris. In the basic study they used a complex protocol with double-blind, multiple changeover design. According to extensive diary notes over 24 weeks the frequency and the severity of angina attacks, as well as the sublingual GTN consumption, were significantly decreased during oral GTN treatment (2.6 mg, 3–6 times daily). Possible tolerance was investigated by careful weekly evaluations of the clinical status of the patients. None showed a decreased GTN effect over the 8 weeks of oral GTN therapy.

Complementary continuous monitoring of the electrocardiograms over 6–10 days with evaluation of the ST depressions during defined physical activities confirmed the sustained antianginal effect of oral GTN. Finally, exercise tolerance tests 4 h after the last tablet ingestion demonstrated a significant enhancement of the exercise capacity and reduced duration of the pain induced by the load. It should be noted that the sustained antianginal effect of GTN was undoubtedly demonstrated, whereas the haemodynamic parameters such as blood pressure or

heart rate showed no significant differences in the chronic phase between placebo and GTN treatment, indicating haemodynamic, but not antianginal tolerance. The conclusions drawn from this study were confirmed by further well-conducted investigations with similar designs (DAVIDOV and MROCZEK 1977; COLE and KAYE 1975). Furthermore, the chronic administration of GTN as ointment has been reported to be effective in patients with stable angina. The enhanced exercise capacity as well as the acute haemodynamic and antianginal effects of sublingual GTN persisted over several weeks. Indications of tolerance were not observed (REICHEK et al. 1974).

The aim of an investigation reported recently (GEORGOPOULOS et al. 1984) was the evaluation of the possible tolerance towards the antianginal effects of GTN administered in a new formulation which provides a continuous transdermal absorption of the drug. In this single-blind, placebo-controlled study over a mean period of 150 days a markedly stable reduction of angina attacks was obtained, treadmill tests provoked less anginal pain and ST segment depression was diminished. Taking into account the fact that in the placebo phase, which was incorporated for each patient at different stages of the study, there was complete disappearance of all GTN effects, "not the slightest indication of any development of tolerance to the antianginal effect of GTN" was found. The sustained antianginal effect has also been documented for the so-called long-acting nitrates such as ISDN. LEE et al. (1978 a) investigated by means of a double-blind protocol patients with stable coronary artery disease who were exposed to exercise tests before and 10 min after sublingual administration of 0.6 mg GTN. This procedure was carried out prior to an 6 h after the last dose of 30 days treatment with 30 mg t.i.d. ISDN or placebo. The authors not only observed unchanged effects of GTN on increased exercise duration and decreased ST depression, but also an improvement of these two parameters before the GTN challenge after 30 days ISDN treatment, which indicates both a lack of cross-tolerance of ISDN to GTN and a sustained antianginal effect of oral ISDN.

Further well-conducted studies designed to evaluate nitrate tolerance in patients with angina pectoris are in agreement with the results of the investigations reviewed. Even though they differ regarding the administration of the nitrate (including ointment), protocol and parameters measured, neither a loss of the antianginal efficacy of the long-acting nitrates nor a desensitisation to the acute effect of sublingual GTN has been found (FREMONT 1961; ARONOW and CHESLUK 1970; GOLDSTEIN et al. 1971; BECKER et al. 1976; DANAHY and ARONOW 1977; LEE et al. 1978 b; DISTANTE et al. 1981; BRUNNER et al. 1981; SCHWARZER and MLCZOCH 1982). In addition to coronary arterey disease, some clinical reports have demonstrated sustained improvement of patients with different types of nitrate preparation administrated with the aim of reducing the load on the heart (for review see ABRAMS 1980).

Controlled clinical trials have been presented by FRANCIOSA et al. (1978 a, b) and FRANCIOSA and COHN (1980). The nitrate therapy resulted, when compared with placebo, in a clear-cut symptomatic clinical improvement or a sustained decrease in the pulmonary wedge pressure induced by ISDN, indicating that tolerance has not been developed. Since the retesting was done 14 h after the last administration, it cannot be ruled out that a possibly developed tolerance had dis-

appeared within this drug-free time interval. Even if this were so, it would mean that tolerance disappears rapidly and is of minor importance. However, the possibility of nitrate dependence was raised in this study because of the remarkable deterioration in the clinical state (including two sudden deaths) of patients who had been taking ISDN prior to the study and then discontinued the drug during the 4-week placebo run-in period. These events were similar to those seen in industrial workers exposed to GTN (see Sect. E.II).

Some investigations reviewed indicate that the haemodynamic effects or the antianginal efficacy of organic nitrates might be attenuated during long-term treatment with these drugs. The fact, however, that well-designed and well-documented trials resulted in controversial deductions leads to the conclusion that tolerance can be induced only under certain conditions. Experimental and clinical studies demonstrate that the dose and dosing intervals are obviously determinant criteria for the possible development of tolerance. The higher the dose and the shorter the dosing intervals the more tolerance must be expected. For ISDN or other long-acting nitrates it seems to be sufficient to keep an overnight period free of drug administration in order to restore the responsiveness and to prevent development of tolerance. Although no valid data are available it could be suggested that a critical plasma concentration for each nitrate exists above which tolerance might be expected. This suggestion is supported by the observation that tolerance disappears rapidly after cessation of nitrate exposure, as well as by the fact that clinical studies with pharmaceutical preparations which provide a low but continuous absorption of nitrates (ointment, patches) failed to demonstrate diminished haemodynamic or antianginal effects.

Although the different nitrates obviously exert their haemodynamic effects via the same receptor, the drugs differ with respect to their tolerance inducing properties. The risk of induction of tolerance seems to be higher for the lipophilic nitrates with high activity such as GTN. On the other hand, its tolerance disappears faster; moreover, GTN still provokes haemodynamic effects when the body has become tolerant – at least partly – to the so-called long-acting nitrates. This means that clinically relevant cross-tolerance to sublingual GTN might not exist during oral long-term treatment with the consequence that a loss of response to sublingual GTN for stopping anginal attacks need not be feared.

In summary, since the individual sensitivity to nitrate action is variable and unpredictable for each patient, the lowest effective dosage schedule should be utilised in long-term treatment. If this is kept in mind, it is suggested that development of tolerance during long-term therapy is not of clinical relevance.

II. Nitrate Dependence

The main source of concern with respect to the development of tolerance towards nitrates has come from the explosives industry. Many reports have unanimously documented withdrawal symptoms in munitions workers. The characteristic syndrome consists of severe typical headaches in exposed people who are absent for 2–3 days from the nitrate-laden environment (LAWS 1910; EBRIGHT 1914; SCHWARTZ 1946). The employees are known to rub GTN into their skin or wear impregnated headbands on weekends or holidays in order to avoid the headaches.

These observations, of course, can be assessed as a sign of dependence. Besides the syndromes mentioned, serious sequelae of nitrate withdrawal have been reported. It has been demonstrated that some explosives workers suffer from chest pain 2–3 days after removal from their nitrate-laden environment (HOGSTEDT and ANDERSSON 1979). In addition, there is strong evidence that the risk of sudden death is enhanced among explosives workers, especially after withdrawal from nitrate exposure (SYMANSKI 1952; CARMICHAEL and LIEBEN 1963; LUND et al. 1968; LANGE et al. 1972; KLOCK 1975; for review see also MORTON 1977). It has been suggested that the withdrawal from GTN or other nitrates leads to an increased sensitivity to vasoconstrictor stimuli and thus to rebound vasoconstriction in the systemic and/or the coronary vascular bed with consequent coronary ischaemia. Experience in explosives workers exposed to GTN or other nitrates thus provides evidence for the occurrence of tolerance (disappearance of headaches after some days at work) and dependence (appearance of headaches, chest pain or sudden death a few days after withdrawal from nitrate exposure) on organic nitrates. But it is unclear whether these observations argue in favour of the occurrence of a relevant tolerance in patients treated with nitrates. It should, however, be remembered that patients are exposed to far smaller amounts of these compounds. Nevertheless, the episodic observations of chest pain, coronary spasms or sudden death in munitions workers or patients who have been withdrawn from nitrates leads to the recommendation that an abrupt cessation of treatment with these drugs should be avoided.

F. Efficacy, Routes of Administration, Formulations and Dosages

I. Stable Angina

1. Treatment of Acute Attacks

a) Trinitroglycerin

It is generally accepted that GTN given either sublingually or as a spray is the most effective therapy for rapid termination of an acute anginal attack (for literature up to 1973 see ARONOW 1975). The usual single doses range between 0.3 and 0.8 mg. KATTUS and ALVARO (1975) showed in 20 patients with documented ischaemic heart disease that anginal pain which had been induced by treadmill walking began to ease off despite continued walking 74.7 s after sublingual administration of 0.3–0.6 mg GTN. Complete or maximal incomplete relief was reached after 190.3 s. Ischaemic electrocardiographic changes reverted to normal in 13 of 20 cases. In a later study the duration of action was tested by successive 10-min walks at identical workloads every 30 min by the same group (KATTUS et al. 1979). A dose of 0.4 mg sublingual GTN gave protection for slightly longer than 1 h in this experimental setting.

b) Isosorbide Dinitrate

Whereas there is no doubt about the acute efficacy of GTN, the effectiveness of sublingual ISDN has been questioned. For example, ARONOW (1975) had found

that sublingual ISDN did not differ from placebo in the treatment of ergometrically provoked angina. However, ample experimental evidence of the excellent acute antianginal activity of ISDN has been accumulated since then. Thus, KATTUS and ALVARO (1975) compared the time to onset of relief of treadmill-induced angina in 20 patients after sublingual administration of 0.3–0.6 mg GTN and of 5 mg ISDN against placebo. Pain began to disappear 107.6 s after sublingual ISDN administration and complete relief was reached at 315.1 s while the patients continued walking at a constant speed. Thus, the onset of action proved to be somewhat slower than after sublingual administration of GTN, but in an identical experimental setting (KATTUS et al. 1979) the duration of protective action of 5 mg ISDN was shown to be 2.5–3 times longer than that of 0.4 mg GTN. According to GRÜNTZIG (1980), the onset of antianginal efficacy in pacing-induced angina and impaired left ventricular function may even be quicker after administration of 1.25 mg ISDN as a spray than that of 0.18 mg sublingual GTN.

2. Prevention of Anginal Attacks

a) Trinitroglycerin

α) Sublingual Administration. The duration of protection against angina after the usual sublingual doses of GTN is approximately 60 min (KATTUS et al. 1979). If administered 2–3 min prior to performing short-lasting activities in which an anginal attack may be anticipated, sublingual GTN can be very effectively used as a prophylactic agent.

Since, however, the majority of angina-precipitating events cannot be predicted so precisely, the development of long-acting principles has been aimed at for decades. Three basic approaches have been tried. First, the development of new chemical entities among the organic nitrates, such as ISDN, PETriN, PETN, mannitol hexanitrate, trolnitrate phosphate and very recently IS-5-MN. Second, a change in the route of administration of GTN such as transdermal devices using ointments or very recently patches. Third, the development of sustained-release formulations for oral administration.

β) Oral Administration. Since the half-life of GTN is in the range of 2–4 min, oral prophylactic treatment has become possible only after the development of preparations with a controlled and sustained-release form of therapeutically effective doses of GTN. WOLF et al. (1976) analysed haemodynamic and electrocardiographic parameters during repeated rapid right atrial pacing after administration of 5 mg long-acting GTN preparation and demonstrated an antianginal efficacy over at least 2 h. WINSOR et al. (1972) reported pharmacodynamic activity, documented by alterations of digital volume pulse, for more than 7 h after 2.6 mg sustained-release GTN. HIRSHLEIFER (1973) observed an increase of forearm plethysmographic response following the same dose of sustained-release GTN over an identical period. Increasing the dose to 7.8 mg resulted in a duration of action of 12 h as compared with placebo. VOLKMER and HOCHREIN (1977) showed haemodynamic and antianginal activity over 6 h after administration of a single oral dose of 6.5 mg sustained-release GTN in patients with coronary artery disease.

Extensive and thoroughly conducted studies by WINSOR and BERGER (1975) have proved that the antianginal efficacy seen after a single dose can be maintained during long-term treatment with oral sustained-release GTN, too. In a double-blind, randomised, crossover trial over 6 months with randomly sequenced 1-month treatment periods of 2.6 mg GTN or placebo t.i.d., GTN reduced the incidence and severity of anginal attacks by about 50%, as well as the consumption of sublingual GTN capsules. On the basis of a polynomial trend analysis over a period of 8 weeks, no signs of tolerance development could be detected. In 15 other patients, ST segments were continuously monitored over 10–12 h during long-term treatment under normal life-style and were compared with those under matched activities during the placebo period. This approach clearly proved a significant prophylactic antianginal activity of sustained-release GTN. Finally, these results were confirmed in 22 other patients by multistage exercise testing 4 h after administration of the usual dose of 2.6 mg sustained-release GTN. Similar results were obtained in a double-blind, randomised group comparison study in 12 patients each with proven coronary artery disease under a 12-week treatment with oral sustained-release GTN or placebo subsequent to a 12-week run-in period with placebo (DAVIDOV and MROCZEK 1976). Doses of 19.5–39 mg/day sustained-release GTN led to a significant decrease in the frequency of anginal attacks, whereas at the same time the exercise capacity was considerably increased (86%).

γ) *Ointment.* Cutaneous exposure to GTN has long been known to have prolonged pharmacodynamic effects (CRANDALL et al. 1931). By cutaneous absorption of the highly lipophilic GTN, the hepatic first-pass degradation of this high clearance drug is circumvented, since only about 10% of the cardiac output passes through the liver. Thus, although absorption through the multilayered epithelium of the skin is usually rather low, sufficient amounts of active drug reach the systemic circulation undecomposed.

The effects of 2% GTN ointment and placebo on exercise tolerance have been studied in 12 coronary patients by DAVIDOV and MROCZEK (1976). Significant antianginal efficacy could be established for 3 h at least. In a similar way, AWAN et al. (1978) showed a cardiocirculatory and antianginal activity after administration of 4 cm GTN ointment over at least 150 min in 9 patients with ischaemic heart disease. KARSH et al. (1978) reported on the basis of a randomised, double-blind study in 10 patients with angina pectoris a significantly increased exercise capacity as well as a reduction in ST segment depression over at least 3 h after administration of 5–8 cm 2% GTN ointment. These results have been confirmed by SALEM and SINGH (1979). Finally, according to DAVIDOV (1981) using 2 cm 2% GTN ointment applied to a 6×8 cm area, a duration of antianginal activity of as much as 8 h may be achieved. Previous studies of REICHEK et al. (1974) had already shown that the antianginal activity after a single administration of GTN ointment is maintained during long-term treatment for periods up to 8–12 weeks.

δ) *Patches.* Although the suitability in principle of transdermal administration of GTN has already been proved by the use of ointments, such ointments have various drawbacks. It is inconvenient and sometimes also unappealing for patients to have to apply an ointment several times daily and to cover it with an

occlusive dressing. Furthermore, precise dosing is difficult and appreciable fluctuations in plasma concentrations with correspondingly increased side effects may occur (IMHOF et al. 1981). Some of these drawbacks have very recently been overcome by the development of transdermal therapeutic systems which guarantee a programmed release of GTN through a semipermeable, microporous membrane from self-adhesive systems or a slow release of GTN from a polymer matrix which is attached directly to the skin (COLFER et al. 1982; DEXTER 1982). GTN concentrations in plasma reach a plateau within 2 h after administration and are claimed to remain constant until removal of the systems (P. MÜLLER et al. 1982). A placebo-controlled, double-blind, crossover study in 13 patients over two periods of 14 days each showed antianginal efficacy as proved by a decreased frequency of anginal attacks and a reduction of exercise-induced ST segment depression after administration of a system containing 25 mg GTN of which 5 mg are released every 24 h (GEORGOPOULOS et al. 1982). On the other hand, O'HARA et al. (1983) failed to demonstrate any antianginal activity of 2 weeks treatment with one patch a day as assessed by a computer-assisted maximal treadmill test in 18 patients in a double-blind, randomised trial. In a similar way, CREAN et al. (1983) could not detect significant differences in objective (exercise ECG, Holter monitoring) and subjective signs of ischaemia in ten patients with frequent stable angina treated with one GTN patch or placebo in a double-blind, double-crossover trial of four 1-week periods. It seems that one patch releasing 5 mg GTN within 24 h might not be sufficient for therapeutic activity, whereas 2–4 of these simultaneously administered systems showed a considerable anti-ischaemic efficacy (THOMPSON 1983) which was in the range of that after 20 mg IS-5-MN given orally (OSTERSPEY et al. 1984). Thus, further clinical experience is needed to assess both the effectiveness and the possible disadvantages of this interesting new way of nitrate delivery such as the frequency of contact dermatitis, which is already known for topically administered GTN (HENDRICKS and WILLIAM 1979; SAUSKER and FREDERICK 1978). In addition, one has to consider the considerable differences in penetration with respect to different skin regions (HORHOTA and FUNG 1978), apart from problems in technology and handling of the transdermal devices which may lead to irregular fluctuations of GTN plasma concentrations. Furthermore, the risk of tolerance development has to be carefully monitored in case sufficiently high dosed systems (e.g. 4 patches/day) are used for chronic treatment.

b) Isosorbide Dinitrate

ISDN is without doubt at present the most popular long-acting nitrate amongst the several chemical entities which have been designed to prolong the duration of action. Up to the mid-1970s, however, its therapeutic usefulness was a matter of debate. Thus, ARONOW (1975, 1976) persistently stated its ineffectiveness, as well as that of other so-called long-acting nitrates. In the meantime, however, several adequately designed studies have proven unequivocally the high antianginal activity of ISDN. Interestingly, one of these studies was conducted by the group of ARONOW himself (DANAHY et al. 1977), which may serve as the most convincing evidence of the therapeutic value of ISDN.

α) *Sublingual Administration.* The longer duration of action of sublingually administered ISDN as compared with sublingual GTN has been established by several studies. KATTUS et al. (1979) showed a protective action of 5 mg ISDN against treadmill-induced angina of 2.5–3 h duration as compared with about 1 h after administration of 0.4 mg GTN in a placebo-controlled trial. STEELE et al. (1975) studied the prevention of myocardial ischaemia in 20 patients with angiographically demonstrated coronary artery disease who underwent atrial pacing before and after 5 mg ISDN administered sublingually. Antianginal activity was present in 19 of 20 patients until the end of the experiment at 65 min. At the same time, left ventricular performance was improved, ST segment depression during pacing decreased and myocardial lactate extraction significantly increased. POLINER et al. (1977) described an onset of action of 5–10 mg sublingual ISDN occurring 15–20 min after administration and a duration of action of 1–1.5 h as measured by the decrease of mean arterial pressure, mean pulmonary arterial pressure and wedge pressure in patients with acute coronary insufficiency. In a later study by STEELE et al. (1978) the effects of 5 mg sublingual ISDN on left ventricular ejection fraction, heart rate, systemic blood pressure and ST segment depression at rest and during exercise were found to be sustained for 3 h in 15 patients with coronary artery disease. Thus, it can be assumed that sublingual administration of 5 mg ISDN exerts a powerful antianginal protection of 1–3 h duration.

β) *Oral Administration.* KASPARIAN et al. (1975) have already provided evidence in a double-blind, placebo-controlled group comparison that oral doses as low as 10 mg ISDN exert beneficial effects on central haemodynamics and left ventricular dysfunction at least up to 60 min after administration in coronary patients. GLANCY et al. (1977) examined blood pressure and heart rate in patients with coronary artery disease who were given small (5–10 mg) as well as large oral doses of ISDN (10–30 mg) and placebo in a double-blind, crossover experiment. The haemodynamic effects became apparent at 15 min and were present up to 3 h after the small dose and were still significant 4 h after the larger dose. The exercise capacity in nine of ten other patients was clearly increased 2 h after oral administration of 7.5–20 mg ISDN. Similar results were obtained by MARKIS et al. (1979) after oral administration of 20 mg ISDN or placebo to patients with stable angina in a randomised, double-blind, crossover study. Mean systolic blood pressure was 25 mmHg less than the control value 4 h after administration. Increased exercise tolerance and reduced ST depression were observed for at least 3 h.

Finally, DANAHY et al. (1977) showed in a double-blind, randomised, crossover study that the acute oral administration of a mean dose of 29 mg ISDN to 21 patients with angina pectoris exerted typical nitrate haemodynamic effects and increased the net exercise time over a period up to 5 h. After initial testing, the patients took the dose of ISDN they had during the acute study for a mean period of 5.6 months before retesting in order to check whether the salutary effect seen after acute oral dosing of ISDN could be maintained during long-term treatment. This procedure revealed that the haemodynamic changes were significantly less during retesting, although the increase in exercise time of up to 5 h was no different initially and at retest. At least partial tolerance to the haemodynamic effects

after chronic use of ISDN is discussed by the authors. Moreover, since retesting was done after a 14-h drug-free period overnight there is the possibility that tolerance with respect to the antianginal efficacy might have already been reversed at the time of retesting (see Sect. E.I.2). The possibility that partial tolerance not only to the circulatory effects, but also to the antianginal effects of ISDN may occur during long-term treatment with high doses of ISDN has been underlined by THADANI et al. (1982). Whereas exercise duration increased significantly for 8 h after acute dosing of 30, 60, and 120 mg each, it was increased for only 2 h during a sustained q.i.d. regimen. Using a sustained-release formulation of ISDN at doses of 20, 40, and 60 mg t.i.d., BLASINI et al. (1980) even reported a complete loss of haemodynamic and antianginal efficacy in a carefully conducted randomised, double-blind, crossover trial. On the other hand, LEE et al. (1978a) observed equivalent improvements in exercise performance and ST depression before and 1 month after therapy with 40 mg sustained-release ISDN every 8 h in a double-blind, randomised group comparison of 28 patients. The obvious inconsistencies of the results already cited on long-term treatment are most probably due to the different protocols used, i.e. the lag time after the last administered dose and retesting, the time schedule for testing, the doses, dosage intervals and formulations used (see Sect. E.I.2). Nevertheless, the controversial results of several well-conducted trials point at least to the possibility of the development of tolerance, especially when high doses, short dosage intervals or sustained-release preparations of ISDN are used.

γ) *Ointment.* It has been shown that administration of 100 mg ISDN as a 10% ointment is able to achieve therapeutically active plasma levels of 3–6 μg/ml up to 12 h (MANSEL-JONES et al. 1978). With 40 mg in healthy volunteers, changes in heart rate, cardiac output and systolic blood pressure could be observed beyond 6 h (SCHINZ et al. 1978). BRUNNER et al. (1980) reported an improved exercise tolerance and ST depression after administration of 150 mg ISDN in 10% ointment for at least 7 h in patients with coronary artery disease. Thus, therapy with ISDN ointment seems to be possible in principle, although it is not very common.

c) Pentaerythrityl Tetranitrate

There are only a few controlled studies on this organic nitrate. KLAUS et al. (1973) compared the effects of acutely administered 5 mg sublingual ISDN, 10 mg PETN, and 10 mg PETriN in patients with angina pectoris. Each drug significantly increased the duration of exercise at 45, but not at 100 min after administration. ARCE-GOMERZ et al. (1980) tested the antianginal efficacy of 80 mg PETN q.i.d. in a double-blind, placebo-controlled study with two complete crossover periods of 4 weeks duration each. The frequency of anginal attacks and consumption of sublingual GTN were significantly lower during each of the active drug periods and the average exercise time was increased.

d) Pentaerythrityl Trinitrate

PETriN 10 mg given sublingually exhibited antianginal activity for 45 min (KLAUS et al. 1973) to 60 min (GILES and HOLDER 1978). The drug was clearly ef-

fective for longer than 0.6 mg sublingual GTN in a double-blind, randomised, placebo-controlled, crossover comparison (VOHRA et al. 1979). It might therefore be useful as a sublingually administrable nitrate.

e) Mannitol Hexanitrate and Trolnitrate Phosphate

Since the U.S. Food and Drug Administration has stated (Federal Register 47, No. 79, 17674, 1982) that no adequate studies proving the effectiveness or bioavailability of either of these compounds are available, they are not further discussed in this chapter.

f) Isosorbide-5-mononitrate

The newest chemical entity which has been introduced into the prophylactic treatment of angina pectoris is IS-5-MN. STAUCH et al. (1975) and MICHEL (1976) were the first to show that IS-5-MN possesses antianginal activity in patients with coronary artery disease after intravenous administration. These experiments, however, as well as later studies by STAUCH and GREWE (1980), were performed in order to prove that NEEDLEMAN's assumption that orally administered ISDN is ineffective, because of its complete metabolic degradation to inactive metabolites, was incorrect. ABSHAGEN and SPÖRL-RADUN (1980) and SEIDEL and MICHEL (1981) were the first to report on the typical nitrate pharmacodynamic activities of IS-5-MN after oral doses in humans, and 20 mg was suggested as the optimal single oral dose (ABSHAGEN and SPÖRL-RADUN 1981). This surprisingly low dose – in view of its far weaker vasodilating potency in comparison with the parent compound ISDN – is due to its 100% bioavailability without any first-pass metabolism, which is in contrast to all other therapeutically used organic nitrates (ABSHAGEN et al. 1981 a).

REIFART et al. (1981 a) were accordingly able to show in a double-blind, randomised, placebo-controlled trial that acutely administered 20 mg IS-5-MN is approximately as active as 20 mg sustained-release ISDN and 20 mg IS-2-MN in reducing the exercise-induced ST depression in patients with stable angina. ISBARY et al. (1981) demonstrated highly significant typical nitrate changes of central and peripheral haemodynamics in patients with coronary artery disease 60 min after oral administration of 20 mg. In a similar setting, BIAMINO et al. (1982) showed even more impressive haemodynamic and antianginal effects after single doses of 40 mg IS-5-MN. Under chronic treatment, G. MÜLLER et al. (1983 a) demonstrated in 18 coronary patients in an ISDN and placebo-controlled, randomised, double-blind, three-way, crossover trial a substantial antianginal activity of IS-5-MN as assessed by exercise capacity, reduction of stress-induced ST segment depression, frequency of anginal attacks and acute nitrate consumption. The duration of protective activity of 20 mg IS-5-MN during chronic treatment using a t.i.d. regimen was evaluated by another double-blind, randomised, crossover study in 18 patients with coronary artery disease by G. MÜLLER et al. (1983 b). The patients were treated either with 20 mg IS-5-MN, a combination of 20 mg IS-5-MN with a β-blocker or placebo t.i.d. for 2 weeks each. The exercise capacity and reduction of ST segment depression at the end of the 2-week treatment period with IS-5-MN were still highly significantly improved in comparison with placebo 10.5 h after the last administration of 20 mg. This proves the considerable long-

acting antianginal activity of this nitrate after multiple dosing and makes the development of nitrate tolerance under this regimen very unlikely. Moreover, direct proof of a lack of the development of tolerance to its action during a 4-week treatment with 20 mg IS-5-MN t.i.d. is given by a comparison of both the antianginal and central haemodynamic activity after the first and the last dose of IS-5-MN (JANSEN et al. 1982). Since IS-5-MN exhibits an inherently long half-life of 4–5 h, even a b.i.d. regimen gives adequate control of angina pectoris without the need for sustained-release formulations, which in principle are critical for high clearance drugs such as all other organic nitrates (PORCHET and BIRCHER 1982; ABSHAGEN and DEMMER 1981). Thus, according to ÜBERBACHER et al. (1983), approximately 70% of patients with stable angina can be effectively treated with 20 mg IS-5-MN b.i.d. Among the nitrates, IS-5-MN might therefore represent a promising new approach to a rational prophylactic treatment of stable angina. This has to be checked by further studies.

II. Unstable Angina and Variant Angina

There is no unequivocal definition of unstable angina. According to CONTI et al. (1979), the syndrome includes three subsets of patients: first, those with new onset of angina at rest or new onset of minimal effort angina; second, patients with progression from stable angina, i.e. increased duration, intensity and/or frequency of attacks; and third, those with recurrent angina immediately following a myocardial infarction. The aggravating factors may be rapid progression of atherosclerotic obstructions, recurrent platelet or fibrin emboli and/or coronary spasm. Coronary spasm, either isolated or superimposed on atherosclerotic lesions, has in particular been shown to represent the main causal factor of variant angina or Prinzmetal's angina (HILLIS and BRAUNWALD 1978). The underlying mechanism of coronary spasm seems to be a localised disorder in coronary vasomotion (HILL et al. 1982 a) due to a variety of autonomic, neurogenic or humoral influences.

1. Acute Treatment

Within the therapeutic armamentarium for this condition, organic nitrates represent the classical first line of approach (GROVES 1977; PLOTNICK 1979; COHN and BRAUNWALD 1980). For initiation of antianginal therapy – in order to interrupt acutely the status anginosus – short-acting nitrates are given sublingually or, in severe cases, intravenously or even intra-arterially.

The most commonly used drug is GTN, but favourable therapeutic results have also been reported with sublingually administered ISDN (WILLIS et al. 1976). The usual single doses are 0.4–0.8 mg at dose intervals of 30–60 min for sublingual GTN (PLOTNICK 1979; RICH et al. 1980) and 2.5–5 mg as often as 1.5–3 h for sublingual ISDN (WILLIS et al. 1976; PLOTNICK 1979). In the majority of patients who do not respond to such multiple dosing of sublingual GTN, relief can be achieved by intravenous administration of GTN (DAUWE et al. 1979; MIKOLICH et al. 1980; HILL et al. 1981). In 89% of patients with prolonged myocardial ischaemia pain relief was achieved immediately or after titration of the optimum intravenous GTN dose. Only 2 of 45 patients developed hypotension requiring reduction of the infusion rate (MIKOLICH et al. 1980). In a similar way,

intravenous GTN was able to control ischaemia-induced high-grade ventricular ectopic activities during a Prinzmetal's angina attack (ANTMAN et al. 1980).

The intravenous administration allows a tailored rate of drug delivery according to the individual haemodynamic situation and clinical condition of the patient being treated. Because of the very short half-life of GTN, the infusion rate can easily be adjusted to the main criteria of efficacy such as relief of pain or decrease of arrhythmias. A drop of mean arterial pressure below the critical value for coronary perfusion must, of course, be avoided. It has been found that it is usually not necessary to reduce mean arterial pressure by more than 10%. Because of the danger of severe hypotension, some authors recommend starting the infusion at a rate of 5–10 μg/min (HILL et al. 1981; FLAHERTY 1982) with a subsequent titration of 5–10 μg/min increments every 3–5 min until these criteria of efficacy are reached. In haemodynamically stable patients, an initial intravenous bolus of GTN of 50–100 μg can be considered (LEINBACH and GOLD 1977; ANTMAN et al. 1980). Similar results to those with GTN in the management of angina at rest have been obtained with continuous infusion of ISDN at a rate of 1.25–5.0 mg/h (DISTANTE et al. 1979).

In patients who are refractory to sublingual or even intravenous GTN, direct intra-arterial administration may be helpful. By this route of administration, high local concentrations of active drug can be achieved without, or with far less, systemic effects. Thus, refractory coronary spasm which had either occurred spontaneously or been induced by ergonovine was successfully treated with doses of 25–100 μg (PEPINE et al. 1982) and of 40 μg (BENTIVOGLIO and GRÜNTZIG 1981), whereas BUXTON et al. (1980) used doses up to three times 300 μg GTN.

In all cases where GTN or ISDN are administered by the parenteral route, care must be taken that the appropriate infusion sets are used since it is known that GTN and ISDN are absorbed by polyvinylchloride sets (COSSUM et al. 1978; LEE and FENTON-MAY 1981; COTE and TORCHIA 1982). This absorption may lead to a fall in potency of up to 70%–80% of the initial value in the first 15–30 min after an intravenous infusion. For this reason, glass and/or polypropylene sets should be used to avoid this phenomenon (LEE and FENTON-MAY 1981; HANS et al. 1982; BAASKE et al. 1982).

2. Preventive Treatment

In order to prevent recurrent episodes of angina at rest, long-acting sublingual or oral nitrates and/or topical GTN have proved to be effective when properly used. The advantage of sublingually or orally administered ISDN as compared with sublingual GTN is its clearly longer duration of action (3–4 h), as has been shown by haemodynamic measurements after single doses in patients with unstable angina (WILLIS et al. 1976). In a similar way, GTN ointment exhibits long-lasting protection against angina due to coronary spasm (PLOTNICK 1979). This has recently been proved by a carefully conducted randomised, single-blind, crossover experiment in ten patients with angiographically documented vasospastic angina, who were given 2% (15 mg) GTN or placebo ointment ever 6 h for a period of 48 h followed by a second treatment period of 24 h. GTN ointment produced a significant reduction of painful and painless ischaemic episodes as documented by continuous ECG monitoring (SALERNO et al. 1981).

It has been reported that patients suffering from variant angina who did not respond to conventional therapy with 2.5–10 mg ISDN every 3–4 h while awake, combined with GTN ointment at bedtime responded promptly to oral therapy with the Ca^{2+} channel blocker verapamil (FREEMAN et al. 1981). Although the open study design does not permit a definite conclusion, the possibility of development of nitrate tolerance has to be considered during high dose therapy at short dosage intervals with organic nitrates (see Sect. E.I.2). Observations during continuous intravenous administration of high doses of GTN in patients with unstable angina (WILKINSON and SANDERS 1980) or cadiac failure and myocardial infarction (SCHULZ et al. 1982) underline this danger.

In contrast to the results of the open study of FREEMAN et al. (1981), recent double-blind, crossover investigations using 20 mg nifedipine, 20 mg ISDN, a combination of both drugs and placebo in 36 patients with predominantly prevailing variant angina showed a superior efficacy of ISDN over nifedipine (SCHULZ et al. 1983). Whereas ISDN proved its antianginal activity irrespective of the type and pathomorphology of coronary disease, nifedipine reduced ischaemic ST segment depression only if high-grade stenoses were present. It was inefficient in selected subgroups of coronary patients with occluded but collateralised coronary arteries supplying viable myocardium – probably due to a steal phenomenon. Thus, if properly used, organic nitrates seem to be at least as effective in the treatment of variant angina as Ca^{2+} channel blockers. HILL et al. (1982 b) showed in a randomised, double-blind, subchronic trial in 16 patients that ISDN at a mean daily dose of 75 mg given in a q.i.d. regimen decreased the mean frequency of angina to 0.77 episodes per day and nifedipine (mean daily dose 65 mg) to 0.69 as compared with 1.71 episodes per day during the run-in phase. Thus, neither drug seemed clearly superior. This finding was confirmed by another randomised, double-blind comparison of nifedipine and ISDN with crossover periods of 5 weeks treatment each in 12 patients with vasospastic angina (GINSBURG et al. 1982). Although nifedipine at a mean daily dose of 82 mg caused a greater mean reduction in pain frequency than ISDN at a mean daily dose of 66 mg (q.i.d. regimen for each), this difference was not statistically significant. Nifedipine, however, was preferred by the majority of patients owing to less side effects, in particular less headaches. On the other hand, it is well known that nitrate-induced headaches disappear rapidly in most patients after initiation of therapy. Thus, these two studies prove that organic nitrates, although sometimes thought of as "grandfather" drugs, are no less effective than the more recently introduced calcium channel blockers, even in angina due to coronary spasm, for which calcium channel blockers claim a special efficacy.

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CHAPTER 11

Molsidomine

J. SCHOLTHOLT

A. Chemistry – Physicochemical Properties

Molsidomine, *N*-carboxy-3-morpholinosydnonimine ethyl ester (SIN-10), molecular weight 242.23 ($C_9H_{14}N_4O_4$), is a derivative of the sydnonimines, a class of nonbenzenoid aromatic compounds that posses a so-called mesoionic structure. Such a compound has never been introduced into therapy despite known multiple pharmacologic properties of different sydnones and sydnonimines (ACKERMANN 1967; DAENIKER and DRUEY 1962 a–c; KIER and ROCHE 1967; OEHME et al. 1965). The drug was synthesized by MASUDA et al. in 1970. The initial pharmacologic characterization was performed by KIKUCHI et al. (1970 a, b) and the drug described as having antihypertensive and antianginal properties.

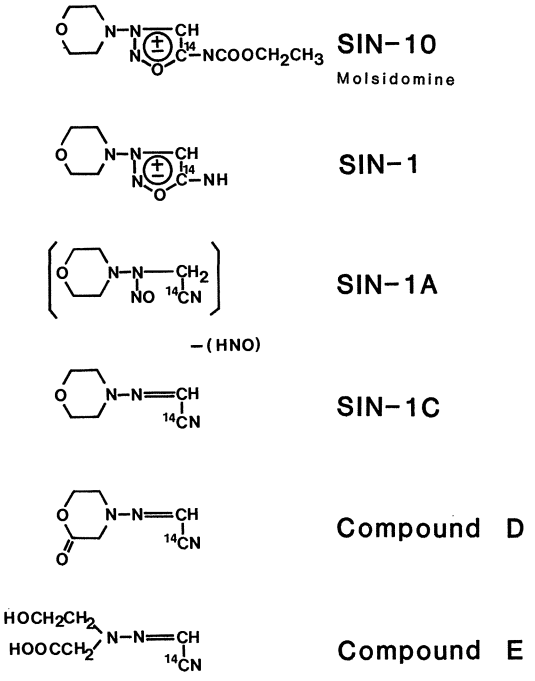

Fig. 1. Structure and metabolic pathway of molsidomine. Modified from TANAYAMA et al. (1974)

The compound (Fig. 1) exists as colorless crystals or white crystalline powder and is tasteless and odorless. The melting point is in the range 140°–141 °C. It can be dissolved in $CHCl_3$, 0.1 *M* HCl, ethanol, ethyl acetate, and methanol. Solubility is limited in water, acetone, and benzene. Stability is good in aqueous solvents at pH 5.7 and less in very alkaline solvents. The p*K* value is 3.0 ± 0.1 at 100 °C (ASAHI et al. 1971; KIKUCHI et al. 1970 b; MASUDA et al. 1970).

B. Metabolism – Kinetics

I. Metabolism and Kinetics in Animals

Figure 1 demonstrates the metabolic fate of molsidomine ^{14}C-5 in rats (TANAYAMA et al. 1974). In the first step, the ethoxycarbonyl moiety of molsidomine (SIN-10) is enzymatically removed to yield SIN-1. Studies in tissue slices of different organs from rats indicate that this occurs mainly, if not exclusively, in the liver. This is further supported by the finding that in hepatectomized rats the blood level of molsidomine is hardly changed and pharmacologic effects cannot be observed. This indicates that the pharmacologic activity of molsidomine is due to an active metabolite and not to the unchanged molecule (HIRANO et al. 1975). Part of the unchanged parent drug is excreted in the urine, the main route of elimination of the drug and its metabolites (85% within 24 h; Fig. 2).

The first metabolite SIN-1, which is also partly excreted in the urine, is converted to SIN-1C via SIN-1A. This conversion ensues nonenzymatically. SIN-1 is readily transformed in aqueous solution to SIN-1A at pH 7 (ASAHI et al. 1971;

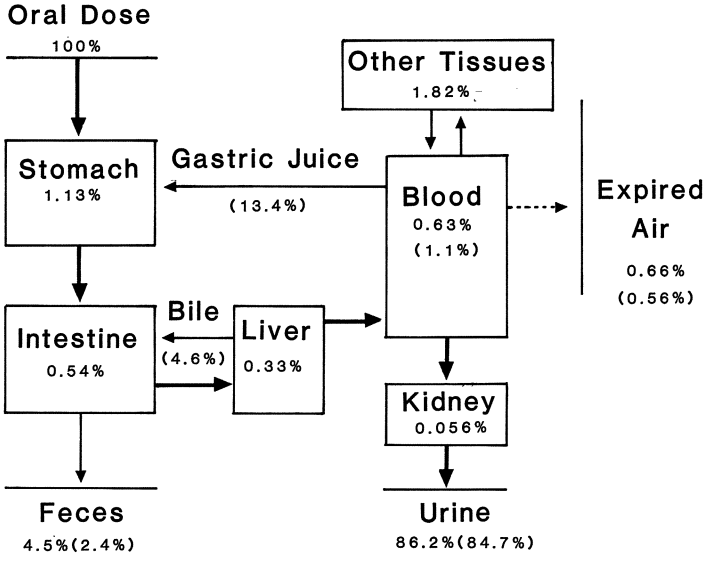

Fig. 2. Fate of radioactivity following oral administration of SIN-10 ^{14}C. Figures denote percentage of dose at 48 h and figures in parentheses represent percentage at 24 h. Modified from TANAYAMA et al. (1970)

MASUDA et al. 1970) which in turn is rapidly converted to SIN-1C. Identification of the unstable SIN-1A is difficult because of rapid conversion to SIN-1C. As shown by in vitro metabolic studies, the oxidation of SIN-1C to compound D is carried out primarily in the liver as has also been demonstrated for the deacylation process of SIN-10 to SIN-1. Some of the polar metabolites excreted in the urine are still not fully identified.

The metabolic fate of molsidomine ^{14}C-5 with regard to absorption, tissue distribution, excretion, and kinetics in blood and tissue (Fig. 2) was studied in several animal species (TANAYAMA et al. 1970; SCHRAVEN 1979; FROMSON et al. 1981). The pattern of excretion is uniform with all species studied (FROMSON et al. 1981; SCHRAVEN 1979). Determination of the unchanged molsidomine with high pressure liquid chromatography (HPLC) (DELL and CHAMBERLAIN 1978) in dogs (SCHRAVEN 1979) revealed that 15–30 min after administration it can be detected in blood. Elimination occurs with a half-life of 30 min; 6 h after administration no unchanged molsidomine can be measured.

II. Metabolism and Kinetics in Humans

Metabolism and kinetics in humans have been studied after single and multiple dosing of the compound (DELL et al. 1978; OSTROWSKI 1979). Figure 3 demonstrates blood levels in humans after single oral and intravenous doses of molsidomine. After intravenous administration, the concentration of the drug declines rapidly during the early phase with a half-life of about 15 min, correlating well

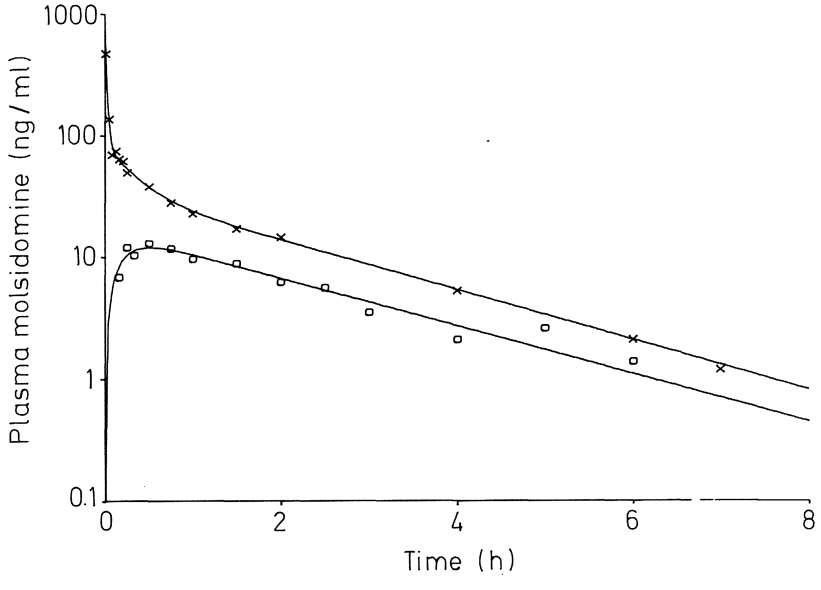

Fig. 3. Plasma level of molsidomine in humans after intravenous (*crosses*) and oral (*circles*) application of the drug; 4 mg intravenously ($N=5$) and 2 mg orally ($N=7$). Modified from OSTROWSKI (1979)

with that observed in animals. The final elimination occurs with a half-life of 1–1.5 h with regard to unchanged molsidomine. The lower curve in Fig. 3 represents the oral kinetics of a single dose of molsidomine. Maximum blood levels are reached after 30–60 min, mean concentration ranges from 10–15 ng/ml. The final elimination is identical for oral and intravenous application. From the areas under the curves (AUC) after oral and intravenous application it was estimated that a first pass of about 30%–40% exists. The drug is practically completely absorbed, nearly 90%–95% of the radioactivity is excreted with the urine after several days. Only 3%–4% is excreted with the feces. The kinetics of unchanged molsidomine in human volunteers after repeated dosing reveal that, with respect to unchanged molsidomine in plasma, no cumulation occurs (OSTROWSKI 1979).

C. Pharmacology

I. Cardiovascular Pharmacology

1. Structure–Activity Relationship of Substituted Sydnonimines

The structure–activity relationship of 3-substituted sydnonimines (KIKUCHI et al. 1970a, b) revealed that, depending on the nature of the 3 substituent, a broad spectrum of pharmacologic effects can be observed. 3-Substituted sydnonimines induce a prolonged hypotension in several animal species if different amino groups (e.g., morpholine, piperidine, dialkylamine) are attached to the 3 position. The 3-morpholinosydnonimine hydrochloride, SIN-1 (Fig. 1) proved to be an especially potent hypotensive and spasmolytic compound with regard to its effect on the peripheral vascular bed, predominantly on the capacity vessels. By rendering the central and autonomic nervous system nonfunctional by such measures as spinal transsection, or pharmacologic blockade of autonomic ganglia and peripheral vascular receptors, it was demonstrated that there was essentially no influence or modulation of the autonomic nervous system. The effects of the drug were related to a direct interaction with vascular smooth muscle.

The most striking effect in anesthetized animals is hypotension, characterized by a decrease in pressure amplitude affecting systolic blood pressure to a larger degree than diastolic. This type of blood pressure reduction can be caused by a reduction in stroke volume and cardiac output without necessarily being accompanied by a reduction in precapillary vascular resistance. Because of the lack of negative inotropic effects reduction in stroke volume was caused by a reduction in venous return. This effect was directly measured. Further results derived from experiments on the isolated hindlimb of dogs confirmed that the compounds influence postcapillary vascular resistance to a greater degree than precapillary resistance.

Based on results of their structure–activity studies (KIKUCHI et al. 1970a, b; TAKENAKA et al. 1968), it was suggested that the hypotensive action of 3-substituted sydnonimines such as SIN-1 (see Fig. 1) is finally due to intermediates following ring opening of the molecule (HIRANO et al. 1975), an event which can be observed in vitro in alkaline solution (ASAHI et al. 1971; MASUDA et al. 1970). The suggested intermediate SIN-1A, *N*-nitroso-*N*-morpholinoaminoacetonitrile, is unstable and releases HNO in vitro (MASUDA et al. 1970). SIN-1A is a rapid, short-

acting potent vasodilator with a profile of action similar to nitroglycerin (HASHIMOTO et al. 1971). To increase stability of the molecule, the imino group in the 5 position was acylated with ethylchloroformiate (KIKUCHI et al. 1970 b). The resulting compound molsidomine [1] (SIN-10, Fig. 1), was introduced into therapy.

2. Hemodynamic Effects of Molsidomine

Extensive cardiovascular studies in different animal species have been performed (FIEDLER and SCHOLTHOLT 1978; HASHIMOTO et al. 1971; HIRANO et al. 1975; HIRATA and KIKUCHI 1970; HIRATA et al. 1975; IRIUCHIJIMA et al. 1971 a; KIKUCHI et al. 1970 b; TAKENAKA et al. 1970). Injection of molsidomine intravenously (i.v.) or intraduodenally (i.d.) to anesthetized dogs (Fig. 4) leads to a decrease in systolic and diastolic blood pressure. The effect is observed with doses as low as 0.05 mg/kg, independent of the route of administration. The effect develops and slowly reaches its maximum after 20–30 min. The duration of effect depends on the dose and can exceed several hours. With excessive i.d. doses (FIEDLER and SCHOLTHOLT 1978) the maximal effect on blood pressure can be achieved with 20 mg/kg i.d. Cumulative doses up to 444 mg/kg i.d. were tolerated by the anesthetized dogs.

In general, the reduction in systolic blood pressure is more pronounced than that in diastolic blood pressure. Left ventricular systolic blood pressure is reduced according to the reduction in peripheral blood pressure. There is a pronounced effect on left ventricular end-diastolic blood pressure. This pressure is lowered while peripheral blood pressure still remains unaffected. Normalization of peripheral blood pressure after drug application is not accompanied by normalization of left ventricular end-diastolic pressure. This reduced left ventricular end-diastolic pressure is long lasting and exceeds the effects on peripheral blood pressure.

Mean pulmonary arterial blood pressure decreases after drug application as was observed with the decrease in left ventricular end-diastolic blood pressure. Molsidomine i.v. or i.d. causes only minor changes in heart rate of anesthetized dogs or other animals. Depending on the route of administration and dose, slight decreases and increases can be observed.

Using dP/dt_{max} or $(dP/dt)/(LVP - LVEDP + c)$, where LVP is left ventricular pressure, LVEDP is left ventricular end-diasolic pressure, and c is a constant, as an index for left ventricular contractility, no negative or positive influence can be detected. Atrioventricular conduction (ECG) remains unaffected even after excessively high i.d. doses (FIEDLER and SCHOLTHOLT 1978). Cardiac output is reduced in different animal species (BERDEAUX et al. 1978; HOLTZ et al. 1978; IRIUCHIJIMA et al. 1971; KIKUCHI et al. 1970 a). Reduction in afterload in addition to reduction in preload should influence left ventricular dimensions (FIEDLER and SCHOLTHOLT 1978; FIEDLER et al. 1980, 1983 b) in dogs. Ultrasonic determination of left ventricular dimensions during systole and diastole revealed that molsidomine clearly reduced these parameters, indicating indirectly a reduction of left ventricular systolic and diastolic volumes (see Fig. 4).

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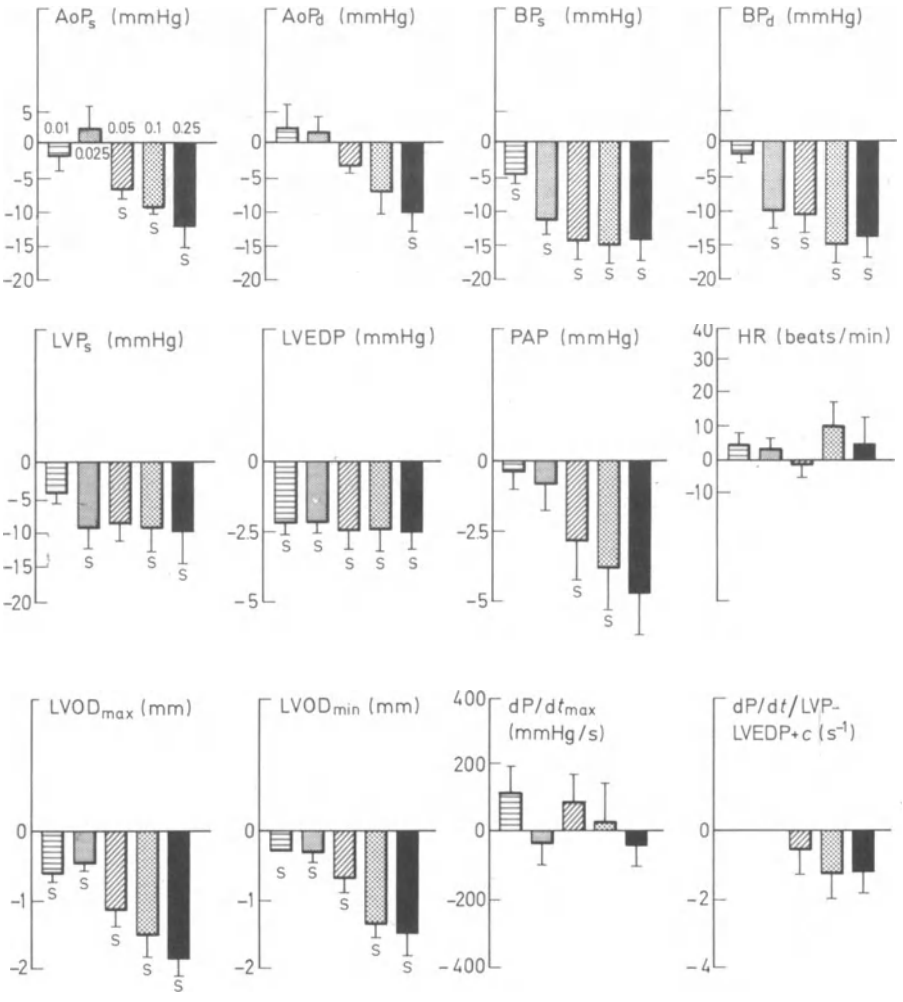

Fig. 4. Mean changes ± SEM of hemodynamic parameters in anesthetized dogs after intravenous injection of molsidomine (mg/kg). Changes were measured 20–30 min after drug application. AoP_s/AoP_d, systolic/diastolic blood pressure aorta; BP_s/BP_d, systolic/diastolic blood pressure arteria femolaris; LVP_s, systolic blood pressure left ventricle; *LVEDP*, left ventricular end-diastolic blood pressure; *PAP*, mean blood pressure arteria pulmonalis; *HR*, heart rate; $LVOD_{max}$, left ventricular maximal outer dimension; $LVOD_{min}$, left ventricular minimal outer dimension; dP/dt_{max}, and $(dP/dt)/(LVP - LVEDP + c)$, indices for contractility of left ventricle

3. Studies on Organ Blood Flow

Comparing the cardiovascular effects of SIN-1A, SIN-1, and molsidomine, differences can be observed not only with regard to the duration of action, but also with regard to the pharmacologic profile (HASHIMOTO et al. 1971; KIKUCHI et al. 1970a). While SIN-1A has direct vasodilating properties comparable to nitro-

glycerin, molsidomine does not influence blood flow of different organs when injected directly into the supplying arteries. This lack of direct vasodilating effect agrees with the results of several studies in which the drug was applied systematically (BUCKLEY et al. 1982; FIEDLER and NITZ 1981, 1982; HOLTZ et al. 1978; KIKUCHI et al. 1970 b; SCHOLTHOLT et al. 1978 a, b; TAKENAKA et al. 1970). In general, coronary blood flow is reduced following application of molsidomine. Oxygen content in coronary sinus blood remains unchanged, clearly indicating metabolic adaption to the reduced needs. Myocardial oxygen consumption decreases. Blood flow in many organs, studied with different methods in different animals, remains essentially uninfluenced by the drug, indicating no major effect on peripheral vascular resistance. But this effect can be observed at higher doses (HOLTZ et al. 1978).

4. Studies on Venous Return

These hemodynamic effects of molsidomine favor a primary action on the venous circulation. Reduction in left ventricular filling pressures without influence on contractility, reduction in cardiac output, and essential lack of effect on precapillary vascular resistance can easily be explained by a dominant effect of molsidomine on the venous system. The effects on the venous circulation were studied by several groups (BASSENGE 1978; BERDEAUX et al. 1978; GRUND et al. 1978; HASHIMOTO et al. 1971; HIRATA et al. 1975; HOLTZ et al. 1978; KIKUCHI et al. 1970 a; TAKENAKA et al. 1970). All studies confirm that the drug increases venous capacity and reduces venous return.

5. Studies in Models of Myocardial Ischemia

The reduction in left ventricular wall tension, which can be derived from the data discussed, should positively influence left ventricular function under acute or chronic ischemic conditions. Studies on regional myocardial blood flow in normal and acute ischemic myocardium revealed some redistribution of blood flow from epicardial to endocardial portions of the myocardium (BERDEAUX et al. 1978; SCHOLTHOLT et al. 1978 b). Coronary collateral blood flow did not change in a model of acute myocardial ischemia in dogs (GROSS and GHARAIBEH 1980).

Other studies in dogs give evidence of reduction of infarct mass following administration of molsidomine (FIEDLER et al. 1982 b; MARTORANA et al. 1982 a, b). These studies are supported by the observation that the elevation of the ST segment of epicardial ECG is reduced. In another study (BERDEAUX et al. 1978), this parameter was negatively influenced, but heart rate increased following application of molsidomine. The positive effects in preventing reperfusion arrhythmias can at the moment only be attributed to the changes in general hemodynamics (MARTORANA et al. 1982 c). The effect might be influenced by some effect on thrombus formation which has been described by FIEDLER (1981, 1982).

In dogs with chronic coronary insufficiency, molsidomine was studied with respect to its influence on collateral blood flow. This was indirectly achieved by measuring retrograde coronary blood flow and blood pressure (HIRATA and KIKUCHI 1970; IRIUCHIJIMA 1971). Molsidomine did not change retrograde coronary blood pressure in spite of reduction in coronary perfusion pressure. This was ac-

companied by an increase in retrograde coronary blood flow. These results can be interpreted as stemming from reduced extracoronary vascular resistance following reduction in venous return, cardiac output, preload, and afterload. It has also been demonstrated that molsidomine dilates large coronary vessels or collaterals (BASSENGE et al. 1982; PUJADAS et al. 1982; SCHULZ et al. 1982). This effect could explain the results.

6. Additional Pharmacologic Studies

The hypotensive effects of molsidomine mainly related to the venous pooling effect imply the possibility that plasma renin activity is influenced and that changes in catecholamine levels in blood take place. This was studied in dogs (STANEK et al. 1980). Molsidomine intravenously or orally applied increased plasma renin levels as well as catecholamine levels to some extent.

In case of emergency, it should be known whether the hypotensive activity of molsidomine can be counteracted. This problem has been studies in dogs (FIEDLER and GÖBEL 1978; FIEDLER et al. 1983 a). Norepinephrine as well as dopamine can reverse the hemodynamic effects of molsidomine. While peripheral blood pressure is increased and cardiac output augmented, the effects of molsidomine on preload are only moderately influenced, if at all. In contrast to norepinephrine and dopamine, dihydroergotamine antagonizes all hemodynamic changes induced by molsidomine.

II. Studies in Isolated Systems

1. Inotropic Effects

SIN-1 increased contractile force only at high doses in isolated, spontaneously beating guinea pig atrium or ventricular strips. This effect could be inhibited either by propanolol or by pretreatment with reserpine (KIKUCHI et al. 1970 a, b). Molsidomine was nearly ineffective. Comparable results were obtained in an isolated papillary muscle preparation from cat where contractility was studied under the influence of SIN-1 and molsidomine. Again molsidomine was ineffective while SIN-1 was partially positively inotropic at higher doses (MATHES and SCHINZ 1979). Using the isolated, blood-perfused dog papillary muscle preparation (HASHIMOTO et al. 1971) or the isolated dog heart preparation (TAKENAKA et al. 1968, 1970), it was demonstrated that molsidomine was ineffective with regard to influence on the inotropic state of the myocardium. Furthermore, no effect on coronary blood flow and myocardial metabolism could be observed.

2. Spasmolytic Effects

The spasmolytic effect of molsidomine and SIN-1 was studied in preparations of isolated guinea pig ileum, contracted with acetylcholine, histamine, and barium and in the isolated rabbit ileum (KIKUCHI et al. 1970 a, b). As shown in Table 1, SIN-1 counteracts the effect of all three spasmogens in comparable doses, indicating a nonspecific muscolotropic effect of SIN-1. Molsidomine, in a comparable preparation, was without effect at reasonable dose levels. The spontaneous motor activity in rabbit ileum was reduced only with SIN-1 and not with molsidomine.

Table 1. Spasmolytic action of SIN-1 and papaverine in the isolated guinea pig ileum. ID_{50} is concentration for 50% inhibition (Modified from KIKUCHI et al. 1970a)

	ID_{50} (g/ml)		
	Acetylcholine 1×10^{-8}	Histamine 1×10^{-8}	Barium chloride 2×10^{-5}
SIN-1	4.2×10^{-6}	5.1×10^{-7}	3.9×10^{-6}
Papaverine	4.4×10^{-6}	2.7×10^{-6}	1.9×10^{-6}

Using vascular tissue preparations, several studies were performed. Rat aortic strips, contracted with norepinephrine could be relaxed by molsidomine only at high doses (−50% at 10^{-3} mmol). SIN-1 was effective at much lower doses (−70% at 10^{-5} mmol). Using potassium chloride (30 mmol), molsidomine and SIN-1 were nearly ineffective (BIAMINO 1979). Since Ca^{2+} antagonists counteract potassium chloride-induced vascular spasm, it was concluded that molsidomine cannot be classified as having Ca^{2+} antagonistic properties.

In more detailed studies in a comparable model, this view was somewhat modified (FLECKENSTEIN-GRÜN et al. 1979). Again, studies were performed on isolated vascular strips of coronary and femoral artery from pigs and rabbits which were contracted with potassium (30 mmol). SIN-1 was preferably used and its effects were compared with those of Ca^{2+} antagonists (verapamil, fendiline, prenylamine, nifedipine) and nitro compounds (nitroglycerin, sodium nitroprusside). While Ca^{2+} antagonists cause a slowly developing relaxation this cannot be seen under the influence of SIN-1 or nitro compounds. Relaxation is nearly complete with Ca^{2+} antagonists, an effect which cannot be achieved with SIN-1 and nitro compounds. Under the influence of Ca^{2+} antagonists, no spontaneous reversibility of relaxation can be observed. This occurs under the influence of SIN-1 and nitro compounds. By comparing the effects of different drugs it was concluded that the relaxing effect of SIN-1 is comparable to that of nitro compounds and due to inhibition of the Ca^{2+}-dependent electromechanical coupling process of vascular smooth muscle. Additional studies on isolated papillary muscles of guinea pig demonstrated that SIN-1 at doses between 20 and 120 mg/l did not influence mechanical contraction amplitude and did not induce changes in the configuration of the action potential. SIN-1 cannot be compared in its effects to the well-known Ca^{2+} antagonists.

3. Effects on Guanylate Cyclase Activity

There is evidence (BÖHME et al. 1978; GRUETTER et al. 1979; KUKOVETZ et al. 1979; SCHULTZ et al. 1975) that cGMP might be involved in the regulation of vascular smooth muscle tone. As for nitro compounds, (nitroglycerin, sodium nitroprusside, sodium nitrate) this has been shown on strips of bovine coronary arteries (KUKOVETZ et al. 1979). A concentration-dependent increase in cGMP content (maximal 40- to 50-fold) was reported, accompanied by a relaxation of the vascular preparation. Since the increase in cGMP concentration preceded the mechan-

ical response this was taken as evidence for a causal relation between cGMP concentration and smooth muscle tone. SIN-1 was also studied in this model (KUKOVETZ et al. 1982) and the findings are in good agreement with those for the nitro compounds. Dependent on the concentration within the organ bath, SIN-1 increased the concentration of cGMP (about 35-fold) in vascular smooth muscle, again followed by the mechanical events already mentioned.

Using a soluble, cell-free, purified guanylate cyclase preparation of vascular origin (pig splenic artery), it was demonstrated (BÖHME et al. 1981, 1982) that the enzyme was stimulated half-maximally by 5×10^{-6} *M* SIN-1. The corresponding preparation from thrombocytes was stimulated half-maximally by 2×10^{-5} *M* SIN-1. Neither molsidomine nor SIN-1C (Fig. 1) was found to be active. This was confirmed (KUKOVETZ et al. 1982) by studies on a purified enzyme preparation from bovine coronary arteries. A maximal stimulation (about 100-fold) could be achieved by SIN-1.

If neither molsidomine nor SIN-1C stimulate purified guanylate cyclase (BÖHME et al. 1982), three possible intermediates must be discussed as mediators of the observed effect: SIN-1, SIN-1A, and HNO (see Fig. 1). The degradation of SIN-1 to SIN-1C ensues nonenzymatically. The velocity of this process can be followed in buffer solution (BÖHME et al. 1982). At a given time the actual concentration of the intermediates (SIN-1A, HNO) can be estimated. Using a different sydnonimine: 3-thiomorpholino-1′,1′-dioxidsydnonimine, which is also relatively rapidly degraded nonenzymatically to its corresponding A form ($t_{1/2} = 0.6$ min), but not further to the corresponding C form with the release of HNO ($t_{1/2} = 90$ min), it was concluded that the effects of SIN-1 on guanylate cyclase could be related to the actual concentration of the A form in the incubate and not to that of HNO. SIN-1A directly stimulates guanylate cyclase and not HNO or a corresponding *S*-nitrosothiol as discussed in the action of nitro compounds (IGNARRO and GRUETTER 1980). This interpretation of SIN-1A being the active metabolite is further supported by other experiments where cysteine (3 m*M*) is added to the incubate. While the effects of nitroglycerin on guanylate cyclase are enhanced, those of SIN-1 remain nearly unaffected (BÖHME et al. 1982).

4. Effects of Thrombocytes In Vitro

Induction of thrombocyte aggregation (human platelets) in vitro by ADP, thrombin, or arachidonic acid can all be inhibited by SIN-1, but not by molsidomine and SIN-1C (BÖHME et al. 1982; NISHIKAWA et al. 1982). SIN-1A was also found to be active (NISHIKAWA et al. 1982). The concentrations of SIN-1 and SIN-1A producing 50% inhibition of platelet aggregation induced by 1 μg/ml collagen were 0.6 and 0.08 μ*M*, respectively. Adding methemoglobin to the incubate attenuates the effects of SIN-1 and SIN-1A. This was taken as evidence for the assumption that the effects of both compounds were mediated by the nonenzymatically released HNO. Methemoglobin is a hemoprotein with high binding affinity for nitric oxides (MURAD et al. 1978). This view is different from that previously discussed (BÖHME et al. 1982). It has not been proven up to now what effect methemoglobin could have directly on SIN-1A. It is still not clear whether the effect on thrombocyte aggregation is dependent on the effect of the drug on guanylate cyclase activity. An inhibition of thrombocytic phosphodiesterase as a cause for the increased concentration of cGMP can be excluded (NISHIKAWA et al. 1982). Using rabbit and human platelets in vitro (BLOCK et al. 1982) it was shown that mainly SIN-1 and not molsidomine inhibits platelet aggregation induced by arachidonic acid and a prostaglandin endoperoxide analog (U-46 619). In ad-

dition, it was observed that thromboxane A_2 was reduced in the thrombocytes. It was also concluded that SIN-1 does not directly influence cyclooxygenase and thromboxane synthetase.

D. Clinical Pharmacology

I. Hemodynamic Studies

Hemodynamic studies in patients with coronary heart disease demonstrate that the effects of molsidomine observed in humans (BLAZEK et al. 1977 b; CYRAN and BOLTE 1979; DETRY et al. 1981; ENKE et al. 1978; FLECK et al. 1979; KARSCH et al. 1978, 1979; LOSSNITZER et al. 1979; MEYER et al. 1978, 1980; MIYAZAKI 1970 a, b; NIEHUES et al. 1978; OSTROWSKI et al. 1980, 1981; RUTSCH et al. 1979; SCHARTL et al. 1978, 1979 a; SCHWEIZER et al. 1979; SLANY and MÖSSLACHER 1979; SLANY et al. 1976; STAUCH et al. 1979; TANEMOTO et al. 1969; TAUCHERT et al. 1979) are quite comparable to those in animals.

Molsidomine reduces both cardiac preload and afterload. Under resting conditions the reduction in peripheral blood pressure – more pronounced for systolic than diastolic – is accompanied by an appropriate reduction in cardiac output. Effects on heart rate are variable, depending on the route of administration. Slight increases or no change have been described. In view of these effects stroke volume must be reduced. Calculated total peripheral resistance does not change.

Studies on left ventricular function reveal no influence on the inotropic state of the myocardium. The reduction in cardiac output cannot be explained by a negative inotropic effect of molsidomine in humans. It is accompanied by a decrease in left ventricular end-diastolic blood pressure. More pronounced is the decrease in pulmonary artery blood pressure, affecting systolic, diastolic, and mean pressure. This reduction in left ventricular filling pressure is followed by a decrease in left ventricular end-diastolic and end-systolic diameters and hence, by a reduction of the respective left ventricular volumes. Consequently, an increase in ejection fraction can be expected under certain conditions as well as improvement of certain dyskinesias of left ventricular wall motion.

The hemodynamic changes induced by molsidomine can be explained by an extracardiac mode of action: increase in venous capacity due to a direct relaxing effect on venous smooth muscle (BIAMINO 1979; SCHARTL et al. 1979 a). The changes all favor a reduction of myocardial oxygen consumption (TAUCHERT et al. 1979). Furthermore, improvement of myocardial perfusion and of disturbed wall motion owing to reduction of extravascular coronary resistance can be expected (DIRSCHINGER et al. 1978; NECHWATAL et al. 1981; WAGNER et al. 1979).

The published data provide evidence that molsidomine induces hemodynamic changes comparable to those induced by organic nitrates with the exception that molsidomine acts for several hours independent of the route of administration: orally, intravenously, or sublingually. The doses by all three routes are about the same (2–4 mg), indicating excellent absorption of the compound. The observed effects on hemodynamic parameters in humans can be related to the blood level of molsidomine (FACH and BECKER 1982; KARSCH et al. 1978; OSTROWSKI 1979, 1980, 1981; RÖHL and LEHMANN 1980). Since the degradation of the enzymati-

cally generated SIN-1 from molsidomine ensues nonenzymatically it can be assumed that the pool of unchanged molsidomine represents the amount of active metabolite. The clinical studies correlating blood level of molsidomine to the effect seem to confirm this assumption.

Under exercise conditions the hemodynamic changes induced by molsidomine are still partly demonstrable. Peripheral blood pressure does not reach the predrug level and remains slightly below it. Since heart rate and cardiac output can exceed the predrug level a reduction in total peripheral resistance is apparent. The increase in left ventricular pump function together with an increased total body oxygen extraction should improve exercise tolerance and capacity. This has been demonstrated in several studies. One prominent effect under exercise conditions is the still remarkably decreased pulmonary arterial blood pressure. It has been suggested that a direct vasodilator effect on pulmonary circulation might be present which could be of interest for the treatment of pulmonary hypertension of different origin (LOSSNITZER et al. 1979; SCHARTL et al. 1979 b).

Nitrates have been used to influence peripheral resistance in the case of acute pump failure, e.g., acute myocardial infarction (AWAN et al. 1981). Several studies with molsidomine (APTECAR et al. 1981; BUSSMANN et al. 1979) suggest that the drug can be used as can nitrates, to influence hemodynamic parameters in patients with acute myocardial infarction.

Efficacy of the drug in the treatment of angina pectoris has been proven in several studies (open, double-blind, crossover) either acutely or during prolonged treatment. In acute studies (BLAZEK et al. 1977 a; BECKER et al. 1979; BENDER and GEBAUER 1979; GLUNZ et al. 1978; GREWE and STAUCH 1977; GUERCHICOFF et al. 1978; JANSEN and KLEPZIG 1976, 1978; KATO and TAKAHASHI 1969; LEHMANN et al. 1979, 1980; MAJID 1980; MANNES et al. 1978; TAKESHITA et al. 1977; WITCHITZ et al. 1981), the drug was effective with respect to reduction of number and severity of anginal attacks and to reduction in nitrate consumption. The most frequently documented evidence for the efficacy of molsidomine is an improvement of ischemic changes in ECG during exercise.

The efficacy of molsidomine in long-term studies has been proven in several studies (BAYER and ABUBA 1979; BLASINI et al. 1981; KALIMANN et al. 1979; KOPP 1979). The effect can be demonstrated after treatment for 6–12 months. There is no indication of development of tolerance to molsidomine.

II. Side Effects

Evidence of side effects is rare (BAYER and ABUBA 1979; GREWE and STAUCH 1977; JANSEN and KLEPZIG 1976, 1978; KALIMANN et al. 1979; KOPP 1979; LEHMANN et al. 1979, 1980; MANNES et al. 1978; STEIM 1979; TAKESHITA et al. 1977). The most frequent complaint is headache, but frequency is low as compared with that following treatment with nitrates. It is a matter of speculation whether this symptom is related to the increase in intracranial pressure observed in dogs (FIEDLER et al. 1982 a). No orthostatic dysregulation has been reported following treatment with molsidomine. No increase of intraocular pressure was observed (LEYDECKER 1978).

III. Effects on Thrombocyte Aggregation In Vivo

In vitro studies indicated that molsidomine might influence thrombocyte aggregation in vivo (SILBERBAUER et al. 1982; WALTER and WEBER 1982). There is evidence that molsidomine reduces platelet aggregation in vivo. In addition, some effects on prostacyclin metabolism have been discussed.

IV. Effects in Hypertensive Patients

The most prominent effect of molsidomine in humans and animals is the reduction in peripheral blood pressure. The drug was administered to patients with hypertension in acute as well as prolonged studies (1 month) (MILEI et al. 1980). the possibility of using molsidomine to treat hypertension is greatly supported by the results obtained.

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CHAPTER 12

β-Adrenoceptor Blocking Agents

B. N. C. PRICHARD

A. Introduction

The idea of different adrenergic receptors originated with LANGLEY in 1905. He suggested that the receptors contained inhibitory and excitatory receptor substances. Sir Henry Dale (1906) observed the next year that while the excitatory actions of adrenaline were blocked by ergot, the inhibitory ones were not, providing evidence for two types of adrenergic receptors. Then in 1948 AHLQUIST published his now classical paper in the *American Journal of Physiology* where he studied the effect of six sympathetic stimulating drugs and revealed two patterns of response. He termed one pattern the α effects which included vasoconstriction, here adrenaline was most potent, followed by noradrenaline. Secondly there were β effects which included smooth muscle relaxation and cardiac stimulation. Isoprenaline was the most active here, adrenaline was third, and noradrenaline least effective (AHLQUIST 1948). The adrenergic receptors have subsequently been further divided into α_1, α_2, β_1 and β_2 receptors (LEFKOWITZ 1976; WILLIAMS and LEFKOWITZ 1978; LEES 1981; ANDERSSON 1982). The first report of β-adrenoceptor blocking activity came in 1958 when the properties of dichloroisoprenaline were discovered in animal experiments. This drug had powerful intrinsic sympathomimetic activity and while its importance as a pharmacological tool was recognised the therapeutic potential of this new approach was not (MORAN and PERKINS 1958; POWELL and SLATER 1958).

When it occurred to Sir James Black that sympathetic overactivity was frequently deleterious to the heart, e. g. in angina pectoris and arrhythmias, he began the quest for therapeutically useful agents that would interfere with the effect of catecholamines on the heart. The pharmacology of pronethalol (nethalide) was reported by BLACK and STEPHENSON (1962), and subsequently the use of β-blocking drugs has been demonstrated in many diseases (PRICHARD et al. 1980); they represent one of the most important therapeutic advances of recent times. Extensive accounts of their pharmacology have been published (CLARK 1976; BARTSCH et al. 1977; WILLIAMS and LEFKOWITZ 1978; HIMMS-HAGEN 1972; PHILLIPS 1980; POTTER 1981; SAS and KOVACS 1981).

B. Pharmacodynamics

I. Classification of β-Blocking Drugs

The β-blocking drugs have a number of associated properties. They can be divided into those which are nonselective and those which have a selective action

Table 1. Classification of β-adrenoceptor blocking drugs[a]

		Intrinsic sympathomimetic effect	Membrane stabilising effect (quinidine-like effect)
Division I: Nonselective block ($\beta_1+\beta_2$)			
Group I	Oxprenolol Alprenolol Penbutolol	+	+
Group II	Propranolol	−	+
Group III	Pindolol	+	−
Group IV	Sotalol Timolol Nadolol	−	−
Division II: Cardioselective block (β_1)			
Group I	Acebutolol	+	+
Group III	Practolol	+	−
Group IV	Atenolol Metoprolol	−	−
Division III: Nonselective block + α-block			
Group II	Labetalol	−	+
Division IV: Cardioselective block + α-block			
No example yet available			

[a] All these drugs have been shown to lower the blood pressure

on the β-receptors, and further into drugs which in addition possess α-receptor blocking properties. They may be subdivided into various groups according to the presence or absence of intrinsic sympathomimetic activity (ISA) (or partial agonist activity) and membrane stabilising activity (MSA) (Table 1; FITZGERALD 1972; PRICHARD 1978).

At doses used in humans the blood concentrations produced are probably too low to have any significant membrane stabilising effect. The D (+) isomer of propranolol, which has the same membrane stabilising action, but not the β-blocking effect of racemic (i.e. ordinary) propranolol, lacks antianginal (WILSON et al. 1969) or antihypertensive effect (WAAL-MANNING 1970; PRICHARD and BOAKES 1977). Any "cardiodepressant" action (a term that is confusing and best avoided) in humans is not a direct effect, but results from the prevention of sympathetic stimulation.

II. The Associated Properties of β-Blocking Drugs

While overall it is true that similarities between the pharmacological properties of β-blocking drugs are dominant, there are a number of differences based on the

presence of their associated properties. Cardioselectivity (β_1 inhibition) must be distinguished from cardiospecificity. Cardioselective agents do not show full selectivity; a serious increase in airways resistance (bronchial receptor) may occur with other than small doses in sensitive asthmatics. For a similar inhibition of exercise tachycardia, cardioselective agents give much less inhibition of isoprenaline-induced tachycardia. This may suggest that while receptors in the heart innervated by the cardiac sympathetic are β_1, others away from the nerve ending responsive to isoprenaline are β_2. The addition of α-blocking properties to β-blocking action produces important haemodynamic differences, principally in acute reduction in blood pressure without a fall in cardiac output.

At rest, an agent with ISA gives less of a reduction of resting heart rate and cardiac output than that seen with a drug without sympathomimetic activity. At modest levels of exercise heart rates may be similar; at high levels of exercise drugs with ISA produce less of an inhibition of exercise tachycardia. Possibly because of less reduction in cardiac output at rest, they may produce less of a reduction of peripheral flow than nonselective agents without this property. ISA does not importantly protect against heart failure or asthma in susceptible subjects. The withdrawal phenomenon is probably less likely with drugs with ISA. The evidence on the pharmacodynamic properties of β-adrenoceptor blocking drugs has been obtained in normal subjects and patients, principally with angina pectoris and hypertension. With a few notable exceptions, e. g. asthma, the pattern of response in health and disease is similar.

III. Blockade of Exogenous Adrenoceptor Stimulation

The β-adrenoceptor blocking drugs are competitive inhibitors (antagonists) at the β-adrenergic receptor. An increase in concentration of the stimulating drug (agonist) e. g. isoprenaline, will overcome any blockade. The net effect on the receptor is proportional to the local concentration of agonist and antagonist; thus there is no such thing as complete β-blockade in terms of an exogenous stimulus (isoprenaline). Any increase in concentration of antagonist can be overcome by increasing the concentration of agonist, which in turn can be blocked again by an increasing concentration of antagonist. A series of dose–response curves to isoprenaline in the presence of increasing doses of β-adrenoceptor antagonist can be constructed. The curves show a parallel shift to the right, with the same response being obtained after the various doses of antagonist by increasing the dose of the agonist, isoprenaline (McDevitt 1977; Richards et al. 1977).

The β-blocking drugs vary greatly in their ability to inhibit isoprenaline. For equivalent inhibition of exercise tachycardia far less antagonism of the cardiac effects of isoprenaline is seen with the cardioselective drugs (Briant et al. 1973; Graham et al. 1973; Walden et al. 1982; McGibney et al. 1983). It does not appear to be due to unopposed vasodilator activity from isoprenaline following cardioselective blockade. Such a fall in blood pressure would produce vagal deinhibition, thus cardiac acceleration, minimising any cardiac blockade of isoprenaline. The prior administration of atropine (Arnold and McDevitt 1982) or angiotensin to maintain blood pressure (McGibney et al. 1983), does not affect this difference.

IV. Blockade of Endogenous Adrenergic Stimulation

The meaningful assessment of β-blockade (McDEVITT 1977) requires a measure of the blockade of endogenous sympathetic activity. The greater the degree of endogenous sympathetic activity the more sensitive the test for β-blockade. The heart rate supine and at rest is the result of a low sympathetic tone, the vagal tone predominates, while on standing there is a modest increase in sympathetic tone. These low levels of sympathetic activity are sufficient for it to be possible to demonstrate a dose–response relationship with a β-antagonist that does not possess ISA (PRICHARD and GILLAM 1971), but much better discrimination is obtained with increased endogenous sympathetic activity. JACKSON et al. (1975) reported a group of angina patients with similar reduction of resting heart rate to 55–60 beats/min, but poor clinical response to propranolol, whose control of symptoms was improved when exercising heart rate was used as a guide for dose. As levels of exercise are increased up until maximum there is an increased discrimination for β-blockade (McDEVITT 1977).

Intravenous propranolol reduces heart rate, and cardiac output; peripheral resistance increases, and thus there is little effect on resting blood pressure (SHINEBOURNE et al. 1967; ULRYCH et al. 1968). The cardiac output and heart rate are reduced to a similar degree after acute and long-term drug administration (TARAZI and DUSTAN 1972; GIBSON 1974), but it has sometimes been found that it is only after prolonged administration that there is a fall in blood pressure and a decline in peripheral resistance (TARAZI and DUSTAN 1972; HANSSON 1973; ABLAD et al. 1976). These findings have been confirmed with other β-blocking drugs that do not possess ISA, sotalol (SVEDMYR et al. 1970), nadolol (TEXTOR et al. 1982), and timolol (DUNN et al. 1978 a; FRANCIOSA et al. 1973).

A β-blocking drug with ISA exhibits certain haemodynamic differences. At rest, a β-blocking agent with ISA gives less of a fall of resting heart rate than that seen with a drug without ISA (PRICHARD et al. 1970 a; McDEVITT et al. 1977; SVENDSEN et al. 1979; TAYLOR et al. 1982; AELLIG 1983; KOSTIS et al. 1982 a). At modest levels of exercise, heart rates may be similar for drugs with and without ISA, as demonstrated in patients with angina by PRICHARD et al. (1970 a), but at high levels of exercise drugs with ISA at maximum dosage produce less of a reduction of exercise tachycardia (McDEVITT 1977; McDEVITT et al. 1977; CARRUTHERS 1982). Exercise tachycardia with a β-blocking drug without ISA is a result of vagal deinhibition, whereas the possession of ISA supplies some modest sympathetic stimulus to increase heart rate further. It should be noted that this difference between drugs with and without ISA may only be seen at maximum blocking dosage, and doses below maximum may not demonstrate this difference. Single dose studies (ERIKSSEN et al. 1982), which do not by definition show any indication that maximum doses have been achieved, are liable to be nondiscriminatory in this regard. At doses to produce just a 15% reduction in exercise tachycardia CARRUTHERS (1982) calculated the following ratios by assessing several separate studies: pindolol was taken as unity, being the most potent drug tested at that time; atenolol 21, oxprenolol 19, practolol 44, propranolol 25, and sotalol 160. In a previous study, also taking pindolol as unity, KALTENBACH and GULDNER (1972) found ratios of propanolol 20, oxprenolol 5.2, alprenolol 80 and prac-

tolol 32. Other more potent drugs than pindolol have been in early evaluation, e. g. bunolol (ROBSON and KAPLAN 1970) and carazolol (BARTSCH et al. 1977.

The changes in heart rate after the administration of β-blocking drugs usually parallel alterations in cardiac output (GIBSON 1977). There is evidence that those drugs which possess ISA when given at low levels of sympathetic activity, e. g. rest, result in less of a reduction in cardiac output; this has been shown with pindolol (SVENDSEN et al. 1979; VELASCO et al. 1982), practolol (SVENDSEN et al. 1979; TAYLOR et al. 1982; MAN IN'T VELD and SCHALEKAMP 1982) oxprenolol (GRANDJEAN and RIVIER 1968; TAYLOR et al. 1982) and this is also associated with less of an increase in pulmonary wedge pressure (TAYLOR et al. 1982). Associated with the absence of a decline in cardiac output with β-blocking drugs with ISA, such as pindolol (VELASCO et al. 1982) peripheral resistance does not increase as is the case with non-ISA drugs, but may indeed fall.

It has been suggested that the possession of cardioselectivity by a β-blocking drug results in less of a reduction in cardiac output for a unit reduction in heart rate compared with a nonselective drug, at least after intravenous administration (GIBSON 1977), but it would appear from the current evidence that this may not be so (MAN IN'T VELD and SCHALEKAMP 1982); VAN-HERWAARDEN et al. (1979) for instance found no difference in the reduction of cardiac output between metoprolol and propranolol, as had TAYLOR et al. (1981) in patients with ischaemic heart disease. Falls in cardiac output from atenolol in hypertensive patients (IBRAHIM et al. 1980) seem similar to those seen in studies with propanolol, and were found to be identical in normal volunteers (SVENDSEN et al. 1981).

The dual action of α- and β-adrenoceptor inhibition as seen with labetalol not surprisingly produces different responses from those of β-blockade alone (RICHARDS and PRICHARD 1979). After continuous oral administration to patients, small reductions in resting heart rate are usually found (LUND-JOHANSEN 1979) though individual changes are influenced by the degree of resting sympathetic drive. Patients with high resting heart rates and thus high sympathetic drive show more marked reductions in resting heart rate after administration of labetalol, particularly following intravenous administration (CUMMING et al. 1979; MARX and REID 1979). The cardiac output at rest does not change much after labetalol treatment (KOCH 1976; EDWARDS and RAFTERY 1976; MEHTA and COHN 1977). On the other hand at high levels of exercise there is some reduction of cardiac output (EDWARDS and RAFTERY 1976), but in patients with ischaemic disease changes have been found to be less than after propranolol treatment (SILKE et al. 1982).

V. Response to Physiological Stimuli in Patients Treated with β-Blocking Drugs

The use of β-blocking drugs is not associated with postural nor exercise hypotension (PRICHARD and GILLAM 1969; PRICHARD et al. 1970 b, c). There is an increase in peripheral resistance on standing, as might be expected, as innervation of the α-constrictor receptor is intact (PRICHARD et al. 1970 c). A rise in the environmental temperature from 7° to 30 °C increases postural and exercise hypotension in

patients treated with sympathetic neurone inhibitory drugs such as bethanidine and guanethidine. This is probably because of uncompensated vasodilation in skin blood vessels, whereas after propranolol treatment an increase in environmental temperature did not affect the response of blood pressure and exercise (PRICHARD et al. 1970 b).

The elevation of blood pressure with dynamic exercise is reduced by β-blockade (SHINEBOURNE et al. 1967; BATEMAN et al. 1979; VAN-HEERWAARDEN et al. 1979; LEENEN et al. 1980). It does not appear that there is any important difference in the response to dynamic exercise between nonselective and cardioselective agents. This has been demonstrated when metroprolol and propranolol were compared in normal volunteers (SKLAR et al. 1982). The rises in systolic blood pressure and heart rate were similarly affected, but neither drug affected diastolic blood pressure. Similar results have been obtained in hypertensive patients with metoprolol and propranolol (CLAUSEN et al. 1979), and with atenolol and nadolol (WILCOX and HAMPTON 1982).

The pressor response to isometric exercise does not appear to be greatly modified by β-blocking drugs. For instance, neither intravenous nor 4 weeks oral timolol in hypertensive patients significantly reduced the rise in blood pressure to handgrip, although after oral administration of timolol the final blood pressure reached was lower owing to the decline in levels of resting blood pressure (DUNN et al. 1978 a). A double-blind study with atenolol indicated that the pressure effect of isometric exercise was the same as with placebo although again the final pressure was lower after atenolol treatment owing to the decline in baseline (BATEMAN et al. 1979). In support of a possible difference between the cardioselective and nonselective agents, WAAL-MANNING (1979 b) found evidence of a less marked rise in diastolic pressure with atenolol than with propranolol, pindolol or oxprenolol following isometric exercise. Similarly NYBERG (1977) found a reduction in the increase of pressor response from metoprolol compared with propranolol, but in a later study in patients with angina he found no difference between metoprolol and alprenolol, both drugs reducing the final blood pressure reached, but not the rise of pressure after handgrip (NYBERG 1979). Likewise MORRISON et al. (1982) found no difference in the effect of metoprolol and propranolol in the pressor response in hypertensive patients to isometric exercise. The addition of α-blocking activity to β-blockade, as in labetalol, was found to reduce the rise of blood pressure to near maximal effort on handgrip in contrast to the absence of effect with propranolol (NYBERG and BERGLUND 1982).

The administration of β-adrenoceptor blocking drugs reduces the cardiac contribution to a variety of other stimuli. Propranolol (PRICHARD and GILLAM 1966), pronethalol (PRICHARD 1964) and practolol intravenously (B. N. C. PRICHARD 1970, unpublished work) reduce the overshoot of Valsalva's manoeuvre after cessation of effort, but without reducing vasoconstriction during effort. Likewise both intravenous and 4 weeks oral timolol reduced the tachycardia of Valsalva's manoeuvre and the pressor overshoot (DUNN et al. 1978 a). Prolonged oral administration of propranolol inhibited vasoconstriction during the effort phase of Valsalva's manoeuvre, which contrasts to the effect of bethanidine, guanethidine, and methyldopa (PRICHARD et al. 1970 b).

Propranolol may reduce blood pressure during coitus (Fox 1970), but labetalol appears more effective in women than propranolol (Riley and Riley 1981). Propranolol does not reduce the pressor response to pain (Nicotero et al. 1968) or cold water (Guazzi et al. 1976; Morrison et al. 1982; Velasco et al. 1982). Likewise the pressor response to cold stimuli was not reduced by metoprolol (Morrison et al. 1982), however the addition of α-blockade to β-blockade as seen with labetalol did attenuate the cold pressor response (Maconochie et al. 1977). The increase in blood pressure from the stress of sorting ball bearings was reduced or abolished by 6 weeks oral propranolol or metoprolol (Dunn et al. 1978 b), but not by methyldopa, although this produced control of resting baseline blood pressure (Dunn et al. 1978 b). The pressor response to mental arithmetic was reduced by propranolol 320 mg/day (Guazzi et al. 1976), but lower doses of propranolol, metoprolol, and alprenolol only reduced peak pressures, and not the overall rise from baseline values (Nyberg et al. 1977). The rise in blood pressure in response to a loud noise has been reported to be increased by propranolol, but not by metoprolol (Andren et al. 1981).

Experiments in normal volunteers indicate that the rise in diastolic pressure in response to smoking is increased by propranolol, in contrast to atenolol which did not. The rise in systolic pressure was reduced by intravenous propranolol, whereas atenolol had no effect. This was thought to be due to antagonism by propranolol of the β-dilator activity of adrenaline liberated during smoking (Trap-Jensen et al. 1979). Forearm blood flow was reduced by smoking after propranolol administration, while atenolol was without effect. However, in contrast, after at least 4 weeks oral metoprolol or propranolol in hypertensive patients, neither drug increased the rise in diastolic (or systolic) blood pressure after smoking (Houben et al. 1981). In a recent study Freestone and Ramsay (1983) reported that neither oxprenolol nor propranolol affected the rise in blood pressure due to combination of coffee and cigarettes, whereas atenolol attenuated the effect. Smoking still causes adverse effects, e.g., increased exercise ST segment depression, in the presence of β-blockade, although the benefit of β-blockade is not entirely reversed by smoking (Fox et al. 1983).

VI. Peripheral Resistance and Peripheral Blood Flow

It has long been known that nonselective β-blockade drugs reduce resting peripheral blood flow as measured in the forearm (Gillam and Prichard 1966; Robinson and Wilson 1968); cold extremities are not uncommon in clinical trials (M. R. C. Report 1981; Zacharias et al. 1972). There is some doubt about the mechanism. It may be consequent on the reduction of resting cardiac output and thus those drugs with ISA would be expected to produce less of a fall in peripheral flow as cardiac output is less reduced (Man in't Veld and Schalekamp 1982). An alternative suggestion is antagonism of the peripheral dilator effect of circulating adrenaline, a β_2 action, and thus the administration of cardioselective (β_1-selective) β-blocking drugs would be expected to result in less reduction of peripheral flow, but they can cause a reduction in peripheral flow (Cruickshank 1981). It

is possible that both mechanisms may be relevant, cardioselectivity may be more important in vascular beds, e. g. muscle, where β_2-receptors are more numerous, than in others where β_2-receptors are not thought to be present, e. g. skin. This theoretical distinction may not be important as neither intra-arterial propranolol nor atenolol influenced exercising flow in the forearm (HARTLING et al. 1980), presumably local metabolic demand overrides β-dilator influence. Likewise JUHLIN-DANNFELT and ÅSTRÖM (1979) found that β-blockade did not affect exercise vasodilation in the leg. However, not all studies in claudication (see Sect. F. I) are in accord.

MAN IN'T VELD and SCHALEKAMP (1982) reviewed the literature and studies in 410 patients and they pointed out that the increase in peripheral resistance associated with the acute administration of β-blocking drugs was very similar with drugs possessing cardioselectivity, e. g. atenolol, metoprolol, and those without cardioselectivity, e. g. propranolol, timolol, whereas least effect on peripheral resistance was seen with drugs possessing ISA, e. g. pindolol, oxprenolol. The longer-term administration of all β-blockers was associated with a decline in peripheral resistance from the levels seen after acute administration, those drugs with high degrees of ISA reaching levels seen before β-blockade or even falling below these levels, e. g. practolol, pindolol.

There is evidence that the possession of ISA results in no, or much less of a reduction in forearm blood flow than is seen with β-blocking drugs without this property (VANDENBERG et al. 1981; OHLSSON and LINDELL 1981; IRELAND and LITTLER 1981; SVENSSON et al. 1982). However, in a series of ten men suffering from ischaemic heart disease who had Reynaud's phenomenon, no difference in peripheral flow could be found when pindolol was given instead of metoprolol (ELIASSON et al. 1982). The combination of α-blockade and β-blockade in labetalol may lead to an increase in digital flow both after intravenous and 6 weeks oral treatment (HECK et al. 1981).

It was found by SVENSSON et al. (1982) that oral pindolol in hypertensive patients reduced resting calf vascular resistance by 14% in contrast to metoprolol, which tended to increase resistance. Likewise while RIECKERT et al. (1982) found a reduction in calf blood flow in 12 normal volunteers from β-blockade, there was less effect from pindolol than metoprolol. SMITH and WARREN (1982) found no fall in resting calf muscle blood flow from 2 weeks administration of atenolol, pindolol or propranolol. However, in patients with intermittent claudication all three drugs reduced exercise muscle flow. Similarly INGRAM et al. (1982) found an improvement in claudication distance, a rise in both resting and exercise blood flow after withdrawal of metoprolol, pindolol or propranolol in 11 patients. Although other investigators have also found claudication worsened by β-blocking drugs (RODGER et al. 1976), this is not so always, even from large doses of propranolol (REICHERT et al. 1975).

VII. Veins

KRAUSS et al. (1972) obtained some indirect evidence that β-blocking drugs increased venous capacity. Treatment with propranolol in ten patients with essen-

tial hypertension reduced the rise in central blood volume and central venous pressure in response to a saline load. These authors therefore concluded that the impairment of cardiac output from salt loading after propranolol treatment was due to reduced venous return as depression of myocardial contractility alone would be expected to increase venous pressure.

It was suggested by LANDS et al. (1967) that the β-receptor in veins was β_2, and therefore cardioselective (β_1)-blocking drugs should produce less of a reduction in venous return. It might be expected that a cardioselective β-blocker should decrease cardiac output less for a given chronotropic and inotropic effect in contrast to a nonselective drug (LEENEN 1979). LUND-JOHANSEN (1976 a) found that the nonselective timolol in the long-term treatment of hypertension gave a greater reduction in cardiac output and stroke volume than atenolol (LUND-JOHANSEN 1976 b), stroke volume after atenolol administration increased. However, in their review of the literature, no such distinction appeared between cardioselective and nonselective β-adrenergic antagonists without ISA (MAN IN'T VELD and SCHALEKAMP 1982).

More direct measurement suggested that pindolol reduced forearm venous tone (ATTERHOG et al. 1976), but RIECKERT et al. (1982) found neither pindolol nor metoprolol altered venous tone. Human in vitro studies, using bath concentrations similar to those reached systematically after 15 mg oral dosage, revealed a direct dilator effect on both arteries and veins from pindolol (THULESIUS et al. 1982), which was not due to α-blockade as the effect was not inhibited by phentolamine. It was thought to be due to β-stimulation as responses were largely antagonised by propranolol and sotalol.

VIII. Regional Blood Flow

The fall in cardiac output from β-blockers is associated with a fall in peripheral flow, and in renal plasma flow after both intravenous and prolonged oral administration (FALCH et al. 1979). While some have confirmed that glomerular filtration (insulin clearance) and effective renal plasma flow (PAH clearance) is reduced by propranolol (BAUER and BROOKS 1979), others have found no effect from propranolol, or pindolol (PASTERNACK et al. 1982). It has in particular been suggested that nadolol may not reduce renal blood flow, unlike other β-blocking agents (HOLLENBERG et al. 1979; TEXTOR et al. 1982). However, others have found that nadolol reduced renal flow in elderly hypertensive patients, whereas atenolol increased renal flow; labetalol resulted in no change; none of the drugs affected glomerular filtration (O'MALLEY et al. 1983).

The reduction in peripheral blood flow does not appear to be uniform throughout all vascular beds; there is no fall in cerebral blood flow after at least 3 weeks administration of various β-blocking drugs (labetalol, metoprolol, oxprenolol, sotalol) (GRIFFITH et al. 1979), although others have demonstrated a reduction with acute β-blockade from intravenous acebutolol (HARES et al. 1977) or intracarotid propranolol (OLESEN et al. 1978). The effect on coronary blood flow is discussed in Sect. D. II.

IX. Bronchial Smooth Muscle

Patients suffering from bronchial asthma are likely to show a significant increase in airways resistance owing to inhibition of the β-receptors in bronchial smooth muscle (BEUMER 1974). While the cardioselective β-adrenergic blocking drugs have less effect than nonselective agents (DECALMER et al. 1978), GRIBBIN et al. (1981) found that even cardioselective agents only show modest selectivity. In a dose–response study of atenolol in asthmatic subjects using doses of 50, 100 and 200 mg atenolol, there was some increase in forced expiratory volume in 1 s (FEV_1) and progressive inhibition of the bronchodilator effect of isoprenaline. The highest dose of atenolol had a greater effect on standing heart rate than the 40 mg propranolol used which produced a larger effect on airways obstruction (ELLIS et al. 1981). A serious increase in airways resistance has been reported with practolol (WAAL-MANNING and SIMPSON 1971). In a further study in asthmatics, GREEFHORST and VAN-HERWAARDEN (1981) found that acebutolol, atenolol and metoprolol all increased FEV_1 at rest and on exercise in asthmatic subjects. RUFFIN et al. (1979) found that metoprolol did not appear any different, in terms of reduction of FEV_1 in mild asthmatics, from propranolol or timolol. Coexistent α-blockade does not appear to prevent bronchoconstriction after β-blockade in patients with asthma, although it may slightly ameliorate it. Bronchoconstriction was seen after administration of 20 mg intravenous labetalol, although this was less than from 5 mg intravenous propranolol in patients with asthma. Intravenous practolol 10 mg had less effect, but more than saline (LARSSON 1982). Treatment for 2 weeks with oral labetalol (200 mg b. i. d.) resulted in symptoms of asthma in 4 of the 14 subjects.

Some investigators have attempted to assess cardioselectivity and the effect of β-blocking drugs in normal subjects by studying the physiological increase in exercising peak flow. While some have achieved a separation of selective and nonselective agents, e. g. intravenous propranolol and practolol (KUMANA et al. 1974) others have failed to do so, e. g. between intravenous metoprolol, acebutolol and propranolol (WOODS et al. 1979). Some studies suggest that ISA results in less effect on exercising peak flow in normal subjects than cardioselectivity; oxprenolol and pindolol did not affect exercising peak flow whereas metoprolol and propranolol did (OH et al. 1978). The validity of using postexercise peak flow as a useful discriminator of β-blocking activity has been doubted (MCDEVITT 1978; WOODS et al. 1979). The findings are in contrast to the effect in asthmatics where cardioselective agents have less effect than nonselective drugs and ISA does not appear important (DECALMER et al. 1978). Another more recent approach in normal subjects has been to plot dose–response curves to salbutamol before and after administration of β-blocking drugs, measuring specific airways conductance (GRIBBIN et al. 1979). Atenolol (50 and 100 mg) produced greater inhibition of exercise tachycardia, but less salbutamol was required to produce a 50% increase in specific airways conductance than with acebutolol (100 and 200 mg) or labetalol (150 and 300 mg) (GRIBBIN et al. 1981). In other experiments practolol had little effect in contrast to the considerable increase in dose of salbutamol required after propranolol administration (GRIBBIN et al. 1979).

The β-blocking drugs probably produce a small increase in airways obstruction in patients with chronic obstructive lung disease (CHESTER et al. 1981). This has been found with both propranolol and atenolol (RANCHOD et al. 1982). The effect of atenolol appears to be less than that seen with oxprenolol (PERKS et al. 1978). It also appears that β-blocking drugs reduce the respiratory response to carbon dioxide (PATRICK and PEARSON 1980). In a more recent study labetalol was found to be without any effect in patients with chronic obstructive airways disease in contrast to propranolol (ADAM et al. 1982).

X. Lipid Metabolism

There seems no doubt that a modest increase in triglyceride levels occurs after β-adrenergic blocking drugs. In subjects receiving a diuretic throughout with atenolol (2.19 mmol), metoprolol (1.79 mmol), pindolol (1.75 mmol) and propranolol (1.85 mmol), each given for 1 month, caused an increase in plasma triglycerides compared with placebo plus thiazide (1.35 mmol) (ENGLAND et al. 1978); cholesterol was unchanged. DAY et al. (1982) performed a within-patient comparison on 53 hypertensive patients with each of four β-adrenoceptor blocking drugs being given for 3 months. The average pretreatment fasting total triglyceride level was 1.45 mmol/l, and increased significantly after administration of each β-blocking drug to 1.91 on atenolol 100 mg b.i.d., 1.76 on metoprolol 100 mg b.i.d., 1.95 on oxprenolol 80 mg b.i.d. and 2.33 mmol/l on propranolol 80 mg b.i.d. The differences between each drug were not significant, but when the results on the nonselective agents oxprenolol and propranolol were pooled, the level of 2.05 mmol/l was significantly higher than on the 1.86 mmol/l selective drugs, atenolol and metoprolol. Some investigators have failled to observe any rise in triglycerides, e. g. from metoprolol (NILSSON et al. 1979; BEINART et al. 1979) PASOTTI et al. (1982) did not observe any change in triglycerides from pindolol. LEHTONEN et al. (1982) found an insignificant rise after 1 month, which they felt was in accord with the results of ENGLAND et al. (1978), while the 6-month readings showed no change. Labetalol does not appear to alter triglycerides (MCGONIGLE et al. 1981).

DAY et al. (1982) found all four drugs they studied increased levels of very low density lipoprotein (VLDL); low density lipoprotein (LDL) showed a minor insignificant decline, whereas high density lipoprotein (HDL) levels fell from 1.31 mmol/l baseline to 1.22 on atenolol, 1.14 on metoprolol, 1.16 on oxprenolol and 1.09 mmol/l on propranolol; the differences between the various β-blocking drugs were not significant. LEHTONEN et al. (1982) found pindolol tended to give an increase in HDL which was significant at 1 month, but not at 6 months. PASOTTI et al. (1982) found 12 weeks pindolol gave an increase in HDL and a fall in the ratio of total cholesterol to HDL cholesterol. However, in contrast, when MIETTINEN et al. (1982) withdrew pindolol from a pindolol–diuretic combination in ten patients who had been treated for 5 years, a rise in HDL was seen. Plasma clearance of soya oil (intralipid) was assessed after 3 months treatment in the study of DAY et al. (1982) in 25 patients and this was reduced from 2.07% to 1.69% per minute.

It was found that alprenolol, metoprolol, oxprenolol and propranolol reduced free fatty acid levels (DAY et al. 1982). This confirmed previous studies with alprenolol (FRISK-HOLMBERG et al. 1977) and with atenolol and propranolol (DEACON 1978) and metoprolol (BEINART et al. 1979). Pindolol also reduced free fatty acids (RAPTIS et al. 1981), but others have not found a fall in basal levels (LEHTONEN et al. 1982); pindolol inhibited the increase in free fatty acids and growth hormone in response to adrenaline, basal growth hormone levels were not affected (RAPTIS et al. 1981). There was much less inhibition of the rise in free fatty acids in response to adrenaline after atenolol treatment and an absence of any effects on growth hormone response. There was no effect on basal free fatty acids or growth hormone form atenolol (RAPTIS et al. 1981).

The β-blocking drugs result in a reduction of lipolysis and therefore there are reduced free fatty acids available for muscle metabolism. Although the evidence is not fully clear, this could be expected to shift metabolic demand on exercise to carbohydrates, which could lead to earlier hypoglycaemia, and or depletion of muscle glycogen. This might be responsible for exercise fatigue that has been reported with β-blocking drugs (JUHLIN-DANNFELT 1982). However, not all have observed a fall of glucose with exercise after administration of β-blocking drugs, e. g. atenolol and metoprolol (FOLGERING et al. 1982). β-Blockade also decreased lactate from muscle, but there is no lactate accumulation, thus presumably less production (FRISK-HOLMBERG et al. 1977; JUHLIN-DANNFELT and ASTROM 1979; TRAP-JENSEN et al. 1976). Reduced cardiac output on exercise, at least on submaximal exercise up to 90% maximum, is compensated for by increased oxygen extraction so this may not be the usual cause of fatigue (JUHLIN-DANNFELT 1982). The alteration of metabolism away from lipolysis may be important for a further reason. The combustion of free fatty acids for a given energy yield requires more oxygen than that of carbohydrate (MJØS 1971; WAHLQUIST et al. 1973; MUELLER and AYERS 1976). It has been suggested that the antilipolytic actions of β-blockade might be relevant in decreasing ischaemic damage of the heart (OPIE and THOMAS 1976; see Sect. D. III.

β-Blocking drugs do not appear to alter cholesterol levels (DAY et al. 1982; LEHTONEN et al. 1982; PASOTTI et al. 1982) neither does labetalol (MCGONIGLE et al. 1981). It should be noted that other cardiovascular drugs alter lipids, hydrochlorothiazide increases cholesterol (AMES and HILL 1978); chlorthalidone, frusemide and mefrusemide increased lipoproteins with nonsignificant increases in cholesterol and triglycerides (GLUCK et al. 1978). Chlorthalidone and clopamide increased LDL (MEIER et al. 1981). Spironolactone increases triglycerides (AMES and HILL 1978). Methyldopa has also been found to raise triglycerides in insulin-dependent diabetic hypertensive patients in contrast to oxprenolol, which had no effect (BENFIELD and HUNTER 1982). It has been reported that the increase in LDL from chlorthalidone is reversed by propranolol or atenolol, and the elevation from clopamide is reversed by pindolol (MEIER et al. 1981). However, the raised VLDL from hydrochlorothiazide was further increased by propranolol, although in this study propranolol had no effect alone (BAUER et al. 1981).

XI. Glucose Metabolism

Glucose metabolism is influenced by the elevation produced by catecholamines and by the secretion of insulin by the pancreatic β-cells. The β-blockers (particularly propranolol) appear to reduce insulin secretion; there may be a modest increase in serum glucose. However, β-blockers inhibit the catecholamine-induced elevation of the blood glucose (POTTER 1981). Inhibition of glucose metabolism involves both α-receptors in the liver and β-receptors in the muscle. Experiments in normal subjects indicate that β-blocking drugs without ISA do not usually affect resting insulin or glucose levels or: the fall of plasma glucose after insulin administration (EKBERG and HANSSON 1977; LAMMINTAUSTA et al. 1977) but severe hypoglycaemia has been rarely reported (BELTON et al. 1980). Those agents with ISA may cause a small elevation of blood glucose (SCHLIERF et al. 1973).

PODOLSKY and PATTAVINA (1973) reported a reduction in insulin secretion in response to a glucose load. However, DAY et al. (1979) failed to show any fall in insulin secretion in response to a glucose load after 3–6 months administration of atenolol or proranolol in hypertensive patients. Not only did DAY et al. (1979) fail to show any reduction of insulin secretion in response to a glucose load after propranolol administration, but there was an insignificantly greater rise than after placebo, and both after 3 and 6 months propranolol, a significantly lower blood glucose following the glucose load. Neither atenolol nor propranolol altered resting glucose levels. This was also found in normal volunteers with metaprolol and propranolol (SYVALAHTI et al. 1977). While this was confirmed in normal volunteers with pindolol (SCHLUTER et al. 1982) it was found that both metoprolol and propranolol reduced insulin release in response to a glucose load. Insulin release in response to isoprenaline is however abolished by intravenous propranolol, only insignificantly reduced by metoprolol (REEVES et al. 1982).

Some have found a moderately increased glucose level in diabetics after treatment with β-blocking drugs and that changing from a nonselective to a cardioselective drug lowers blood sugar, e. g. metoprolol (WAAL-MANNING 1976), but others have not observed any difference, e. g. between metoprolol and propranolol (WRIGHT et al. 1979). Modest elevations of blood glucose in mild diabetics not on insulin need not be regarded as a contraindication to the use of β-blocking drugs (WRIGHT et al. 1979). BENFIELD and HUNTER (1982) found no effect from 12 weeks oral oxprenolol in insulin–dependent diabetics. Similarly, KOLENDORF et al. (1982) found no effect on glucose or insulin dosage after 12 weeks treatment with metoprolol in insulin–dependent hypertensive diabetic patients.

As has been pointed out, β-blocking drugs can often be given to diabetics without serious problems (FITZGERALD 1968), but there are three possible ways that the effects of hypoglycaemic episodes can be more serious in diabetics. First, the rate of recovery of glucose levels after insulin-induced hypoglycaemia is inhibited and the increase of plasma glycerol is reduced, as these depend in part on the reflex liberation of catecholamines in response to the hypoglycaemia and consequent β-adrenergic stimulation. The nonselective β-blocking drugs prolong insulin-induced hypoglycaemia (DEACON et al. 1977; BOLLI et al. 1982), but selective agents probably do not (DEACON et al. 1977). RAPTIS et al. (1981) demonstrated

in normal volunteers that pindolol attenuated the rise in glucose response to an infusion of adrenaline (0.1 μg kg^{-1} min^{-1} for 1 h whereas atenolol was without effect. There have indeed been reports of diabetics treated with β-blockers experiencing prolonged hypoglycaemia (HESSE and PEDERSEN 1973; WRAY and SUTCLIFFE 1972). Hypoglycaemia in response to sulphonylurea drugs does not seem to be increased by β-blocking drugs; on the other hand it was found that 3 days oral propranolol or acebutolol partly inhibited the effect of glibenclamide, reducing the rise of blood glucose after glucose load, presumably owing to an inhibition of sulphonylurea-induced insulin release (ZAMAN and KENDALL 1982). Second, both nonselective and selective β-blocking drugs inhibit the important cardiac symptoms, tachycardia and palpitations of hypoglycaemia (WAAL-MANNING 1979 a). Sweating is not reduced and has in fact been found to be increased in normal volunteers given insulin on metoprolol, pindolol or propranolol (SCHLUTER et al. 1982). Third, the cardiovascular response to adrenaline, a fall in diastolic pressure and a rise in systolic, is converted to a rise in both pressures from a block of the β-dilator activity of adrenaline (PRICHARD and ROSS 1966); less effect is seen with cardioselective agents (JOHNSSON 1975). It is not surprising therefore that there is an increased rise in blood pressure in a hypoglycaemic episode after β-blockade. This potentiation is more marked with nonselective block, e. g. from propranolol, than with a cardioselective agent, e. g. metoprolol (DAVIDSON et al. 1976) or atenolol (RYAN et al. 1983), but considerable rises have been reported after metoprolol administration (SHEPHERD et al. 1981).

XII. Noradrenaline and Adrenaline

Overall evidence suggests that plasma noradrenaline levels do not fall with β-blocking drugs, with non-selective drugs, with or without ISA e. g. oxprenolol (JONES et al. 1980), penbutolol (HANSSON and HÖKFELT 1975), pindolol (ANAVEKAR et al. 1975), propranolol (FRANCO-MORSELLI et al. 1978; MORGANTI et al. 1979; WATSON et al. 1980; ESLER et al. 1981; PLANZ and PLANZ 1981; VANDONGEN et al. 1981; KIRSTEN et al. 1982) or with cardioselective agents, e. g. acebutolol (WATSON et al. 1980), atenolol (IRVING et al. 1974; DISTLER et al. 1978), metoprolol (HANSSON et al. 1977; LIJNEN et al. 1979; WATSON et al. 1980). ESLER et al. (1981) measured noradrenaline plasma clearance and found that this fell in nine of ten hypertensive patients and that this was responsible for a small insignificant rise in plasma concentration after 1 month oral propranolol, up to 320 mg/day. They thus concluded that to gauge sympathetic neurone activity by plasma noradrenaline levels would be unreliable because of this reduced clearance. However, they found that noradrenaline spillover rates remained in the normal range after propranolol treatment, falling in six, but increasing in four patients. A fall in resting noradrenaline has been reported with long-term pindolol (BRECHT et al. 1976) and after acute oral administration (KIRSTEN et al. 1982; DOMINIAK and GROBECKER 1982). These later investigators, however, found no decrease in the exercising noradrenaline levels as have others (LIJNEN et al. 1979; WATSON et al. 1980).

TRAP-JENSEN et al. (1982) did not observe a change in resting levels of noradrenaline or adrenaline from a variety of single oral doses of β-adrenoceptor

blocking drugs, labetalol, metoprolol, pindolol or propranolol. After pleasant psychic stress (a television game) pindolol alone prevented the rise of noradrenaline seen, while serum adrenaline levels were unchanged after administration of placebo and pindolol, but increased after treatment with the other drugs. BRISSE et al. (1982) found a small rise of noradrenaline after single doses of metoprolol at rest, but no change after pindolol administration; resting adrenaline and cyclic AMP was not altered by either drug. After the stress of oral surgery, pindolol prevented a rise of adrenaline, noradrenaline and cyclic AMP, whereas metoprolol did not. Again, after the stress of insulin-induced hypoglycaemia the rise in adrenaline after administration of placebo and single doses of pindolol were similar, but after metoprolol and propranolol treatment the rise was enhanced (SCHLUTER et al. 1982). Similarly the rise of serum noradrenaline from the stress of 40 mg intravenous frusemide was abolished by 10 mg intravenous oxprenolol in normal subjects and hypertensive patients (MUIESAN et al. 1975).

Some reports have suggested an increase in supine (LIJNEN et al. 1979; MORGANTI et al. 1979; JONES et al. 1980; ESLER et al. 1981) in standing (HANSSON et al. 1977; FRANCO-MOSELLI et al. 1978) and postexercise noradrenaline from β-blockade (IRVING et al. 1974; DISTLER et al. 1978; PLANZ and PLANZ 1981). While acute administration of propranolol, acebutolol or metoprolol may increase exercise plasma noradrenaline (WATSON et al. 1980) levels were not above control after chronic treatment (WATSON et al. 1980). A doubling of exercise plasma noradrenaline was seen in normotensive subjects 2 h after acute oral administration of propranolol 120 mg, a smaller increase was seen after 10 weeks of 80 mg t.i.d. when measurements were made 8 h after the last dose of propranolol. However, 2 h after an extra dose of 120 mg oral propranolol, the rise in noradrenaline was similar to the rise after acute administration (PLANZ and PLANZ 1980, 1981).

An increase in supine adrenaline was seen after intravenous administration of propranolol (MORGANTI et al. 1979) in patients with essential hypertension, but not in normal subjects after 7 days oral propranolol (VANDONGEN et al. 1981) although serum levels in the tilt position were increased. Also in normal subjects acute or chronic oral treatment with propranolol did not increase supine adrenaline levels, but these were increased after exercise in both circumstances (PLANZ and PLANZ 1980). Changes of plasma noradrenaline in response to various sympathetic activities, sleeping, supine, awake, standing, walking and cycling are not reduced by β-blockade (WATSON et al. 1980). The α-blocking drugs have long been known to increase catecholamine levels so that responses to combined α- and β-blocking drugs are the result of both properties; intravenous labetalol elevates supine, standing and exercise noradrenaline and standing adrenaline (CHRISTENSEN et al. 1978).

XIII. Renin Blocking Activity

Plasma renin is lowered by β-adrenergic blocking drugs in both normal subjects (WINER et al. 1969) and hypertensive patients (BÜHLER et al. 1972; MICHELAKIS and MCALLISTER 1972) although the β-adrenergic stimulation is not the only factor involved in renin release as renin levels rise after administration of diuretics in patients on propranolol (BRAVO et al. 1975) and the response of the renin

angiotensin system to tilting, provided tilt was performed for long enough, was not abolished by metoprolol or propranolol (SONDODI et al. 1982). It has been suggested that reduction in renin levels correlates with the antihypertensive effect of β-adrenergic blocking drugs, although others have disputed this (PRICHARD 1982).

XIV. Stimulation of Vasodilator Prostaglandins

DURAO et al. (1977) found that indomethacin, a potent inhibitor of prostaglandin synthesis, attenuated the antihypertensive action of propranolol, and it was therefore suggested that chronic β-receptor blockade might stimulate the formation of vasodilator prostaglandins. The antihypertensive effect of oxprenolol is also blunted by indomethacin (SALVETTI et al. 1982). This effect of indomethacin is not specific as both propranolol and diuretics are antagonised to a similar degree (LOPEZ-OVEJERO et al. 1978; WATKINS et al. 1980). There is a reduction in urinary excretion products of prostaglandin metabolism (prostaglandin $F_2 \alpha$ M) when indomethacin is added to either drug, particularly with propranolol (WATKINS et al. 1980).

C. Pharmacokinetics

I. Absorption and Metabolism

β-Blocking drugs are variably absorbed from the gastrointestinal tract; more than 90% for alprenolol, metoprolol, pindolol, propranolol, sotalol and timolol (SHAND 1974b; JOHNSSON and REDÄRDH 1976; ANTTILA et al. 1976; ROUTLEDGE and SHAND 1979; FRISHMAN 1979). Oxprenolol is about 70%–90% absorbed while for atenolol the level appears to be 45%–60% (REEVES et al. 1978).

Lipid-soluble β-blocking drugs, e.g. alprenolol, metoprolol, labetalol, oxprenolol, propranolol, are extensively metabolised in the liver after absorption, the first-pass effect, and therefore a comparatively small amount of the drug that is absorbed reaches the systemic circulation. This hepatic metabolism is inherently variable and thus those compounds that are susceptible to it can show considerable variation in plasma concentration after the same oral dose (SHAND 1974, ROUTLEDGE and SHAND 1979; MELANDER et al. 1977). In addition the relationship between the dose and the area under the plasma concentration curve (AUC) varies, at low doses, i.e. less than 200 mg alprenolol (ABLAD et al. 1972) or 40 mg propranolol (SHAND and RAGNO 1972), changes in AUC are nonlinear and smaller incremental increases are seen than at greater dose levels. Oxprenolol, however, which is also metabolised in the liver, appears to produce a dose-related linear increase in plasma concentration from the lowest doses (RIESS et al. 1974). The first-pass effect becomes saturated at high doses, but even with larger doses of propranolol systemic biovailability does not exceed 50% (NIES and SHAND 1975). The hepatic metabolism and steady state plasma concentrations depend on hepatic blood flow (SHAND et al. 1973; ROUTLEDGE and SHAND 1979), and thus conditions which reduce liver blood flow, e.g. congestive heart failure or cirrhosis, will reduce hepatic clearance and prolong half-life. Drugs, such as pro-

pranolol, which reduce cardiac output and hepatic blood flow will slow their own metabolism and that of any other drug metabolised by the liver. While single doses have a plasma elimination half-life of 2–3 h, it may extend to 6 h with chronic administration.

First-pass effects are less important for pindolol; only about 50% is metabolised in the liver (GUGLER et al. 1974). The ISA of pindolol and oxprenolol results in these drugs having less effect on cardiac output at rest, and thus it would be expected that plasma half-lives would be similar after acute and chronic administration (GUGLER and BODEM 1978). The renal excretion of pindolol also means that it is less dependent on hepatic blood flow for plasma clearance. Plasma concentrations are greater in the elderly after repeated doses, terminal half-life is increased (CASTLEDEN and GEORGE 1979; VESTAL et al. 1979; HITZENBERGER et al. 1982); this is also the case with labetalol (KELLY et al. 1982) and pindolol (HITZENBERGER et al. 1982). Compounds that are excreted by filtration also accumulate in the elderly, e. g. sotalol (ISHIZAKI et al. 1980).

The lipid-soluble β-blockers are largely metabolised in the liver by hepatocyte detoxification mechanisms that include glucuronide conjugation of the parent molecule, and/or oxidative deamination (RIESS et al. 1974). The hepatic metabolism of β-blocking drugs such as propranolol is slowed in liver disease, in contrast to the absence of effect with atenolol or sotalol (SOTANIEMI et al. 1983). Oxprenolol is excreted through the kidneys almost entirely as a pharmacologically inactive glucuronide of unaltered oxprenolol. In contrast, other compounds such as propranolol and alprenolol have a more complex metabolism and give rise to several metabolites some of which are pharmacologically active (THOMPSON et al. 1972; WAAL-MANNING 1976); this is the case with acebutolol; with metoprolol these relatively inactive metabolites are produced by oxidation (BORG et al. 1975).

A small proportion of subjects exhibit defective metabolism of β-receptor blocking drugs and the drug has a prolonged half-life. This has been reported with alprenolol (ALVAN et al. 1982); bufuralol (DAYER et al. 1982); metoprolol (ALVAN et al. 1982; LENNARD et al. 1982; SHAH et al. 1982); propranolol (SHAH et al. 1982) and timolol (ALVAN et al. 1982), and it is associated with poor hydroxylation of debrisoquin which serves as a marker of this genetic polymorphism of the metabolism of the metabolised β-blocking drugs (LENNARD et al. 1983). Poor hydroxylators of debrisoquin represent about 9% of the population, at least in the United Kingdom (PRICE EVANS et al. 1980). Some investigators regard this variation in metabolism as a skew distribution of metabolism rather than a specific genetic variation (JACK et al. 1983).

Most β-adrenergic blocking drugs reach peak plasma concentrations within 3 h of oral dosage or a little later in the case of acebutolol and atenolol (4 h). The magnitude of the peak and the shape of the subsequent elimination curve depend on metabolic climination and sequestration into body tissues and especially fat. The plasma elimination half-lives of alprenolol, metoprolol, oxprenolol, pindolol, propranolol and timolol are about 2–5 h; about 8 h for acebutolol and atenolol; 13 h for sotalol and 24 h for nadolol (ABLAD et al. 1972; REGARDH and JOHNSSON 1980; ROUTLEDGE and SHAND 1979). These figures represent data derived from chemical analysis of the drugs in plasma and should not be confused with the duration of biological effects which are longer and derived from haemo-

dynamic responses to standardised stimuli. Tissue depots exert considerable influence on plasma concentrations particularly after single or early oral doses of lipid-soluble agents. In chronic dosing, however, it is metabolic elimination that exerts the major influence. This fact also partly explains the greatly differing steady state plasma concentrations of lipid-soluble drugs such as propranolol and metoprolol after single oral doses (SHAND 1974 b; VON BAHR et al. 1976).

II. Transport and Distribution

It is the free concentration of a drug that is responsible for its biological activity, i.e. the degree of β-blockade (MCDEVITT et al. 1976), even for β-blocking drugs with similar structure plasma protein binding is very variable. For a number of reasons variation of the degree of plasma binding does not greatly influence metabolism of β-blocking drugs (JOHNSSON and REGARDH 1976). Binding is usually low, but it can be high with lipid-soluble drugs, at 85%–93% for alprenolol and propranolol (SHAND 1976). Alterations in plasma proteins affect binding, for example both oxprenolol and propranolol achieve higher plasma concentrations in patients whose plasma proteins have been altered by illness (KENDALL et al. 1979).

The possession of lipid solubility enables a drug to cross cell membranes rapidly. Such drugs are absorbed more quickly and are metabolised to a greater extent by the liver. In contrast, the water-soluble β-blockers reach predictable plasma concentrations independent of liver metabolism. Atenolol, for instance, shows a variation of two- to fivefold in plasma concentrations between individuals (BROWN et al. 1976; FITZGERALD et al. 1978), much less than is seen with, for example, propranolol. Volumes of distribution vary about eightfold according to lipid solubility (0.7–5.6 l/kg for atenolol and propranolol respectively), and mostly exceed the physiological body space (JOHNSSON and REGARDH 1976). Distribution tends to be slightly reduced in renal failure or in the elderly, e.g. sotalol (ISHIZAKI et al. 1980). Volumes of distribution above total body water imply concentration into certain tissues (particularly lung, liver and heart), and this has been confirmed in animal tissues (DOLLERY and JUNOD 1976; BODIN et al. 1974). High lipid solubility is associated with rapid equilibration across the blood–brain barrier, e.g. alprenolol and propranolol (JOHNSSON and REGARDH 1976). Propranolol reaches about 20 times the concentration of atenolol. The lung is a major organ of deposition for propranolol (DOLLERY and JUNOD 1976). While the lipophilic substances have the larger volumes of distribution, they have shorter plasma elimination half-lives (JOHNSSON and REGARDH 1976).

III. Elimination

The water-soluble compounds, either active metabolites or parent substances, are excreted in the urine. Water-soluble atenolol and sotalol are therefore excreted unchanged in the urine. Half-life is increased in renal insufficiency, with atenolol a three- to fourfold increase has been reported (SASSARD et al. 1977; WAN et al. 1979), which sotalol an eightfold increase has been found in end stage renal failure (TJANDRAMAGA et al. 1976). Likewise with practolol a linear inverse relationship was found between creatinine clearance and elimination half-life (EASTWOOD et

al. 1973; BODEM et al. 1974). Doses of these drugs will need to be reduced in renal failure. The plasma half-life of hydrophilic β-blocking drugs is shortened by dialysis (EASTWOOD et al. 1973; BODEM et al. 1974; TJANDRAMAGA et al. 1976). In contrast the elimination of lipid-soluble metabolised drugs is not altered by renal failure, e. g. labetalol (WALSTAD et al. 1982). The active hydroxy metabolites of metoprolol show a threefold increase in plasma half-life when renal filtration rate is reduced by 80% (HOFFMAN et al. 1980).

The elimination of pindolol combines hepatic metabolism and renal excretion. About 90% of a pindolol dose can be accounted for in the urine with 40% appearing as unaltered drug. Patients with renal insufficiency show increased metabolic hepatic clearance to compensate (OHNHAUS et al. 1974), and more than a 50% reduction in dose is seldom necessary. Although 90% of an oral dose of metoprolol is excreted in the urine, less than 10% is unchanged drug (REGARDH and JOHNSSON 1980). Under 2% of a 160 mg dose of oxprenolol appeared unchanged in the urine, which contrasts with, for instance, nadolol, which is scarcely metabolised by the liver at all (BOBIK et al. 1979).

Liver metabolism is important in the termination of action of alprenolol, metoprolol, oxprenolol, propranolol, for instance, whereas pindolol (see Sect. C. T) is unusual with its dual and interchangeable routes of elimination (OHNHAUS et al. 1974). Products from hepatic metabolism are either directly, or after conjugation, excreted by the kidneys so that about 90% of the oral doses can be accounted for by products in the urine. Because the liver is the principal organ of plasma elimination, half-lives of these compounds are not prolonged in renal failure (LOWENTHAL et al. 1974). Although most metabolic products produced by the liver are pharmacologically inactive, occasionally water-soluble active derivatives are produced which accumulate in renal failure (DRAYER 1976, 1977). An active metabolite of propranolol which exerts a considerable effect has been found to accumulate in renal failure (THOMPSON et al. 1972).

D. Basis for the Use of β-Antagonists in Ischaemic Disease

A number of mechanisms may play a part in the anti-ischaemic effect of β-blocking drugs. The principal mechanism is the reduction of myocardial oxygen consumption that is consequent on β-adrenergic inhibition. β-Blocking drugs that do not possess ISA alter cardiac dynamics at rest, but all β-blocking drugs, including those with ISA, inhibit the effects of sympathetic induced tachycardia on exercise and following various types of physiological stress. Overall there is an improvement in the ratio of oxygen supply to use. β-Adrenergic blocking drugs may also alter the distribution of myocardial blood flow so more blood is diverted towards ischaemic areas from better perfused zones now receiving less oxygen. The increase in diastole that occurs with a reduction in heart rate alters the cardiac cycle to make it more favourable for flow to poorly perfused myocardial muscle. Improvement in oxygenation reverses the arrhythmogenic effect of anoxia, but in addition β-blocking drugs have an antiarrhythmic effect on pacemaker cells; perhaps this is particularly important against the excess catecholamines released in myocardial ischaemia. In addition these drugs have other actions that may be rel-

evant. They improve metabolism of the ischaemic myocardium, they shift the oxygen dissociation curve to the right and this improves delivery of oxygen to the tissues, and they reverse the abnormal sensitivity of platelet aggregation that has been reported in ischaemic patients.

I. Haemodynamic Effects and Oxygen Consumption

The sympathetic neurones to the heart liberate noradrenaline which stimulates β-adrenoceptors; there follows an increase in cardiac work and myocardial oxygen consumption. The heart rate, isometric force and maximum velocity of shortening of ventricular muscle fibres all increase (SONNENBLICK 1962). Chemical energy release is increased by aerobic metabolism, and can be estimated by the rise in myocardial oxygen consumption (SONNENBLICK et al. 1968). A high concentration of noradrenaline also produces a direct increase in myocardial metabolism – the so-called oxygen-wasting effect (SARNOFF et al. 1965). Work in animals has shown that isoprenaline-induced tachycardia results in an increase in infarct size (MAROKO et al. 1971, 1972) which is greater than that resulting from similar levels of tachycardia achieved by ventricular pacing (SHELL and SOBEL 1973). Myocardial wall tension is also a major determinant of cardiac oxygen consumption and this increases with any rise in intraventricular pressure and volume (Laplace's Law); however, both these tend to decrease when cardiac contractility is enhanced by sympathetic nerve stimulation (SONNENBLICK and SKELTON 1971). The net increase in myocardial demand for oxygen resulting from sympathetic stimulation is normally balanced by an increase in coronary blood flow (LOMBARDO et al. 1953). Alterations in cardiac metabolism such as a rise in free fatty acids (FFA) utilisation also increases oxygen consumption, as FFA metabolism is basically oxidative (MJØS et al. 1974). The mechanisms principally affecting oxygen demand by the left ventricle are therefore heart rate, ventricular systolic pressure and the size of the left ventricle (BRAUNWALD 1971; ROBINSON 1971). Other factors include the basal metabolic requirements of the myocardial cells and the energy required to activate contraction.

The heart rate and systolic pressure are the most important factors as they correlate well with oxygen consumption (NELSON et al. 1974). It was found by ROBINSON (1967) that their production in any individual patient with angina pectoris tended to be about the same whether angina occurred spontaneously or was precipitated by exercise, or stress such as mental arithmetic. The tension time index ("product heart rate", systolic blood pressure and systolic ejection period) correlates less with oxygen consumption (SARNOFF et al. 1958; JORGENSEN et al. 1973).

There is a reduction in heart rate and velocity of cardiac contraction from the administration of β-blocking drugs, and thus work done falls and longer is allowed for diastolic filling. There is a reduction in the rise of blood pressure on exercise (SONNENBLICK et al. 1965; FURNIVAL et al. 1970; THADANI et al. 1973; MUELLER et al. 1974). They inhibit the tachycardia, and so limit the rise in oxygen consumption in response to a variety of physiological stimuli besides exercise (GIBSON 1974). They reduce the tachycardia associated with everyday stresses, for instance public speaking (TAGGART et al. 1973), car driving (TAYLOR and MEERAN 1973 a) or motor racing (TAGGART and CARRUTHERS 1972), passenger travel by

car or air (TAYLOR and MEERAN 1973 b) and in pilots undergoing simulated flights (ELIASCH et al. 1967).

Although the reduction in heart rate and force of contraction from β-blockade reduces energy demand there is an increase in left ventricular size in normal subjects from β-blocking drugs, e. g. pronethalol (CHAMBERLAIN 1966), propranolol (SONNENBLICK et al. 1965) and patients with ischaemic heart disease (CRAWFORD et al. 1975; KOSTIS et al. 1982 a). FRISHMAN et al. (1975) found a dose-dependent increase in cardiac size from propranolol, while CRAWFORD et al. (1975) found those patients with the largest hearts before the administration of propranolol showed the largest increase after the administration of the drug. Nadolol also increases cardiac size at least as much as propranolol in patients with angina (TURNER et al. 1978) supporting the view that it is β-receptor inhibition which is important, not the membrane activity, as nadolol does not have this property (LEE et al. 1975). Drugs with ISA probably produce less of an increase in heart size, e. g. pindolol (KOSTIS et al. 1982 a). This increase in heart size and consequent influence to increase oxygen consumption partly offsets the beneficial effects of β-adrenergic blocking drugs in ischaemic heart disease. The increase is no doubt responsible for the reduction in pressure–rate product for a given work load that is seen after β-adrenergic blocking drugs. The increase in left ventricular size results in increased wall tension and therefore oxygen consumption for the same amount of work at a given pressure (ROBINSON 1971).

It has been found that when glyceryl trinitrate relieves angina it decreases the pressure–rate product (ROBINSON 1968), but when the work load is increased sufficiently to raise this product to the control level, anginal pain will still occur. Following the administration of β-blocking drugs, although exercise tolerance increased, when pain occurs during acute exercise the pressure–rate product has been found to be less than that reached prior to drug administration (BATTOCK et al. 1969; GIANELLY et al. 1967). BATTOCK et al. (1969) found that in their patients the pressure–rate product at the onset of pain was reduced by 30% of the control level after administration of the β-blocking drugs. ALDERMAN et al. (1975) found a progressive reduction in the pressure–rate product as dosage of propranolol (80, 160, 320 mg/day) was increased. The intravenous administration of β-blocking drugs that differ in their associated properties; propranolol (membrane stabilising action), oxprenolol (membrane stabilising action and ISA), practolol (ISA and cardioselective blockade) and sotalol (minimal membrane stabilising action) depressed the pressure–rate product at the onset of pain to a similar extent, about 20% in the patients studied (PRICHARD 1971). There is some suggestion that nadolol may depress the pressure–rate product to a greater extent than propranolol (TURNER et al. 1978); however, this may not be so when equivalent β-blocking doses are considered. This depression of the pressure–rate product after β-blockade at the onset of pain is presumably due to the rise in oxygen consumption from the increase in cardiac size after β-blockade.

The β-adrenergic blocking drugs overall reduce myocardial oxygen consumption, e. g. from 9.20 to 7.20 ml/100 g in the experiments of MUELLER et al. (1974). The oxygen consumption of the heart at any given work load is reduced (WOLFSON and GORLIN 1969; JORGENSEN et al. 1973), or for the same oxygen consumption there is an increase in the amount of external work performed (JORGENSEN

et al. 1973). The decrease in oxygen consumption after propranolol treatment reflects a fall in oxygen requirement, arteriocoronary sinus oxygen difference decreases, coronary sinus oxygen tension increases, and there is improved myocardial lactate metabolism (MUELLER et al. 1974).

While there is an overall reduction of contractility, there is in contrast an improved contraction of ischaemic myocardium after the administration of the β-blocking drug. This has been observed with ventriculographic studies with propranolol (LUDBROOK et al. 1973), echocardiographic studies with pindolol and practolol (HEIKKILA and NIEMINEN 1978) and radionuclide angiographic studies with propranolol (BATTLER et al. 1979). This seems to be indicative of improved oxygenation of the ischaemic myocardium and thus improved muscle function.

II. Effect of β-Blockade on Coronary Blood Flow

The fall in heart rate from β-blockade and consequent prolongation of diastole will facilitate coronary flow (BOUDOULAS et al. 1979, 1981). However, a reduction of coronary blood flow has been observed after administration of propranolol in anaesthetised dogs (PARRATT and GRAYSON 1966; NAYLER et al. 1967). A decrease in coronary blood flow with propranolol is also seen in humans with an increase in calculated coronary vascular resistance. This is associated with the fall in oxygen consumption (WOLFSON and GORLIN 1969; MUELLER et al. 1974). Propranolol and the cardioselective atenolol behave similarly and it appears that neither has significant coronary vasoconstrictor properties, and cardioselectivity does not appear to be important with regard to the coronary circulation (SIMONSEN 1977; STEPHENS et al. 1978). In a study in 12 patients of the effects of atenolol and propranolol on coronary flow it was found that both drugs produced a similar reduction in heart rate and myocardial oxygen consumption. Changes in coronary sinus flow after rapid atrial pacing were closely related to alteration in tension-time index, and this relationship was not altered by either drug (STEPHENS et al. 1978). Although coronary flow is reduced, there is improved myocardial oxygen balance, as seen in the experiments of MUELLER et al. (1974) in 20 postinfarction patients.

As a result of studies in dogs it has been suggested that internal shunting occurs in the coronary circulation after β-adrenoceptor blockade, so that blood flow to an ischaemic area is maintained or improved even if there is an overall fall in coronary flow (PITT and CRAVEN 1970; VATNER et al. 1977; FOX et al. 1980). This shunting occurs particularly to the subendocardial region that is most at risk from anoxic injury (BECKER et al. 1971; MOIR 1972; BERDEAUX et al. 1978; GROSS et al. 1978). BERDEAUX et al. (1978) found that whereas shunting was seen after administration of propranolol and pindolol, it was not seen after administration of the cardioselective practolol or the D (+)isomer (non-β-blocking) of propranolol. However, others have not found any alteration in the ratio of endocardial to epicardial flow following β-blockade after coronary occlusion (KLONER et al. 1976; PETER et al. 1978). More recently RAINWATER et al. (1982) using ^{201}Tl imaging have found impaired myocardial blood flow distribution in humans after propranolol treatment in angina patients ($N=15$), but not in patients who had a myocardial infarction. Changes in regional blood flow might be important in re-

ducing exercise-induced shifts of the ST segment observed after β-adrenoceptor inhibition in ischaemic patients (GIANELLY et al. 1967; PRICHARD et al. 1970a; SOWTON and SMITHEN 1971; SANDLER and PISTEVOS 1972; THADANI et al. 1973; FOX et al. 1980).

III. Myocardial Metabolism

The chief energy substrates of the heart are FFA, although glucose and lactate are also metabolised (NEELY et al. 1972). Following coronary occlusion the raised catecholamine levels increase tissue lipolysis (KURIEN and OLIVER 1966; MUIESAN et al. 1970; OPIE 1975). The high plasma levels of FFA enhance myocardial FFA uptake and increase myocardial oxygen consumption (CHALLONER and STEINBERG 1966; MJØS 1971; OPIE 1975) and increase infarct size (KJEKSHUS and MJØS 1973). Metabolism of FFA is reduced in the ischaemic myocardium because of oxygen lack, but glucose metabolism is maintained by an anaerobic route which may be important in minimising cardiac ischaemia (MAROKO et al. 1972). However, experimental evidence indicates that this pathway is rapidly inhibited by the accumulation of acid metabolites (OPIE 1975). Raised FFA levels have also been shown in experimental infarction to increase the occurrence of arrhythmias (KURIEN et al. 1969). There is some evidence of adverse effects of raised FFA levels in humans. Measurements made within 60–72 h of myocardial infarction showed that 41% of 50 patients had levels of FFA over 800 μmol/l and extraction ratios of FFA of greater than 10% of the arterial level. These patients had low myocardial respiratory quotients averaging 0.76, indicative of preferential utilisation of FFA. Complications such as arrhythmias, left ventricular failure and hypotension were more common in these patients than those with lower levels of FFA and higher respiratory quotients (MUELLER and AYRES 1976). β-Blocking drugs inhibit the catecholamine-increased rise in FFA levels. The administration of intravenous propranolol in 20 postinfarction patients appeared to reduce plasma FFA levels (from 938 to 873 mol/l, not significant), and increase the respiratory quotient from 0.81 to 0.93 ($P < 0.001$), indicating improved utilisation of carbohydrate (MUELLER et al. 1974), and an increase in myocardial glucose extraction was shown, from 0.4% to 3% of arterial concentration. Similar findings have been found in animals (OPIE 1976). Lactate metabolism improves after propranolol treatment, from 10% production to 4% extraction (HANEDA et al. 1973), from 70% production to 4% extraction (RELIGA et al. 1973). Findings in patients after acute myocardial infarction have been similar (MUELLER et al. 1974).

There is further evidence suggesting improved metabolism following propranolol administration. Propranolol produced a 20% increase in tissue creatinine phosphate, a 39% increase in the levels of ATP and AMP and a 40% decrease in tissue lactate concentration in the globally ischaemic rat heart (KLIGFELD et al. 1975). Studies in the dog have shown that propranolol reduced the drop of creatinine phosphate, ATP, glycogen and the rise in inorganic phosphate in the ischaemic area (OBEID et al. 1976). A lowering of ATP results in a loss of ionic homeostasis, a loss of cellular potassium, and an increase in cellular sodium and calcium (NAYLER 1981).

IV. Effect of β-Blocking Drugs on the Blood

While the clinical relevance of these findings remains to be defined, the β-adrenergic blocking drugs effect a number of changes in blood constitutents, which may have therapeutic potential. Propranolol appears to shift the haemoglobin oxygen dissociation curve to the right. This was shown in vitro (PENDLETON et al. 1972), but this appeared to be a nonspecific effect as it was seen with the D (+) isomer more effectively than the (−) isomer; however the concentrations used in these experiments were about 1,000 times those used therapeutically. However, similar results were found in patients who had received a low dose of propranolol, 10 mg q.i.d. for 24 h (OSKI et al. 1972), but others obtained less impressive results after the acute administration of propranolol (BRAIN et al. 1974; LICHTMAN et al. 1974). On the other hand, more recently SCHRUMPF et al. (1977) also demonstrated a shift to the right of the oxygen haemoglobin dissociation curve in anginal patients who had received chronic oral treatment with propranolol (40–240 mg/day). The partial pressure of oxygen at which haemoglobin was 50% saturated was 31.7 ± 0.1 mmHg on propranolol, and 28.2 ± 0.9 mmHg when propranolol was stopped ($P < 0.001$). OSKI et al. (1972) reported that 30% of red cell 2,3-diphosphoglycerate (DPG) was bound to cell membranes and that propranolol released this binding and the released DPG combined with desoxyhaemoglobin and so produced the rightward shift in the dissociation curve. BRANN and NEWMAN (1973) could not, however, find evidence of any binding of DPG to the cell membrane. Total red cell DPG is not increased by propranolol (SCHRUMPF et al. 1977). Another possible mechanism may be an effect on the cell membrane, decreasing intracellular pH and so shifting the oxyphaemoglobin equilibrium curve to the right (MANNINEN 1970; AGOSTONI et al. 1973). This reduced affinity of haemoglobin for oxygen allows a useful increased delivery of oxygen to the tissues which will be of value in ischaemic conditions. It will also serve to offset the reduction in cardiac output and hence general reduction in blood flow associated with the administration of β-adrenergic blocking drugs.

There are in vitro studies with β-blocking drugs (GIBELLI et al. 1973) and also investigations in ischaemic patients on propranolol (MEHTA et al. 1978; KEBER et al. 1979) to indicate that there is an inhibition of platelet aggregation to ADP, adrenaline (MEHTA et al. 1978) and fibrinogen (KEBER et al. 1979) and in hypertensive patients to thrombin or arachidonic acid (CAMPBELL et al. 1981). A study in 20 patients with angina pectoris demonstrated that the 10 patients randomised to propranolol had a decrease in platelet sensitivity to aggregation by ADP from a dose of 1.32 μmol/l required to produce aggregation on placebo to 3.43 after 16 weeks propranolol, and 12.9 μmol/l after 50 weeks. When propranolol was withdrawn sensitivity reverted back to 1.0 μmol/l. Similar changes were seen in the response to adrenaline-induced aggregation; 1.02 μmol/l was required on placebo, 1.9 μmol/l after 16 weeks, 13.2 μmol/l after 50 weeks propranolol and 0.57 μmol/l for aggregation after withdrawal of propranolol. The placebo control group showed no change in platelet aggregation throughout (FRISHMAN et al. 1978). Studies in hypertensive patients revealed an increase in the threshold to maximum platelet aggregation at rest by ADP from propranolol (6–8 weeks)

which declined to control values 2 days after propranolol was stopped, some patients showed an increased sensitivity compared with control (VLACHAKIS and ALEDORT 1980). Exercise resulted in a decrease in the amount of ADP required for platelet aggregation both before (0.55 μmol/l) and after propranolol administration (0.25 μmol/l), the differences were not significant. The administration of propranolol 80–240 mg/day for 24–79 days in normal subjects had indicated that platelet survival is reduced (7.8 days) during the withdrawal phase compared with control (10 days $P < 0.05$) (GOLDSTEIN et al. 1981). CAMPBELL et al. (1981) showed in hypertensive patients that thrombin- and arachidonic acid-induced platelet aggregation and thromboxane synthesis was inhibited by propranolol (640 mg/day) and the D (non-β-blocking) isomer of propranolol (640 mg/day), but not by propranolol 160 mg/day. The aggregating platelets liberate the prostaglandin, thromboxane A_2 which constricts coronary vessels (ELLIS et al. 1976), so inhibition of aggregation might be expected to be of value because of this, besides any obstruction of vessels from platelet adhesion. It has been found that alprenolol reduced blood viscosity (DINTENFASS and LAKE 1976); this is likely to help blood flow, particularly in diseased vessels (DINTENFASS 1977). A further observation that may be relevant in the effects of stress is that propranolol has been shown to reduce the rise in clotting factor VIII induced by adrenaline (INGRAM and JONES 1966).

V. Cardiac Arrhythmias

Electrical properties of the myocardial cell membrane are altered by anoxia. Electrical excitability increases and there is a shortening of the refractory period and a lowering of the threshold for ventricular fibrillation, which may be reduced by about 75% in the infarcted myocardium (SHUMWAY et al. 1957; PHIBBS et al. 1961). The release of catecholamines by the ischaemia also increases the susceptibility to arrhythmias (LOWN and WOLF 1971). The β-blocking drugs have been assessed in a variety of arrhythmias (SINGH and JEWITT 1974). They result in a reduction of the slope of sinus or ectopic pacemaker potential, particularly when the slope has been increased by catecholamines (HOFFMAN and SINGER 1967) or ouabain (CARMELIET and VERDONCK 1967). β-Adrenergic drugs increase the refractory period of atrioventricular conduction tissue including re-entry circuits that appear to be responsible for many cases of paroxysmal supraventricular tachycardia (GOLDREYER 1972). As the concentration of propranolol in vitro in isolated cardiac muscle necessary to produce a membrane effect is 100–500 times that required to suppress cardiac arrhythmias (COLTART et al. 1971; SHAND 1974 a, 1976), it therefore seems that the membrane depressant properties of β-receptor antagonists are unlikely to be of relevance in the treatment of arrhythmias; in addition β-blocking drugs without membrane depressant activity, e. g. practolol, are effective antiarrhythmic agents. Sotalol has additional antiarrhythmic activity designated class III (SINGH and VAUGHAN WILLIAMS 1970). It prolongs the cardiac action potential, effective refractory period and QT interval of the electrocardiogram (BENNETT 1982; NATHAN et al. 1982; NEUVONEN et al. 1982).

VI. Mode of Action of β-Blocking Drugs in Angina

There are thus several ways by which β-blocking drugs may minimise myocardial ischaemia; a reduction of myocardial oxygen consumption, possibly improved delivery of oxygen, better distribution of coronary flow and enhanced substrate utilisation. A reduction in platelet adhesion may possibly inhibit actual occlusion. It seems most likely that the reduction in oxygen consumption, principally as a result of the reduction in heart rate and particularly under conditions of sympathetic stress, is the most important factor.

Whether the action of these drugs is simply a matter of producing these changes, or is more complicated, β-adrenergic blocking drugs, irrespective of whether or not they possess ISA, local anaesthetic (membrane stabilising action) or whether they produce general or selective blockade of β-adrenoceptors, have all brought about some increase in acute working capacity before pain occurs. It appears that benefit therefore results from their common property, blockade of cardiac β-adrenoceptors (WILSON et al. 1969; PRICHARD et al. 1970a; BOAKES and PRICHARD 1973).

Propranolol, as generally used, is a racemic mixture of the dextrorotatory (+) and laevorotatory (−) isomers. Both isomers possess membrane stabilising activity, but only the (−) isomer has significant β-blocking activity (BARRETT 1969). Similar results have been found in humans (BENNET et al. 1970). The (+) isomer has been found to be ineffective in angina (WILSON et al. 1969), even in doses of up to 80 mg intravenously (BOAKES and PRICHARD 1973). Similarly the (+) isomer of alprenolol is ineffective in angina (BJORNTORP 1968).

E. Clinical Use of β-Adrenergic Blocking Drugs

I. Division I: Nonselective β-Blocking Drugs

1. Group I: Membrane Stabilising Activity and Intrinsic Sympathomimetic Activity

The oral administration of 300 mg pronethalol was found to produce an average increase of 44% in exercise tolerance (APTHORP et al. 1964). The effectiveness of β-blocking drugs in long-term treatment of angina was first demonstrated with pronethalol (FULTON and GREEN 1963; PRICHARD et al. 1963; ROBINSON and PILKINGTON 1963). The dosage required resulted in many side effects, and its use was discontinued when it was found to produce tumours in mice (ALCOCK and BOND 1964).

Parenteral oxprenolol increased exercise tolerance by 26% in the first post-drug assessment and by 33% in the second (PRICHARD et al. 1970a). The intravenous (0.2 mg/kg) and acute oral administration (80 mg) of oxprenolol was found to increase acute exercise tolerance in a study by THADANI et al. (1973). In a variable dose trial using 60–400 mg/day oxprenolol, with an adequate run-in period, but only 2 weeks on each treatment in 18 patients, WILSON et al. (1969) showed a definite benefit from oxprenolol. It was found that 17 of the 18 patients had less angina on oxprenolol and the remaining patient the same on placebo and ox-

prenolol. Less impressive results were obtained by BIANCHI et al. (1969) using a lower fixed dose, 40 mg q. i. d., and SANDLER and PISTEVOS (1972) did not find any significant benefit in a short duration trial using a fixed dose, 80 mg t. i. d.

SEALEY et al. (1969) found that intravenous alprenolol 0.1 mg/kg increased exercise tolerance by 29% ($P<0.02$) in the patients with angina pectoris. The same group of workers found that total work increased following oral alprenolol administration by 9% after 50 mg (insignificant), 25% after 100 mg ($P<0.95$), and 17% after 200 mg (insignificant) (SEALEY et al. 1971). Alprenolol 100 mg orally increased acute exercise tolerance in a study in 17 patients to 14.9 mins compared with 11.8 min on placebo ($P<0.01$) (ADOLFSSON et al. 1974).

Some studies with alprenolol in doses of up to 400 mg/day have shown unconvincing results, perhaps illustrating the importance of the pretrial (run-in) period in angina trials. WASSERMAN et al. (1970) using a total of 160 mg (3 patients), or 400 mg per day (6 patients) with 4 weeks on each treatment, found an average of 13 attacks of angina per week on placebo and 16 per week on alprenolol. Likewise acute exercise studies performed during this study showed no significant effect from alprenolol. This trial had no proper run-in period, only 3–4 weeks without any medication prior to the trial. LYON and NEVINS (1971) briefly reported a study where 200 and 400 mg/day alprenolol did not reduce the frequency of anginal attacks.

On the other hand BJORNTORP (1967) performed a variable dose trial, using between 200 and 400 mg/day alprenolol in 13 patients. In this trial there was an adequate run-in period consisting of 2 weeks without treatment then 10 weeks during which dosage was gradually increased. There were eight patients who were finally satisfactory for comparative purposes. They had an average of 10 attacks of angina weekly on alprenolol and 12.5 on placebo ($P<0.01$). AUBERT et al. (1970) used a less than optimum run-in period consisting of 4 weeks on placebo, but demonstrated a significant effect in 18 patients from a fixed dose of alprenolol (100 mg q. i. d.) in terms of a reduced frequency of anginal attacks. HICKIE (1970) used and 8-week pretrial period in a large multicentre trial in 50 patients and showed a significant reduction in the number of anginal attacks (33%) and in glyceryl trinitrate consumption (32%) on alprenolol compared with placebo ($P<0.005$ in both cases). BJORNTORP (1971) showed in nine patients that sustained-release alprenolol (200 mg b. i. d.) appeared as effective as the standard preparation, 100 mg q. i. d. SOWTON and SMITHEN (1971) reported a fixed multidose study which is perhaps better regarded as separate studies of several dose levels, as the various dose levels were not given in random order. They used twice daily doses of 100, 200 and 400 mg alprenolol. Exercise tests at the end of each treatment period showed that compared with placebo, there was an increase in exercise tolerance of 21% from 200 mg/day ($P<0.02$), 17% from 400 mg/day ($P<0.05$) and 14% from 800 mg/day (not significant). Although this study shows that alprenolol is effective, the lack of random administration of increasing drug dosages means that no conclusion can be drawn about the presence or absence of a dose–response relationship (PRICHARD 1974).

Penbutolol is a further member of this group (HEEL et al. 1981). This drug has been found effective in angina; for instance AGARWAL et al. (1976) in a double-blind study found that it was superior to placebo in doses up to 50 mg/day. Other

studies have confirmed the efficacy of penbutolol (HILLIS et al. 1980; HEEL et al. 1981).

2. Group II: Membrane Stabilising Activity, but no Intrinsic Sympathomimetic Activity

The intravenous administration of propranolol 5 mg increased work performance by 40% in an open study involving 14 patients (GRANDJEAN et al. 1966) whilst PRICHARD et al. (1970a) in a double-blind study reported that work increased by 32%–51% ($P<0.05$) in 6 patients given an average dose of 34 mg intravenously. Acute oral administration of propranolol also prolongs exercise tolerance; THADANI and PARKER (1979) found that the effect was maintained for 8 h after 80 and 160 mg, and was still significant at 12 h.

There have been numerous studies that have demonstrated that oral propranolol is an effective antianginal drug, reducing angina attacks and glyceryl trinitrate consumption. This has been shown with fixed dose trials (SRIVASTAVA et al. 1964; KEELAN 1965; GINN and ORGAIN 1966; NESTEL 1966; GIANELLY et al. 1967; HARLEY and DAVIES 1968; RHABKIN et al. 1966; GRANT et al. 1966), fixed multidose trials (HEBB et al. 1968; MIZGALA et al. 1969; ALDERMAN et al. 1975) with most convincing results from variable dose trials (WOLFSON et al. 1966; MILLER et al. 1975b; GILLAM and PRICHARD 1965; AMSTERDAM et al. 1969).

In variable multidose trials each patients receives an individually adjusted dose, but in addition receives a permutation on this individual dose. GILLAM and PRICHARD (1965) has used up to 400 mg/day, a dose considerably larger than that used in any other published report with propranolol at that time. This raised the question: were these larger doses necessary for maximum benefit. GILLAM and PRICHARD (1966) described a trial where again an individually adjusted dose to a maximum of 100 mg q.i.d. was used (average dose 304 mg/day) besides placebo, half-strength tablets (i.e. average dose 152 mg) were also given. Patients responded significantly better on full dose than on half dose. In a later trial in 16 patients 4 different dose levels and placebo were used (PRICHARD and GILLAM 1971). In the run-in period the dose of propranolol was found that resulted in a resting heart rate of 55 to 60 beats/min in the supine position, provided that side-effects did not intervene. Patients received 80–1,280 mg/day with an average of 417 mg. Identical tablets containing 40, 20, 10 and 5 mg propranolol and placebo were given for 2 weeks in random order so that after 10 weeks the patients had received each strength once. This 10-week cycle was repeated twice, a total of 30 weeks for the trial, each patient having received each treatment for 6 weeks. The average dosages were therefore 417, 208, 104, 52 mg and zero.

There was a progressive reduction in the number of anginal attacks and in glyceryl trinitrate consumption as dosage increased. There were an average of 84.9 attacks of anginal pain on placebo for the 6-week period, 67.2 on an average dose of 52 mg, 56.9 on 104 mg, 48.9 on 208 mg and 37.8 attacks of pain for the 6-week period on an average dose of 417 mg/day. The reduction in glyceryl trinitrate consumption closely followed the fall in angina attacks and studies in ten patients showed an increase in acute exercise tolerance. This dose–response study therefore showed a dose-dependent reduction of attacks of angina pectoris from pro-

pranolol. It should be noted that high doses (range 320–1,920 mg/day) do not appear to be associated with adverse haemodynamic effects (ZITO et al. 1980).

Although early studies with propranolol used more frequent dosage, more recent work indicates that dosage may be given twice daily without loss of benefit in terms of angina attacks and glyceryl trinitrate consumption (THADANI and PARKER 1980) and exercise tolerance studies (THADANI and PARKER 1980; BASSAN and WEILER-RAVELL 1983). A number of studies with a delayed-release preparation of propranolol have indicated that when it is given once daily it has similar antianginal activity to the standard preparation given once daily (HALKIN et al. 1979; SCOTT and BALNAVE 1980; LEENEN and VAN DER VIJGH 1981; PARKER et al. 1982).

3. Group III: Intrinsic Sympathomimetic Activity but no Significant Membrane Stabilising Activity

Pindolol produced a significant exercise tolerance in a study in 11 patients (STORSTEIN-SPILKER 1970), but details of dosage were not given. Intravenous pindolol 1 mg increased exercise tolerance in five patients by 28% ($P<0.05$) compared with saline, while doses of 4 and 16 mg produced an increase in 47% ($P<0.01$) and 32% ($P<0.025$) respectively (BOAKES and PRICHARD 1973). Nifenalol (INPEA) is also a member of this group, but has a low therapeutic ratio and a significant antianginal effect was not found when nifendolol was given intravenously (PRICHARD 1971).

Uncontrolled studies using oral pindolol have claimed benefit from pindolol in angina pectoris (YITITBASI and NALBANTGIL 1970; ARAVANIS and MICHAELIDES 1970). NAIR (1972) in a double-blind between-patient trial found that the 15 patients given pindolol 10 mg/day experienced fewer attacks of angina and had a lower glyceryl trinitrate consumption than an equal number of patients given placebo. SAINANI and MUKHERJEE (1972), in a similarly designed study involving 50 patients, found 40% less angina during treatment with pindolol 10 mg (25 patients) than during placebo (25 patients) ($P<0.05$). DWYER et al. (1982) performed a randomised double-blind study in 12 patients and found that pindolol 10 mg t.i.d. significantly reduced the angina attack rate from 8.3 per week on placebo to 6.3 on drug ($P<0.05$), and glyceryl trinitrate consumption by 7.8 and 5.0 per week ($P<0.025$), respectively; 15 mg/day gave a significant reduction of glyceryl trinitrate consumption at 5.7 per week, but the 7.2 per week angina attack rate was not importantly different from placebo. No prolongation of exercise tolerance was found, but the considerable training effect on placebo before and during the double-blind phase makes interpretation difficult. A within-patient study of 40 mg pindolol given once, twice and four times daily resulted in similar angina attack rate and exercise tolerance, but with the once daily regime evidence of declining haemodynamic benefit on exercise from β-blockade was obtained with significantly greater ST depression (KOSTIS et al. 1982 b).

Carteolol (ODENTHAL 1983) is a recently evaluated long-acting member of this group. In a between-patient trial 10–40 mg gave a reduction of angina attack rate of 72%, with a reduction of 19% on placebo; both cases compared with baseline

attack rate. Glyceryl trinitrate consumption followed a similar pattern and carteolol also gave an increase in acute exercise tolerance (ALCOCER et al. 1982).

4. Group IV: No Membrane Stabilising or Intrinsic Sympathomimetic Activity

Intravenous sotalol (average 50 mg) increased exercise tolerance by 33% after the first test after drug administration, and by 45% after the second (PRICHARD et al. 1970a). Oral sotalol 480 mg increased exercise tolerance by 21% in five patients (ATKINS et al. 1971). TOUBES et al. (1970) briefly reported a fixed multidose level study in nine patients given 80, 160, 320, 640 and 1,280 mg/day sotalol. Unfortunately only 1 week on each dose level was used, but there was a significant reduction in glyceryl trinitrate consumption and patients had fewer and less severe angina attacks on sotalol ($P<0.05$). In a multicentre study sotalol up to a maximum of 480 mg/day resulted in an average of 5.1 attacks of angina per week. It was found superior to placebo, average 8.0 attacks per week (GOODING and BERMAN 1974). BRAILOVSKY (1974) reported a very large multicentre trial of timolol in 307 patients. The average weekly angina attack rate on placebo was 8.9, on timolol 3.5 ($P<0.01$). The average dose of timolol was 30 mg, maximum 45 mg. Nadolol is a recently described β-blocker (HEEL et al. 1980; FRISHMAN 1980; GROSS 1981) with a long half-life of 17–23 h. It has been found an effective antianginal drug (FURBURG et al. 1978; TURNER et al. 1978); these studies compared it with propranolol and are discussed in Sect. E. VI. 6.

II. Division II: Cardioselective β-Blocking Drugs

1. Group I: Membrane Stabilising Activity Intrinsic Sympathomimetic Activity

Acebutolol has been found to be an effective antianginal agent (TREMBERLAY et al. 1981; STEELE and GOLD 1982). In a within-patient study in 20 men with angina acebutolol 300 or 400 mg t. i. d. increased exercise tolerance to 8.1 min compared with 6.8 min on placebo ($P<0.05$); ST segment depression was also reduced; the angina attack rate was reduced, average 9.0 per week on placebo, 6.4 on drug ($P<0.05$), as was the glyceryl trinitrate consumption, 9.0 and 7.4 per week, respectively ($P<0.05$) (STEELE and GOLD 1982).

2. Group III: Intrinsic Sympathomimetic Activity, but no Significant Membrane Stabilising Activity

Acute studies demonstrated that practolol was an effective antianginal agent (ARESKOG and ADOLFSSON 1969; COLTART 1971; WILSON et al. 1969; PRICHARD et al. 1970). Oral studies demonstrated that practolol was an effective antianginal agent (GEORGE et al. 1970; SOWTON et al. 1971), although some studies gave unconvincing results (SANDLER and CLAYTON 1970). However, severe sensitivity reactions have been reported with long-term administration of practolol so that the drug is no longer being given as a prophylactic in angina (RAFTERY and DENMAN 1973; FELIX et al. 1974; BROWN et al. 1974).

3. Group IV: No Membrane Stabilising or Intrinsic Sympathomimetic Activity

ASTROM and VALLIN (1974) found an increase in acute exercise tolerance after administration of 5 mg atenolol (ICI 66,082) in ten anginal patients, however, ROY et al. (1975) found an increase in exercise tolerance after oral administration of atenolol 200 mg b.i.d. of about 20%, but the change was not statistically significant; however they found that in all patients atenolol was effective in significantly reducing the number of glyceryl trinitrate tablets consumed at a dosage of 50 mg b.i.d. (average 8.5 in 2 weeks). 100 mg b.i.d. (average 9.2) and 200 mg b.i.d. (average 7.6) when compared with placebo (average 20.8). The attacks of angina also showed a significant reduction. MAJID et al. (1979) found an anginal attack rate on atenolol 100 mg of an average of 10 per 4 weeks and 200 mg (9 per 4 weeks), significantly different from placebo (32 per 4 weeks). Acute exercise tolerance was also prolonged at 3 h postdrug. In a single-blind chronic study of 14 months in doses up to 200 mg atenolol, the reduction of anginal attacks was maintained (SCHWARTZ et al. 1981).

ADOLFSSON et al. (1974) found that oral 40 mg metoprolol in 17 patients produced a 42% increase in acute exercise tolerance ($P < 0.01$). In another acute exercise study metoprolol 100 mg was superior to placebo, and while an 800-calorie meal reduced exercise tolerance after administration of placebo, there was no such reduced tolerance in the presence of metoprolol (DELAGE et al. 1980).

III. Division III: Nonselective β-Blockade plus α-Blockade

An initial study with intravenous labetalol has indicated that in normotensive anginal patients it is less effective as an antianginal agent than propranolol (BOAKES and PRICHARD 1973). Data from patients with coexistent angina and hypertension is encouraging (BESTERMAN and SPENCER 1979). When labetalol is used in doses which control blood pressure in individual patients, their angina also markedly improves. In an open oral study in six hypertensive patients with angina, labetalol appeared to reduce anginal attacks and increase exercise tolerance. The rise in blood pressure on exercise was significantly reduced, but the decline in exercise heart rate was not statistically significant (HALPRIN et al. 1980). It may be that, because of the particular combination of the α- and β-blockade, labetalol is valuable in the anginal hypertensive patient. However, controlled clinical trials will be awaited with interest.

IV. β-Blocking Drugs in Combination with Nitrates

From the very first studies of β-adrenergic blocking drugs in angina pectoris, these drugs have been used in combination with glyceryl trinitrate given for the acute attacks (PRICHARD 1974; RICHTSMEIER and PRESTON 1977), a rational combination in view of their differing modes of action that is supported by animal experiments (SPONER et al. 1981). Glyceryl trinitrate with β-blockade improves exercise tolerance (MACALPIN et al. 1965). The combination of β-blockade plus glyceryl trinitrate may result in improved exercising haemodynamics. For instance, the reduced tachycardia, rate of rise of left ventricular pressure in systole (dP/dt), and the reduced left ventricular work index on supine exercise after intravenous

administration of propranolol is only insignificantly reduced by the combination of β-blockade and glyceryl trinitrate (WIENER et al. 1969). On the other hand angina is associated with an abnormal rise in left ventricular end-diastolic pressure on exercise and this abnormal rise is reduced or abolished by glyceryl trinitrate (PARKER et al. 1966, 1971) this reduction is not significantly inhibited by propranolol (WIENER et al. 1969). However, it should be remembered that the haemodynamic effects of glyceryl trinitrate are influenced by dose, posture and state of the myocardium (PRICHARD and VRHOVAC 1975); however, these results are probably broadly applicable.

A synergistic effect of propranolol and isosorbide dinitrate (ISDN) in single-blind acute exercise studies has been reported (RUSSEK 1968; BATTOCK et al. 1969). BASSAN and WEILER-RAVELL (1983) also found that ISDN (5–30 mg), in contrast to placebo, added to propranolol, improved acute exercise tolerance; a 182-s ($P<0.001$) increase was demonstrated at 1 h; a 63-s increase ($P<0.002$) remained at 6 h. Similarly TURNER et al. (1981) found that ISDN added to propranolol increased exercise tolerance by 24 s ($P<0.05$) and with isosorbide plus hydralazine, still further (42 s, $P<0.005$) whereas hydralazine alone reduced exercise tolerance by 25 s ($P<0.05$). In a double-blind exercise study, ADOLFSSON et al. (1972) found a combination of pindolol 2 mg and ISDN 5 mg to be synergistic, the total work on this combination (average 7,717 kp m) being significantly greater than that obtained with either pindolol 2 mg (6,800 kp m) or isosorbide 5 mg (6,043 kp m) alone. On the other hand, DAVIES et al. (1969) added oral ISDN 10 mg/day to propranolol 40 mg/day, but did not find any further reduction of glyceryl trinitrate consumption. KEYRILAINEN et al. (1973) reported alprenolol (100 mg q. i. d.) significantly better in terms of glyceryl trinitrate consumption and the severity of the anginal attacks than ISDN (5 mg q. i. d.).

We found (PRICHARD et al. 1981) in a further factorial trial that ISDN average dose 84 mg divided daily, added to propranolol half dose ($N=6$) or placebo ($N=4$) resulted in a significantly greater antianginal activity. When the larger dose of propranolol was given, the addition of ISDN produced very similar effects. We found pentaerythrityl tetranitrate (at 539 mg/day) ineffective in contrast to propranolol, which was not enhanced in combination with pentaerythritol (PRICHARD et al. 1981).

V. β-Blocking Drugs in Combination with Calcium Antagonists

There have been a number of reports of the use of nifedipine, a calcium antagonist with a relatively greater effect on vascular smooth muscle and little effect on cardiac conduction tissue (FLECKENSTEIN et al. 1983), with β-blocking drugs. LYNCH et al. (1980) in a randomised double-blind study with 16 patients compared placebo, nifedipine 30 and 60 mg/day, propranolol 240 and 480 mg, a combination of nifedipine 30 mg and propranolol 240 mg, and of 60 and 480 mg of these drugs. The drugs were each given divided three times a day. Both nifedipine and propranolol produced a significant reduction in angina attacks and glyceryl trinitrate consumption, but propranolol was more effective than nifedipine ($P<0.001$). High-dose (60 mg) nifedipine was significantly better than low-dose, but the further reduction in attack rate with 30 mg nifedipine plus propranolol 480 or 240

mg/day was not significant. The high-dose combination however was significantly better than propranolol alone ($P<0.01$). (The actual angina attack rates, etc. are not given; levels of significance are quoted and results are illustrated.) In a double-blind study of nine patients receiving either metoprolol or oxprenolol, the addition of nifedipine (10 mg t. i. d.) reduced angina attacks from 15 per week on placebo to 11.2 on nifedipine ($P<0.05$); glyceryl trinitrate consumption was reduced from 12.6 to 9.1 per week, respectively ($P<0.05$) and acute exercise tolerance was increased from 241 s on placebo to 306 s on nifedipine ($P<0.05$). The ECG changes of exercise were also delayed (JENKINS and NAGLE 1982). MOSES et al. (1981) studied 19 patients with attacks of angina at rest refractory to propranolol up to 320 mg/day; the addition of nifedipine, 30–120 mg a day, abolished rest pain in 14 patients, improved it in 2, but was ineffective in 3.

Exercise precardial ST mapping also revealed a greater reduction from propranolol compared with nifedipine, but significantly more effect was seen with the combination (LYNCH et al. 1980). A similar pattern of results was seen from changes in St depression on exercise recorded by 24 h ambulatory monitoring. There was no improvement from high-dose propranolol compared with low-dose, but propranolol was better than nifedipine, and the combination gave the greatest changes.

FOX et al. (1981) confirmed improved exercise tolerance with propranolol (average dose 300 mg/day) combined with nifedipine (average dose 50 mg/day). Likewise the addition of 10 mg nifedipine in ten patients on propranolol (average 218 mg/day) increased acute exercise tolerance over placebo by 123 s 1 h postdrug ($P<0.01$), and by 57 s up to 8 h postdrug ($P<0.01$) (BASSAN et al. 1982 b). Similarly, improved acute cardiac tolerance was demonstrated by atrial pacing studies where sublingual nifedipine (20 mg) prolonged pacing time to angina from 285 to 421 s ($P<0.01$) in ten patients on propranolol 80 mg t. i. d. ($N=5$) or its equivalent of another β-blocking drug (DAILY et al. 1982).

The resting blood pressure is reduced by the addition of nifedipine to propranolol (DARGIE et al. 1981; BASSAN et al. 1982 b; DALY et al. 1982), as were pressures at submaximal exercise (BASSAN et al. 1982 b), but not at the onset of angina (BASSAN et al. 1982 b). Heart rate was not affected in some studies (DARGIE et al. 1982; FOX et al. 1981; BASSAN et al. 1982 b), but 20 mg sublingual nifedipine did increase resting heart rate from 69 to 77 beats/min in the study of DALY et al. (1982), possibly a reflection of the larger dose and route of administration of nifedipine. Nifedipine added to β-blockade increases cardiac output and coronary blood flow (DALY et al. 1982). The combination of propranolol and nifedipine has been found to reduce pressor responses to cold and mental arithmetic to a greater degree than either agent alone (DARGIE et al. 1981).

Occasionally the addition of nifedipine to β-blockade may cause excessive hypotension; this has been reported with atenolol (OPIE and WHITE 1980). Another unusual untoward reaction is the precipitation of heart failure in patients already on β-blockade (atenolol) with outflow obstruction given nifedipine (ROBSON and VISHWANATH 1982); it has been reported in angina patients without this complication (ANASTASSIADES 1982).

A number of reports have suggested that intravenous verapamil is dangerous and may result in asystole when given to patients taking β-blocking drugs

(BENAIM 1972; BOOTHBY et al. 1972; KRIKLER and SPURRELL 1974). The combination is regarded as contraindicated (OPIE 1980) and severe reactions have been reported even after oral verapamil added to metoprolol (WAYNE et al. 1982). However, in a study of ten patients on propranolol the addition of a single dose of verapamil 120 mg improved acute exercise tolerance by 118 s compared with placebo (BASSAN et al. 1982 a).

VI. Comparison of Adrenergic Blocking Drugs

The exercise studies after the acute administration of approximately equipotent β-blocking doses of propranolol, oxprenolol, practolol and sotalol revealed no significant difference between any of these drugs (PRICHARD et al. 1970), or between propranolol and pindolol (BOAKES and PRICHARD 1973). THADANI et al. (1973) found no significant difference, in 16 patients, in the symptomatic ECG and circulatory effects of oxprenolol, practolol and propranolol after intravenous and acute oral administration of dosages selected to give equal suppression of the exercise heart rate. The most meaningful comparison of two drugs requires that they be given in optimum dosage. The dosage of β-blocking drugs that can be tolerated varies considerably, thus a full comparison requires a variable dose comparative trial.

1. Propranolol and Practolol

Other studies of acute tolerance have failed to reveal any difference between practolol and propranolol, after both intravenous (WILSON et al. 1969) and oral administration (COLTART 1971). SANDLER and CLAYTON (1970) utilised a fixed dose of propranolol (320 mg/day), but variable doses of practolol of between 400 mg/day and an arbitrary upper limit of 1,200 mg/day. The 15 patients received each treatment for 4 weeks, but only the findings of the last 2 weeks were assessed. Propranolol produced a significant reduction ($P<0.05$) in attacks of angina (5.8 attacks per week compared with 8.3 on placebo) whereas practolol did not (9.1 attacks per week). Neither drug reduced glyceryl trinitrate consumption: both surprisingly produced an increase. PRICHARD et al. (1971) reported a variable dose comparative trial of practolol and propranolol. In this study average daily dosages of 766 and 95 mg propranolol and 1,004 mg practolol were used. Only 2 of the 14 patients received the arbitrary upper limit of practolol of 2,400 mg/day; side effects limited the dosage in the remainder. Four periods of 2 weeks were used for each treatment, i.e. total of 8 weeks for each treatment. Propranolol was found to be significantly better than practolol in terms of amelioration of anginal attacks, glyceryl trinitrate consumption and well-being.

2. Propranolol and Alprenolol

In multiple fixed doses of alprenolol (400–800 mg/day) and propranolol (160–320 mg/day) HEATHERINGTON et al. (1973) found an increase in exercise tolerance from both drugs compared with placebo, but no significant reduction in angina attacks or glyceryl trinitrate consumption. Possible reasons for this have been discussed (PRICHARD 1974).

3. Propranolol and Pindolol

No significant differences were found in the decline in angina attacks from baseline between pindolol ($N=23$) 10 mg q.i.d., and a rather low dose of propranolol ($N=18$) 40 mg q.i.d., in a between-patient study (FRISHMAN et al. 1979). In another between-patient study graded doses of propranolol 10, 20, 40 mg q.i.d. ($N=25$) gave a reduction in angina attacks from 29 per week on placebo to 18 per week on the highest dose of propranolol, a 39% reduction. Pindolol was also given in increasing doses, 2.5, 5 and 10 mg q.i.d. and with this drug the attack rate fell from 16 to 9 per week, a 48% reduction. The large difference in baseline might reduce the discriminatory power of this study; differences between the drugs were not significant. Both drugs produced a similar increase in exercise tolerance (KOSTIS et al. 1982 a).

4. Atenolol and Pindolol

In an open crossover study in 20 patients of atenolol 600 mg/day, and pindolol 5 mg t.i.d., each given for 6 weeks, the placebo run-in agina attack rate was reduced from 7.6 to 1.8 per week on atenolol and to 2.9 on pindolol (MAGNANI et al. 1983). At 6 weeks of treatment in this study atenolol had a significantly greater effect, but not at 6 weeks for glyceryl trinitrate consumption. On atenolol subjects exercised for 13.38 min, on pindolol for 11.98 min ($P<0.001$). However, in this study the exercising heart rate was inhibited to a greater degree with atenolol ($P<0.001$); the actual figures were not given. It is therefore possible that the optimum dose of pindolol was not given; this coupled with the openness of the study makes definitive conclusions difficult.

5. Propranolol and Sotalol

Sotalol and propranolol have been compared in a variable dose trial using a design similar to that of PRICHARD et al. (1971). Propranolol was found to be the more effective agent (HORN and PRICHARD 1973). However, sotalol was significantly better than a low dose of propranolol.

6. Propranolol and Nadolol

In a between-patient study, nadolol, average dose 100 mg given once daily, produced a reduction compared with predrug placebo from an average of 5.3 to 2.1 attacks of angina per week in 14 patients. An almost identical percentage reduction was seen in 10 patients from propranolol, average 112 mg q.i.d., from 6.2 to 3.0 attacks per week. The reduction in glyceryl trinitrate consumption and increase in acute exercise tolerance were also similar (FURBERG et al. 1978). Doses of 80, 160 and 240 mg of each drug showed a similar reduction in average glyceryl trinitrate consumption from 15 per week on placebo to 8 per week with propranolol given divided q.i.d. and to 5 per week on nadolol given b.i.d. in a between-patient study ($N=14$). Both drugs also produced a similar increase in exercise tolerance, but at 240 mg/day patients on nadolol had slightly fewer anginal attacks ($P<0.05$) (TURNER et al. 1978). However, as the authors themselves found, nadolol was given in greater β-blocking amounts as on a weight basis it

is a more potent drug (FRISHMAN 1980). In another study of doses up to 240 mg, nadolol once daily was as effective as propranolol q. i. d., but nadolol gave greater increase in acute exercise tolerance (PRAGER 1979).

7. Propranolol and Acebutolol

KHAMBATTA (1974) reported a study of acebutolol and propranolol, finding the former more effective. However, the dosage of propranolol used was very small, only 80 mg/day in 20 of the 25 patients, which is much below optimum. The comparison of either agent versus placebo is not possible as placebo administration was not blind.

DIBIANCO et al. (1982), in a double-blind crossover study in 46 patients, titrated acebutolol up to 600 mg t. i. d., average dose 1,650 mg/day, and propranolol up to 80 mg t. i. d., average dose 219 mg/day, with 6 weeks at stable dose on each drug. Both drugs similarly reduced angina attack rate by 56% and 54% respectively and glyceryl trinitrate consumption by 57% and 47% compared with predrug placebo. Treadmill testing also showed an increased exercise tolerance on both drugs. The differences from the placebo phase between drugs or at the end of the trial were not significant; however, these phases only lasted 1 week.

In a further between-patient study in nine patients acebutolol 400–800 mg was compared with propranolol 160–320 mg, both given t. i. d. in divided doses. The angina attack rate was 6.1 per week on propranolol, 8.9 on acebutolol; other parameters, glyceryl trinitrate consumption or acute exercise tolerance (8.3 min on propranolol and 6.9 min on acebutolol), were not significantly different.

8. Propranolol and Metoprolol

In a between-patient study in 19 patients, metoprolol (average 276 mg) and propranolol (average 293 mg) were both found to produce a similar improvement in exercise tolerance and reduction in angina attacks (FRICK and LUURILA 1976).

9. Propranolol and Atenolol

JACKSON et al. (1978) compared propranolol 80 mg t. i. d. with atenolol 25, 50 and 100 mg b. i. d. in a randomised double-blind study in 14 patients with 4 weeks on each treatment. They considered randomised placebo unethical. The average number of angina attacks in the last 2 weeks of pretrial placebo was 35, on propranolol 14 and on atenolol 100 mg b. i. d. 18; glyceryl trinitrate consumption was 22, 4 and 9 per 2-week period, respectively. Exercise tests showed a similar prolongation on both drugs and the exercise heart rate on 80 mg t. i. d. of propranolol and atenolol 100 mg b. i. d. was identical. In a follow-up study in nine of the patients, once daily atenolol was found as effective as twice daily administration.

VII. Comparison with Other Treatment

HANSEN et al. (1973) were not able to demonstrate any differences between alprenolol plus pentaerythrityl tetranitrate in an acute exercise study. AUBERT et al. (1970) found that alprenolol was significantly better in terms of glyceryl trinitrate

consumption which was not different from placebo. Likewise PRICHARD et al. (1981) found propranolol better than pentaerythritol, which was ineffective. KEYRILAINEN et al. (1973) reported alprenolol (100 mg q.i.d.) significantly better in terms of glyceryl trinitrate consumption and the severity of the anginal attacks on ISDN (5 mg q.i.d.).

LYNCH et al. (1980) reported that propranolol 240 and 480 mg/day was superior to nifedipine 30 and 60 mg/day. LIVESLEY et al. (1973) reported a comparative trial of fixed doses of propranolol and ISDN and two dose levels of verapamil. Patients had first 2 weeks on placebo, then 4 weeks on t.i.d. doses of verapamil 80 and 12 mg, propranolol 100 mg, ISDN 20 mg, and placebo. The design of the trial could be criticised as treatments were not given in random order and the degree of blindness of the trial is in doubt (PRICHARD 1974). Assessment of the final 2 weeks of each treatment period showed no significant difference between propranolol and the higher dose of verapamil. Propranolol treatment resulted in fewer anginal attacks than treatment with verapamil 80 mg t.i.d. ($P<0.05$), but these treatments did not differ significantly in terms of glyceryl trinitrate consumption or the response to an acute exercise test. ISDN was not significantly different from propranolol.

Some other studies have shown verapamil to be similar to β-blocking drugs in terms of reduced glyceryl trinitrate consumption and angina attack rate, 120 mg t.i.d. and propranolol 80 mg t.i.d. (JOHNSON et al. 1981; FRISHMAN et al. 1982 a), as have studies with similar dosages in hypertensive angina patients (FRISHMAN et al. 1982 b), and with 120 mg t.i.d. and 160 mg b.i.d. propranolol (SOUTHALL et al. 1982), or 120 mg t.i.d. and metoprolol 200 mg b.i.d. (ARNMAN and RYDEN 1982). A number of studies have shown that verapamil prolongs exercise tolerance to a greater extent than β-blocking drugs, at least at the dose used (ARNMAN and RYDEN 1982; BALA-SUBRAMANIAN et al. 1982; FRISHMAN et al. 1982 a, 1982 b; SOUTHALL et al. 1982). SADICK et al. (1982) found no sinificant difference between propranolol (80 mg q.i.d.) and verapamil (80 mg q.i.d.) in terms of prolongation of exercise or in time to 1 min ST segment depression.

VIII. Regulation of Dose in Patients with Angina Pectoris

There is evidence that the optimum dose varies between patients. It was shown with propranolol that greatest benefit is obtained with maximum tolerated dose (PRICHARD and GILLAM 1971). It is improbable that other β-blocking drugs will differ in this respect although in some cases the dose range may be less. The dosage of propranolol may be commenced at 10 mg t.i.d. or q.i.d. and increased as often as the patient is assessed until either the angina is controlled or the pulse rate is reduced to about 55 beats/min in the standing position; provided that this dosage does not cause troublesome side effects. Previously we had used a supine rate of 55–60 beats/min, but as this produces results still on the straight line part of the dose–response curve (PRICHARD and GILLAM 1971) the standing rate which represents a high state of sympathetic activity is a better guide. JACKSON et al. (1975) found that the reliance on a supine rate of 55–60 beats/min could result in inadequate dosage, and in 15–21 patients previously considered unresponsive to β-blocking drugs they obtained improvement when dosage was increased to

produce a maximum exercising heart rate of 100 beats/min or 100–125 beats/min that was unresponsive to further dose increments. Exercise which represents a high state of sympathetic activity is clearly a more sensitive guide to dosage and this is particularly so with β-blocking drugs with intrinsic sympathetic blocking activity. However, measuring the exercising heart rate is more troublesome and for ordinary routine purposes standing is sufficient, except for those drugs with significant ISA, the use of exercising rate being reserved for the more refractory case. An alternative approach is gradually to increase dose until some minor side effect prevents any further increment, an approach used to some degree in our first trial of propranolol in angina (GILLAM and PRICHARD 1965).

An important source of the variation in dosage required in angina pectoris is the difference in plasma levels seen after an administration of propranolol (SHAND 1976) which also occurs in ischaemic patients. ALDERMAN et al. (1975) observed a tenfold variation in plasma levels although levels were measured over a range of 1.5–3 h after the last dose. Additionally the actual serum concentration of propranolol required to produce maximum therapeutic response also varies considerably; a sixfold range has been found (PINE et al. 1975).

β-Adrenergic blocking drugs introduced more recently for metabolic reasons, particularly less first-pass metabolism in the liver, show less variation in plasma levels after a given oral dose. Another advantage is that some of the later drugs, e. g. sotalol, atenolol, nadolol, have long half-lives and can therefore usually be given once daily (FRISHMAN 1979). Once daily administration can be achieved in a drug with a shorter half-life in a sustained-release formulation (see Sect. E. I. 2).

IX. Indications for β-Blockade

If the contraindications of asthma and cardiac insufficiency are observed and treatment is started at a low dosage, the use of these drugs is relatively safe. An effective prophylactic taken for angina will reduce the pain on exercise, anticipated or not, and reduce pain precipitated by other causes such as emotion. Although β-blockade may not totally relieve pain it does allow more pain-free exercise. It seems reasonable to use an effective prophylactic such as a β-blocking drug in any anginal patients who are experiencing regular attacks of pain. β-Blockade does not interfere with exercise training programmes that have been found useful in improving exercise tolerance in angina patients (PRATT et al. 1981). Glyceryl trinitrate can be used as usual, its hypotensive effect is not increased by propranolol (PRICHARD and GILLAM 1971).

It has been suggested that some patients with angina pectoris do not respond to β-blocking drugs. The failure of chest pain to respond to β-blockade may be due to misdiagnosis. In one series there were 77% of failures on propranolol in "angina" patients without arteriographic changes, and 14% failures in those with coronary arteriographic changes (AMSTERDAM et al. 1969). Failure to respond might occur in patients with poorly controlled heart failure, (although these patients should not be so treated) as in these patients the disadvantageous increase in the size of the heart resulting from β-blockade may be greater than is usually seen. A larger heart requires a greater increase in wall tension for ejection, and an extra large increase in oxygen consumption from this source might out-

weigh the beneficial effects of β-blockade. However, at least this sequence is not invariable, GILLAM and PRICHARD (1965) reported a patient who developed heart failure after 2 days on propranolol 10 mg q.i.d., but subsequently tolerated the drug (50 mg q.i.d.) after treatment with digitalis and diuretics. Later she became more breathless on exertion, and this was relieved by reducing the propranolol dosage. However, a reduction in dosage was associated with increased angina pectoris. Her symptoms of heart failure and angina were inversely related to the dose of propranolol taken. A compromise of some breathlessness on exertion was acceptable for some relief of her angina. A frequent cause of so-called failure of angina pectoris to be improved by β-blockade is failure to use an adequate dose. Higher dosages with individual dosage adjustment are associated with a low incidence of nonresponders.

1. Unstable Angina

β-Adrenergic blocking drugs have been found useful in the treatment of unstable angina (HULTGREN et al. 1977; WILES et al. 1977; GODENIR et al. 1983). In a study in 30 hospitalized patients atenolol 100 mg mostly but up to 400 mg a day was associated with relief of chest pain in 43%; with relief in a further 27% when given in combination with other drugs, while in the remaining 30% it was ineffective.

2. Prinzmetal's Variant Angina

Prinzmetal's variant angina (PRINZMETAL et al. 1959; COHN and BRAUNWALD 1980) in contrast to typical angina shows an erratic response to β-blocking drugs. ROBERTSON et al. (1982) found that propranolol at a dose of 40 and 160 mg q.i.d. prolonged the duration of angina attacks, but not their frequency in six patients with angina due to coronary artery spasm. YASUE et al. (1978) also found propranolol worsened angina in 13 patients with rest pain associated with ST segment elevation.

X. Withdrawal of β-Blocking Drugs

Studies with β-blocking drugs in angina have demonstrated the occurrence of an increased incidence of angina above control levels when placebo was substituted for active treatment (WILSON et al. 1969; PRICHARD and GILLAM 1971). The initial report was in a study of oxprenolol in angina where 7 cases of status anginosus occurred in 19 patients when placebo was substituted for active treatment (WILSON et al. 1969). In another study in the same year ZSOSTER and BEANLANDS (1969) reported 2 cases of severe ischaemia in a trial of propranolol when placebo was substituted in 20 patients with angina. One patient required hospital admission for acute coronary insufficiency and one patient died from coronary occlusion the day after the propranolol (40 mg q.i.d.) was stopped. In a multidose study of propranolol in angina pectoris it was found that the patients experienced a higher incidence of chest pains during the first week of placebo compared with the second week (PRICHARD and GILLAM 1971). Then SLOME (1973) reported two cases of myocardial infarction when propranolol was abruptly stopped in patients with angina pectoris. ALDERMAN et al. (1974) reported episodes of severe ischaemia in six

patients with angina pectoris when propranolol (80 or 160 mg/day) was stopped. They all experienced unstable angina: there was one case of sudden death; three patients had infarcts, one of whom died, and one patient developed multiple ventricular ectopic beats.

MILLER et al. (1975a) reported 2 ischaemic deaths, and 4 other serious reactions in a total of 20 outpatients, but in contrast they had not observed any episodes in a "large number" of "symptomatic coronary patients" who had propranolol stopped abruptly prior to cardiac catheterisation, which might suggest that limitation of physical activity provided protection against withdrawal exacerbations of the disease.

In a retrospective study in a series of 51 patients with angina, propranolol, average 149.2 mg (range 40–320 mg) was abruptly stopped for coronary arteriography on 53 occasions (MYERS and WISENBERG 1977). In this series there were 14 patients with one-vessel disease, but with greater than 70% stenosis, while the rest had significant narrowing, i. e. over 50% of two or three vessels and all but 4 at least 70% stenosis. There were two patients who had experienced unstable angina on propranolol, one had a recurrence off propranolol which responsed to restarting propranolol, the other patient, however experienced a fatal myocardial infarction 10 days after stopping propranolol. Again, as was the case in the report of MILLER et al. (1975a) those patients with more severe disease appeared to be at greater risk. This appears to be supported by the findings of MIZGALA and COUNSELL (1976) who reported 15 acute coronary events in 14 patients with severe angina on propranolol withdrawal: 6 experienced transmural infarctions, 3 intramural infarctions with 1 of these developing ventricular fibrillation and 6 patients had episodes of acute coronary insufficiency.

In a series of 100 patients with angina admitted to hospital for coronary arteriography, propranolol was abruptly stopped after an average duration of treatment of 8.2 months and at an average dose of 216 mg (MYERS et al. 1979). Three patients had minor increases in chest pain and two patients had nontransmural infarctions prior to the time propranolol was stopped; and the same number of minor and major episodes occurred after the cessation of the drug. The occurrence of ischaemic episodes was not related to propranolol withdrawal, but to the severity of the disease as all four patients who developed nontransmural infarction had class IV New York Heart Association symptoms. SHIROFF et al. (1978) reported a series of 55 patients who had propranolol (average dose 127 mg range 20–30 mg) stopped before cardiac catheterisation. There was only one patient who experienced any increase in pain. There were another 47 patients who continued on propranolol (average 143 mg, range 80–320 mg). The overall incidence of chest pain in the two groups while they were in hospital was similar, 27% in those who stopped propranolol, and 28% in those continuing propranolol. However, there was one patient in the group who stopped propranolol who had a ventricular dysrhythmia and myocardial infarction, but this was following selective coronary artery dye injection. It was concluded that propranolol withdrawal syndrome is infrequent in hospital patients. KADISH et al. (1979) studied blood pressure and incidence of atrial arrhytmias in patients undergoing coronary bypass surgery. It was observed that stopping propranolol 48 or 10 h preoperatively was associated with a greater rise in blood pressure during intubation and a higher in-

cidence of postoperative atrial arrhythmias than in those patients who had half their usual dose of propranolol on the morning of operation and 1 mg q.i.d. intravenously in the intensive care unit.

The withdrawal phenomenon has been reported with several β-blocking drugs. The withdrawal of propranolol and metoprolol in 20 patients with angina pectoris led to 1 patient experiencing a fatal infarct when placebo was substituted for metoprolol and in the same circumstances another patient experienced severe angina (FRICK and LUURILA 1976). MEINERTZ et al. (1979) also reported a case of myocardial infarction in an anginal patient when metoprolol was stopped; however, this coincided with the commencement of nifedipine treatment which may have contributed as its administration can be associated with a tachycardia (BEELEY and TALBOT 1979).

There have been several explanations proffered for the β-blocker withdrawal phenomenon (PRICHARD et al. 1983). An increased sensitivity to isoprenaline after β-blocking drugs have been stopped has been seen in normal subjects after propranolol (BOUDOULAS et al. 1977) or atenolol treatment (WALDEN et al. 1982), and in hypertensive patients after propranolol (NATTEL et al. 1979), or metoprolol treatment (RANGNO et al. 1982). However, not all have found increased responsiveness to isoprenaline after propranolol treatment (GOLDSTEIN et al. 1981). In support of the suggestion of BOUDOULAS et al. (1977) that the withdrawal phenomenon was due to the generation of additional β-receptors, recent radioligand studies in 12 healthy volunteers revealed a 43% average increase in β-receptor density in human lymphocytes, maximum after 5 days propranolol administration, which returned to baseline 4–7 days after propranolol was stopped (AARONS et al. 1980). In contrast to non-ISA β-blocking drugs it appears that the administration of pindolol is not associated with increased sensitivity after withdrawal (RANGNO and LANGLOIS 1982; WALDEN et al. 1982); additionally, β-receptor population is reduced by pindolol (MOLINOFF et al. 1982). There is no evidence that increased circulatory catecholamines are responsible for the β-blocker withdrawal phenomenon (PEDERSEN et al. 1979; PANTANO and LEE 1976; MALING and DOLLERY 1979; GOLDSTEIN et al. 1981; BOLLI et al. 1981). In spite of some evidence to the contrary (KRISTENSEN et al. 1978; ROSS et al. 1980), raised thyroid hormone levels are probably not important (RANGNO et al. 1982; WALDEN et al. 1982).

Another factor which could be relevant is unmasking of the progressing disease process so that in the absence of β-blockade oxygen supply is insufficient to meet the requirements of the heart even when at rest (DIAZ et al. 1974). Other possible factors are a reversal of the favourable rightward shift of the oxyhaemoglobin dissociation curve produced by propranolol (PENDLETON et al. 1972; OSKI et al. 1972; BRAIN et al. 1964; SCHRUMPF et al. 1977), and a reversal of the reduced platelet aggregation produced by propranolol (MILLER et al. 1975a; FRISHMAN et al. 1978).

Thus it seems that the β-blocker withdrawal syndrome is a real phenomenon. Although some of the more formal trials have not confirmed this, they have been studies of inpatients. An additional factor, ambulation, seems necessary for this development of the syndrome. When it is necessary to stop a β-blocking drug the dosage should be reduced gradually and the patient advised to minimise exertion for 2–3 weeks.

F. Side Effects

The majority of side effects from β-blocking drugs can be readily ascribed to blockade of the β-receptor, and are often therefore predictable. Particularly important side effects, heart failure and asthma, can be avoided by proper patient selection.

I. Cardiovascular Side Effects

When patients are in heart failure, or have incipient left ventricular insufficiency (they may have no signs of heart failure on physical examination or chest X-ray, but merely a suggestive history) they are crucially dependent on sympathetic activity to the heart to maintain their cardiac output. If it is felt necessary for these patients to have a β-receptor blocking drug, they should first receive digitalis and diuretics. If the dyspnoea is then relieved it is reasonable, with extra care, to start the patient on a β-blocking drug. There have been reports that patients with angina who have been put in failure by propranolol have been subsequently able to tolerate the drug after the administration of digoxin and a diuretic (GILLAM and PRICHARD 1966; AMSTERDAM et al. 1969). If heart failure is uncontrolled, β-adrenergic blocking drugs should not be given.

It was shown by DUNER and PERNOW (1973) that neither propranolol nor pindolol prevented the inotropic action of digitalis. CRAWFORD et al. (1975) have provided evidence to support the use of digoxin with propranolol. They found that propranolol administration to a group of 20 patients with angina pectoris reduced the frequency of attacks, but in 8 with evidence of abnormal left ventricular function there was a reduction in acute exercise tolerance after propranolol administration. However, the administration of digoxin abolished this reduction. The acute exercise tolerance in other patients without evidence of abnormal ventricular function was not improved with the addition of digoxin. Digoxin alone did not affect angina attack rate or acute exercise tolerance, but it reduced the increased left heart dimension produced by propranolol, by 0.7 mm/m^2 in those with normal ventricular function and by 1.6 mm/m^2 in those with abnormal ventricular function. The increased heart size after administration of digoxin plus propranolol was not significantly different from that while on placebo, an increase of 0.5 mm/m^2 in both groups.

In spite of some theoretical and haemodynamic considerations to suggest the contrary, β-adrenergic inhibitory drugs with intrinsic sympathomimetic stimulating action can also precipitate heart failure; alprenolol (LUND-LARSEN and SIVERTSSEN 1969; LYON and NEVINS 1971), INPEA (DEL BIANCO et al. 1966), oxprenolol (BIANCHI et al. 1969; FORREST 1972), pindolol (PODRID and LOWN 1982), and pronethalol (APTHORP et al. 1964). This is probably because partially compensated cardiac insufficiency represents a state of high sympathetic tone and therefore a β-blocking drug with ISA will produce a marked reduction in heart rate, even if less than one without this property. The presence of α-blockade also does not necessarily prevent heart failure in susceptible subjects because heart failure has occurred with labetalol (FRAIS and BAYLEY 1979). There is no evidence

that the direct membrane effect contributes significantly to heart failure (COLTART et al. 1971).

It had been thought that patients receiving β-blocking drugs might be at special risk of developing acute heart failure if they sustained an intercurrent myocardial infarction. However, controlled trials of the intravenous followed by oral administration of β-blocking drugs in ischaemic patients indicate that there has not been a greater incidence of heart failure in the treated group, with progranolol (NORRIS et al. 1980) and atenolol (YUSUF et al. 1980). On the other hand larger doses of propranolol, 0.15 mg/kg (CAIRNS and KLASSEN 1981) in contrast to the 0.1 mg/kg of NORRIS et al. (1980) was associated with left ventricular failure, and similarly older patients over 65 years given alprenolol (PEDERSEN et al. 1979) had a more frequent incidence of severe reactions, including severe bradycardia requiring atropine, and left ventricular failure. The cardioprotective effect of β-adrenergic blocking drugs (PRICHARD 1983) and thus their use if given early after development of symptoms is associated with a reduction of infarct size and indeed of the late development of heart failure (YUSUF et al. 1980). The administration of β-blocking drugs prophylactically to high-risk patients, e. g. postmyocardial infarction, is not associated with an increased incidence of the development of heart failure, but is overall beneficial. A number of the studies can be criticised on methodological grounds (FITZGERALD 1976; HAMPTON 1981) and there have been some negative results (BABER et al. 1980; WILCOX et al. 1980), but there have now been numerous reports that indicate β-blocking drugs are effective in reducing the recurrence rate of myocardial infarction by about 25% (WILHELMSSON et al. 1974; AHLMARK et al. 1974; MULTICENTRE INTERNATIONAL STUDY 1975; HANSTEEN et al. 1982; Hjalmarson et al. 1981; NORWEGIAN MULTICENTER STUDY GROUP 1981; BHAT 1982).

It is the commencing doses that give the greatest change in the sympathetic environment of the heart, and therefore it is then that heart failure is most likely to be precipitated (PRICHARD 1974). This has been supported by reports of adverse reactions which have confirmed that the greatest danger of precipitating heart failure is at the start of treatment. In one study, seven of eight patients with life-threatening adverse reactions due to impaired cardiac function were receiving doses of less than 40 mg/day propranolol (GREENBLATT and KOCH-WESER 1974). A small percentage increase in dose leyels entails less risk of suddenly precipitating heart failure than the first dose. Our only case of sudden cardiac decompensation was with 2 days treatment at commencing dose of 10 mg propranolol q. i. d.

An important fall in blood pressure is rare after oral administration of β-blocking drugs, but has been reported in patients with cardiomyopathy after propranolol treatment (BETT 1968; TAYLOR 1968). It has occurred in high-risk patients after intravenous administration of β-blocking drugs, e. g. postinfarction with propranolol (CAIRNS and KLASSEN 1981), with alprenolol (PEDERSEN et al. 1979). Some degree of bradycardia at rest occurs with β-blocking drugs without ISA, and to a lesser degree with many agents with this property. This bradycardia is rarely important in uncomplicated hypertensive patients, but it may occur associated with myocardial infarction (CAIRNS and KLASSEN 1981). β-Blocking drugs should be avoided in the sick sinus syndrome.

β-Adrenergic blocking drugs not uncommonly cause cold extremities (M. R. C. REPORT 1981) presumably as a result of peripheral vasoconstriction due to the reduced cardiac output and peripheral β-adrenergic blockade. It was found in 25 of the series of 311 patients of ZACHARIAS et al. (1972) necessitating stopping propranolol in 3 patients. MARSHALL et al. (1976) found symptoms of Raynaud's phenomenon more commonly in patients receiving β-blockers than methyldopa; they thought this was less likely to occur in patients receiving a cardioselective agent. However, cardioselective agents can cause a reduction in peripheral flow (CRUICKSHANK 1981) and the exceptional case of gangrene has been reported (VALE and JEFFERYS 1978) as has also been the case with nonselective drugs, and even with some drugs with ISA (GOKAL et al. 1979). There is evidence to suggest that β-blocking drugs with ISA produce less of a reduction in skin blood flow (IRELAND and LITTLER 1981; OHLSSON and LINDELL 1981; VANDENBERG et al. 1981).

It has been suggested by some investigators that intermittent claudication is worsened by β-adrenergic blocking drugs (RODGER et al. 1976). While a small controlled trial failed to reveal any adverse effect of even large doses of propranolol in claudication (REICHERT et al. 1975), others have found that claudication has been made worse by various β-blocking drugs (SMITH and WARREN 1982; INGRAM et al. 1982). Recently, in contrast to the usually observed therapeutic antiarrhythmic activity (HOMBACH et al. 1983; YUSUF et al. 1983) there has been a report of an increase in episodes of arrhythmias in response to electrical stimulation in 6 of 12 patients suffering from paroxysmal atrial fibrillation from the administration of intravenous atenolol (RASMUSSEN et al. 1982).

II. Respiratory Side Effects

Increasing airways obstruction in susceptible subjects is another side effect clearly related to β-receptor blockade. The cardioselective agents have less effect, but even these can produce significant effects in asthmatic subjects (see Sect. B. IX) and therefore β-blocking drugs, even cardioselective ones, should be avoided if possible. As already discussed, small degrees of airways obstruction may be detected in normal subjects. Some increase in airways obstruction may also be found in patients with chronic obstructive lung disease (CHESTER et al. 1981). This has been found with both propranolol and atenolol (RANCHOD et al. 1982). It also appears that β-blocking drugs reduce the respiratory response to carbon dioxide (PATRICK and PEARSON 1980).

III. Central Nervous System Side Effects

Several central nervous system side effects have been reported. Sleep disturbances, insomnia, increased dreams and tiredness are not uncommon. There have been reports of cases with hallucinations, depression, acute brain syndrome, delirium, headache and dystonic reactions (TURNER 1983). Troublesome dreams are not uncommon in patients taking large doses of β-blocking drugs and vivid dreams occurred in 11 of the 311 hypertensive patients reported by ZACHARIAS et al. (1972). This side effect can often be controlled by taking the last dose no

later than early evening and reducing the last dose in the day if necessary. There is evidence that the β-blocking drugs which are lipid insoluble and therefore have much reduced brain penetration, such as atenolol (CRUICKSHANK 1980; WESTERLUND 1982; BETTS and ALFORD 1983) or sotalol (GREIL 1980) produce fewer central nervous system side effects.

IV. Fatigue

There are several possible explanations to account for the occurrence of fatigue from β-blocking drugs (CRUICKSHANK 1983). These include the exercise reduction in cardiac output, depressed lactic acid release from muscle and reduced blood glucose on exercise after β-blockade that occurs after nonselective β-blockade with pindolol, but not after treatment with acebutolol or metoprolol (KOCH et al. 1981). Another possible mechanism might be interference with β_2-sensitive sodium efflux and potassium influx from the cell (CLAUSEN and Flatman 1980). There are some observations to suggest that cardioselective drugs (atenolol) interfere less with exercise than nonselective drugs (propranolol) (KAIJSER et al. 1980).

V. Gastrointestinal Side Effects

Indigestion, often with some nausea, is a not uncommon side effect and can be avoided by taking the drug with meals (PRICHARD and GILLAM 1969). Diarrhoea is unusual (ZACHARIAS et al. 1972); constipation was more common than diarrhoea with practolol (WISEMAN 1971).

VI. Genitourinary Side Effects

Disturbances of sexual function are uncommon. There were no cases of impotence in the series of ZACHARIAS et al. (1972); of eight patients who had impotence on previous therapy, in two it was improved, in four it disappeared, while in two others it was unchanged. Impotence was more common on propranolol than placebo in the Medical Research Council trial in mild hypertension (M. R. C. Report 1981), but only a third the incidence on bendrofluazide.

VII. Glucose Metabolism

The inhibition of glucose mobilisation requires simultaneous blockade of α-receptors in the liver and β-receptors in muscle. Experiments in normal subjects indicate that β-blocking drugs without ISA do not usually affect resting insulin or glucose levels or the fall of plasma glucose after insulin treatment (EKBERG and HANSSON 1977; LAMMINTAUSTA et al. 1977), but severe hypoglycaemia has been rarely reported (BELTON et al. 1980). These agents with intrinsic sympathomimetic activity may cause a small elevation of blood glucose (SCHLIERF et al. 1973). The problem of diabetes and β-blockade has already been discussed.

VIII. Sensitivity Reactions

Dry eyes and corneal ulceration (WRIGHT 1975) were found to be relatively common with practolol. It was found to reduce tear lysozyme concentration, unlike

other β-blocking drugs (MACKIE et al. 1977). Dry eyes, skin lesions, particularly a psoriasiform eruption can occur from 3 weeks and up to 3 years (on average 10 months) and have occurred with practolol (FELIX et al. 1974) together with sclerosing peritonitis (BROWN et al. 1974). An antibody binding to epithelial tissue has been demonstrated after practolol treatment (AMOS et al. 1975). Patients with the practolol syndrome may have a positive antinuclear factor (ANF), but there was no correlation between the syndrome and the presence of ANF (JACHUCK et al. 1977). The only other β-blocker that may be associated with a high incidence of ANF appears to be acebutolol (BOOTH et al. 1980, 1982; CODY et al. 1979). The oculomucocutaneous syndrome, if it does occur with other β-blocking drugs, is rare (COCCO et al. 1982; CRUICKSHANK 1983).

Several skin reactions, most often psoriasiform or lichenoid, are associated with β-blocking drugs. Skin lesions were more common on propranolol than on diuretics or placebo (M. R. C. Report 1981) and lesions occur with a variety of other β-blocking agents (CRUICKSHANK 1983). Retroperitoneal fibrosis has been reported in patients taking β-blocking drugs, but this may be coincidental rather than causative (MITCHINSON 1972; CRUICKSHANK 1983). Sclerosing peritonitis has been associated with practolol, but probably does not occur with other β-blocking drugs, e. g. oxprenolol and propranolol (MARIGOLD et al. 1982).

G. Cardioprotective Effect

There is increasing evidence from postmyocardial infarction studies that patients given a β-adrenoceptor blocking drug have a reduced recurrence rate. The possible underlying mechanisms have been discussed in Sect. D. If there is a reduction in cardiac necrosis, there should be less likelihood of developing pump failure (MAROKO and BRAUNWALD 1973) which is likely to occur when 40% or more of the left ventricle is involved (PAGE et al. 1971; ALONSO et al. 1973). Notwithstanding the well-known propensity of β-blocking drugs to precipitate heart failure in susceptible subjects (PRICHARD 1974), ischaemic patients on β-blocking drugs do not appear to have a higher incidence of heart failure than those not on these drugs (FOX et al. 1975).

Experimental studies in animals suggest that infarct size is reduced by β-blocking drugs (MAROKO et al. 1971; KLONER et al. 1977; RASMUSSEN et al. 1977). Likewise, studies in humans after acute myocardial infarction suggest that β-blocking drugs reduce the extent of the infarct, provided they are administered sufficiently promptly. This has been shown with postinfarct ST segment mapping (PELIDES et al. 1972), monitoring cardiac enzyme changes (PETER et al. 1978; YUSUF et al. 1980; JURGENSEN et al. 1981), R wave changes (YUSUF et al. 1980) and chest pain (ANDERSEN et al. 1979), all parameters showing improvement after β-blockade. Overall trials of β-blocking drugs after infarction indicate the drugs produce benefit (BABER and LEWIS 1982; HAMPTON 1982; ANONYMOUS 1982; ROSE 1982; TURI and BRAUNWALD 1983), although like all drugs, there is a benefit : risk ratio (BRECKENRIDGE 1982). A number of the studies can be criticised on methodological grounds (FITZGERALD 1976; HAMPTON 1981) and there have been some negative results (BABER et al. 1980; WILCOX et al. 1980), but there have now been numerous reports that indicate β-blocking drugs are effective in reducing the re-

currence rate of myocardial infarction (AHLMARK et al. 1974; WILHELMSEN et al. 1973; MULTICENTRE INTERNATIONAL STUDY 1975; HJALMARSON et al. 1981; NORWEGIAN MULTICENTER STUDY GROUP 1981; BHAT 1982; HANSTEEN et al. 1982; JULIAN et al. 1982; TAYLOR et al. 1982). This evidence and that for there being an effect in acute myocardial infarction suggests that there is a cardioprotective effect in high-risk patients following myocardial infarction. There is also some evidence to indicate, as might be expected from the postmyocardial infarction studies, that patients with angina have fewer infarctions if they are being treated with a β-receptor blocking drug (FOX et al. 1975; LAMBERT 1976).

H. Future Developments

Although β-adrenoceptor blocking drugs have long been established in therapeutics, they remain an active area of research and the introduction of new agents. There has been a continuing search for new, more cardioselective drugs, bisoprolol (EM 33-512) (MANALAN et al. 1981) is a new, highly selective drug being evaluated that appears more selective than the agents at present in use.

There are several drugs with a combination of β-blocking and vasodilator properties, some of which may be related to α-blockade, which are in varying stages of early development. BM 12,434 (VON MÖLLENDORF et al. 1981), bucindolol (DEITCHMAN et al. 1983), carvedilol (SPONER et al. 1982), sulfinalol (SYBERTZ et al. 1982), prizidilol (BIANCHETTI et al. 1982), development of this latter drug being halted because of animal toxicity. Medroxalol is a drug that is similar to labetalol in possessing both α- and β-blocking properties (JAILLON et al. 1982), as is YM-09538 (TAKENAKA et al. 1982). The place of these drugs in angina pectoris is not yet clear, or whether they will be better there than a drug with β-receptor blocking properties alone.

J. Conclusion

The β-adrenergic blocking drugs are firmly established in the treatment of angina pectoris. They are overall probably the most effective group of drugs in current use. They have been used since earliest studies in combination with acutely administered glyceryl trinitrate. They can, however, usefully be applied in combination with long-acting nitrates and certain calcium antagonists such as nifedipine.

There are a number of mechanisms that may be important in the action of β-blocking drugs, but it seems that the most important one is the reduction in heart rate increases associated with various physiological stimuli, after β-blockade. While β-receptor antagonists vary in the possession or not of various associated properties, cardioselectivity, ISA, membrane stabilising activity, there is not at present good evidence to suggest that they vary in their antianginal activity.

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CHAPTER 13

Calcium Antagonists

P. G. HUGENHOLTZ

A. Introduction

Since their clinical introduction in the early 1970s in Japan and Europe, calcium antagonists have enjoyed great interest in the cardiological community. This is undoubtedly due to the fact that they are an entirely new group of compounds with a novel therapeutic principle, the blocking of calcium ions from entering the cell's interior. GEVERS (1981), who has aptly called calcium the "managing director", thus emphasized their significance, for "who would dare to block the entry of the director!" Thus far, these drugs have indeed been shown to have great clinical efficacy for several difficult syndromes and diseases.

From the literature which has appeared over the last decade, a selection has been made of reports on three major calcium antagonists: nifedipine, verapamil, and diltiazem. The many other compounds which are claimed to be Ca^{2+} antagonists, are either incompletely investigated, poorly tolerated, less effective, or still under investigation. They are therefore not discussed in this chapter in any detail. The discussion of each drug is subdivided into two sections, one dealing with the chemistry and pharmacokinetics and the other with its pharmacodynamics and practical application. The pharmacokinetics will be discussed in terms of absorption and bioavailability, their distribution and extent of protein binding, and their elimination. The experimental data relate to studies on the mechanism of action, while the clinical effects of the three drugs will be detailed according to intracoronary, intravascular, and oral or sublingual administration, rather than in general, as different modes of action will prevail depending on the route of administration. Since it was the first well-studied compound, more space is devoted to nifedipine and its mode of action than to the other two. Their similarities and differences will be emphasized, the various indications and contraindications for angina pectoris outlined, and the areas in which our understanding is still lacking specified. This analysis of the literature is of necessity incomplete, but at least reflects the broad current understanding of these compounds.

B. Mechanism of Action of Calcium Antagonists

FLECKENSTEIN et al. (1969), FLECKENSTEIN (1977), and FLECKENSTEIN and FLECKENSTEIN-GRÜN (1980) have proposed that the term calcium blockers, or calcium antagonists, or perhaps best calcium channel blockers, be restricted to those compounds whose pharmacologic efficacy is primarily related to this latter action. Although it is generally known that the different agents also have, to varying

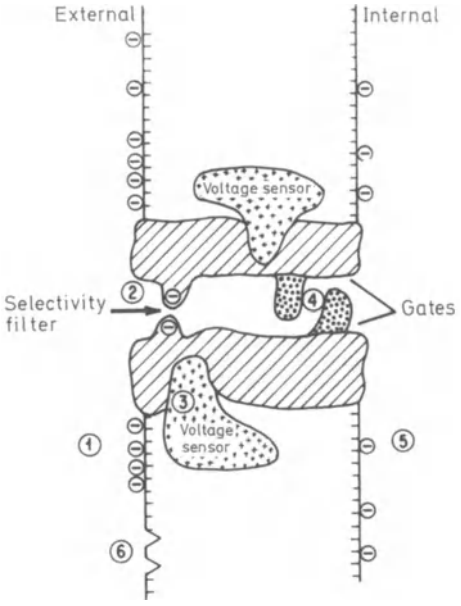

Fig. 1. Schematic representation of a calcium channel in the cell membrane. The channel is depicted as a membrane pore containing within it a negatively charged site (2) of dimenions and charge density appropriate to act as a "selectivity filter" to distinguish between different cations. Also shown are voltage sensor components (3), which confer voltage dependence on channel opening and closing, and channel gates (4), which determine the open or shut character of the channel. Negatively charged sites on the external (1) and internal (5) membrane surfaces serve as cation binding sites, particularly for divalent cations, where the transmembrane potential detected by voltage sensor components can be modulated. A receptor site (6) is shown adjacent to the channel. TRIGGLE (1982)

extents, a blocking influence on other transport sites, the idea is to reserve the term Ca^{2+} antagonist only for the drugs that in the main work on the channel depicted in Fig. 1. This clarifies the classification as it limits the discussion to verapamil, nifedipine, and diltiazem (LEE and TSIEN 1983), although their derivatives such as nimodipine, ALLEN et al. (1983) nitrendipine, and nisoldipine, KAZDA et al. (1983), to name but a few, should also be included in this group.

In his excellent review on the mechanisms of action of calcium channel blocking agents, BRAUNWALD (1982) describes in detail the current concepts on the role of calcium ions in the various subsystems of the human body. Two illustrations from his article have been reproduced to help us understand the action of calcium channel blockers on the function of the vascular smooth muscle cell (Fig. 2 a) and on the myocyte itself (Fig. 2 b), in particular during ischemia (Fig. 3).

From this and other studies it becomes clear that when the entry of Ca^{2+} through voltage-dependent channels is restricted – one can visualize the action of nifedipine as actually plugging these pores (Fig. 1) – intracellular availability of Ca^{2+} for the contraction of the myosin-actin complex is strongly reduced, thus interfering with contraction of the vascular smooth muscle cell, i.e., inducing

vasodilation of the vascular bed. It is here already that the compounds originally from one parent show their diversity. Nimodipine strongly dilates cerebral vessels, nisoldipine mainly the coronary vessels, and nifedipine also the renal vasculature. But even in this plugging action there are differences, as BRAUNWALD (1982) suggests, that unlike nifedipine, verapamil, and diltiazem are "use dependent", i.e., their action is a function of the frequency of contraction, similar to the inhibition of Na^+ channels by type I antiarrhythmic drugs.

According to BRAUNWALD (1982) at least seven mechanisms may control the myoplastic Ca^{2+}. As indicated in Fig. 2b (mechanisms 1A and 1B), there is first of all the inward movement of Ca^{2+} along its concentration gradient across the sarcolemma. Next (mechanism 2) there is a bidirectional Na^+/Ca^{2+} exchange system which, up to a point, regulates the movement of excess intracellular Ca^{2+}. The direction of this exchange depends on the relative concentrations of Na^+ and Ca^{2+} so that when cardiac glycosides inhibit Na^+, K^+-ATPase, intracellular

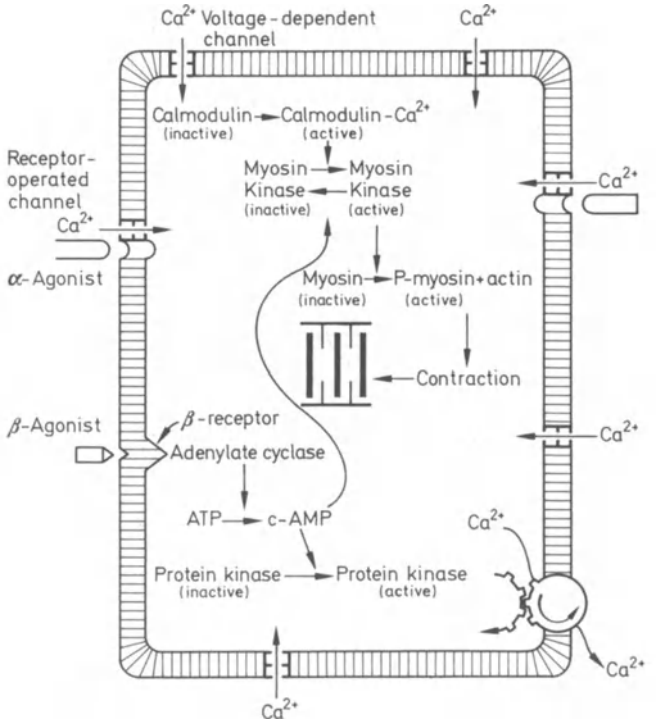

Fig. 2. a The role of Ca^{2+} in vascular smooth muscle. Ca^{2+} can enter the cell through voltage-dependent channels; additional receptor-operated Ca^{2+} channels can be recruited as a consequence of activation of α-adrenergic receptors in the sarcolemma. Activation of β-receptors results in a reduction of intracellular (Ca^{2+}) through two possible mechanisms, both dependent on cyclic AMP. P denotes phosphorylated. (BRAUNWALD 1982). **b** The role of (Ca^{2+}) in the myocardium itself. *Mit.*, mitochondrion; *SR*, sarcoplasmic reticulum; *TT*, transverse tubule; *numbers in circles*, specify mechanisms described in the text

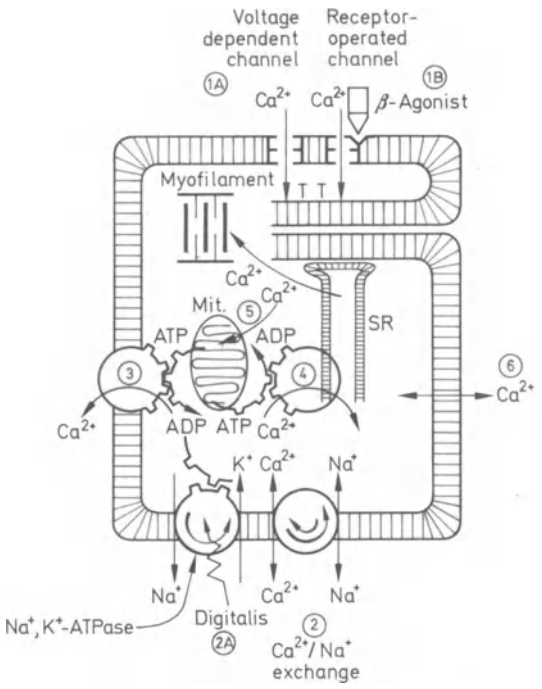

Fig. 2 b

Na^+ is elevated. As a consequence Ca^{2+} enters the cell and this results in the positive inotropic effect known to be exerted by cardiac glycosides.

The next mechanism resides in the sarcolemma which posesses a Ca^{2+}-ATPase which extrudes Ca^{2+} from the cell in an energy-requiring process (mechanism 3). A fourth mechanism transport Ca^{2+} into the lumen of the sarcoplasmic reticulum and sequesters it there also in an energy-requiring process. This mechanism works via phospholamban, a protein which controls the uptake of Ca^{2+} and thus regulates the more rapid contraction and relaxation of cardiac muscle, particularly when catecholamines drive cyclic AMP faster. Another mechanism (5) which works intracellularly, particularly in the mitochondria, depends on ATP generated by the mitochondria. It is an excess of this uptake which ultimately is the beginning of disturbed mitochondrial function. The final two mechanisms (6) allow selective movement of Ca^{2+} along its concentration gradient directly across the sarcolemma. According to BRAUNWALD (1982):

> It will be clear that normal cardiac contraction and relaxation are critically dependent on precisely timed modulations of myoplasmic [Ca^{2+}]; therefore it is evident that abnormalities in any of the systems described above can directly affect myocardial performance.

The calcium channel blockers (see Fig. 1) have been shown by FLECKENSTEIN et al. (1969) to produce selective blockade of the slow inward current and thus lead to electromechanical uncoupling of heart muscle. This is further clearly demonstrated in Fig. 7 where mechanical action of the human heart all but ceases while the electrical activity continues normally. It has been pointed out by many

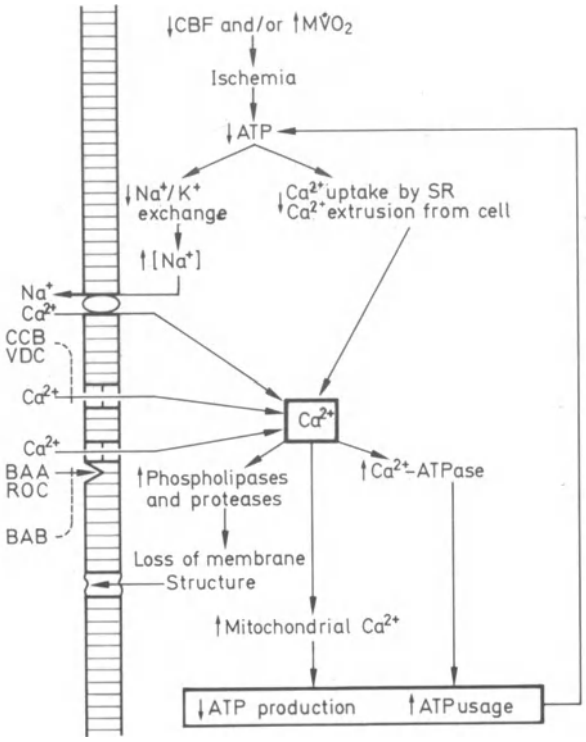

Fig. 3. Interactions between myocardial ischemia and (Ca^{2+}). A reduction of coronary blood flow (CBF), sometimes accompanied by an increase in myocardial oxygen requirements ($M\dot{V}O_2$), causes myocardial ischemia, which in turn reduces cellular ATP stores. This reduction interferes with the transsarcolemmal Na^+/K^+ exchange, which elevates intracellular Na^+, raising intracellular Ca^{2+} through an enhanced Na^+/Ca^{2+} exchange. Lowered ATP stores also reduce Ca^{2+} uptake by the sarcoplasmic reticulum (SR) and reduce extrusion of Ca^{2+} from cells. The resultant augmented intracellular Ca^{2+} causes mitochondrial Ca^{2+} overload, which depresses ATP production further; activation of intracellular CA^{2+}-ATPases, which augment ATP usage, and activation of sarcolemmal phospholipases and proteases, which impair the integrity of the cell membrane. Calcium channel blockers (CCB) interfere with Ca^{2+} influx through voltage-dependent channels (VDC). β-Adrenergic agonists (BAA) recruit additional receptor-operated channels (ROC). β-Adrenergic blockers (BAB) reduce CA^{2+} influx by interfering with the recruitment of ROC. BRAUNWALD (1982)

authors that the exact site of action and the diversity of molecular structures of the different Ca^{2+} channel blockers are consistent with varying types of action, rather than with binding of these drugs to one specific receptor, such as is the case with β-adrenergic blockers. Although FLECKENSTEIN et al. (1969) insist on defining as calcium channel blockers only those drugs which have at least this mechanism as their dominant mode of action, recent evidence from several laboratories has indicated that multiple mechanisms must be assumed. Particularly intriguing in this regard is the evidence that the calcium antagonists also have an intracellular mode of action as described later in this chapter.

C. Nifedipine

I. Chemistry and Pharmacokinetics

This compound, 4-(2′-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbon acid dimethylester, was synthesized by VATER et al. (1972) in the late 1960s and then extensively studied under experimental conditions by Fleckenstein and his group (FLECKENSTEIN 1983). RAEMSCH (1981) states that until May of that year, 1,380 pharmacologic and clinical studies had been published. The formula of this compounds is given in Fig. 4.

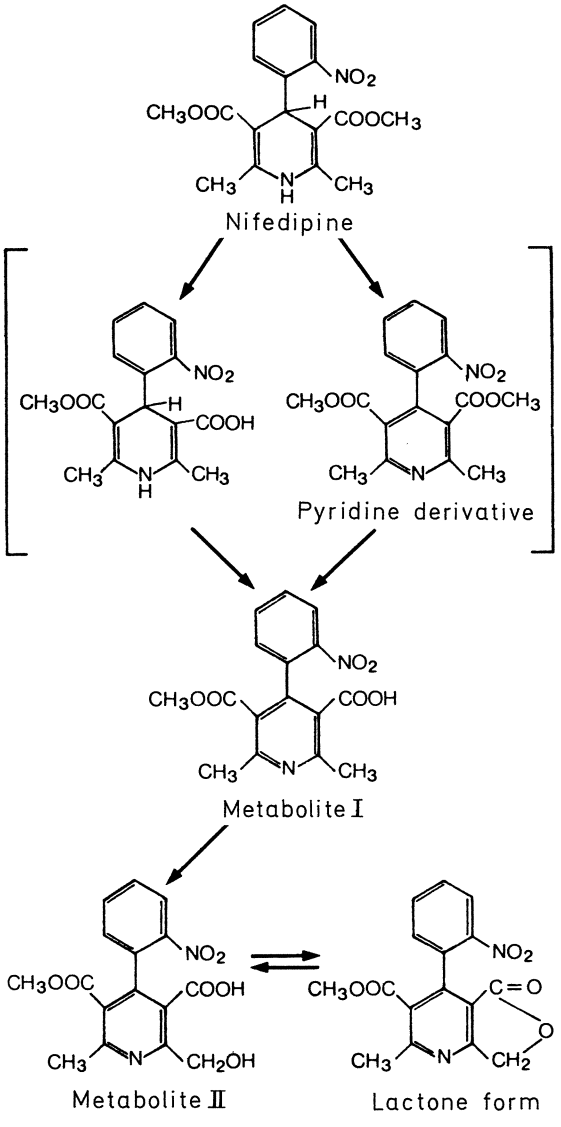

Fig. 4. The chemical formula of nifedipine and its metabolites. RAEMSCH (1981)

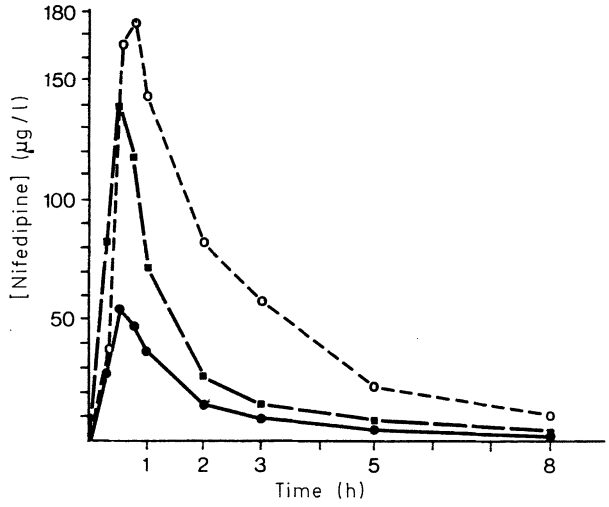

Fig. 5. Increasing concentration of nifedipine, obtained in plasma after administration of 5 mg (*full circles*); 10 mg (*Squares*); and 20 mg nifedipine (*open circles*). With the higher doses, there is a slight delay in resorption, but very high levels are reached in the first 2 h after ingestion. RAEMSCH (1981)

1. Absorption and Bioavailability

Nifedipine is usually nearly completely absorbed. HÖRSTER (1972/1977) indicates that 90% enters the circulation mainly via the upper part of the small bowel. The compound reaches in 10–15 min (time required for the capsules to open) after oral administration (and even more rapidly with sublingual dosages) a significant level with a peak at 1 h (Fig. 5). The height of this peak depends on the dose given. The recently introduced tablets (20 mg retard) lead to somewhat lower blood levels, peaks occur later compared with the capsules, but the duration of clinically effective plasma levels is prolonged. During the first pass through the liver, about 40% of the absorbed drug is biotransformed to inactive metabolites; accordingly, the bioavailable part of active unchanged drug in the circulation amounts to 50%–60% of the oral dose.

2. Distribution

Nifedipine and its metabolites are rapidly distributed in all tissues and organs. Sites of excessive accumulation were not detectable in animal experiments using radiolabeled nifedipine. In different experiments in vitro and in vivo, the plasma protein-bound part of nifedipine was found to be 91%–99%.

3. Elimination

Besides the first-pass metabolism after absorption, the nearly complete elimination of nifedipine from the circulation occurs by biotransformation. The metabolites formed mainly in the liver are shown in Fig. 4 (RAEMSCH 1981). In humans,

70%–80% of the metabolites are excreted in the urine, 20%–30% with the bile. In the phase after reaching the distribution equilibrium in the blood, nifedipine has a half-life of about 1 h, metabolite I has a half-life of 10 h, and metabolite II a half-life of 4–5 days.

When the drug, in a dose of 3×10 mg/day orally was given repeatedly over 7 days, no accumulation of the compound could be demonstrated. In a study over 3 months, the main metabolites reached an accumulation equilibrium after about 30 days of treatment. As they are neither pharmacologically nor toxicologically active, these observations have little clinical relevance. Recently, BOS et al. (1983) studied the effect of chronic oral nifedipine on cardiac performance at rest and during exercise. They found no evidence of tachyphylaxis after 3 months of 40 mg/day. Excretion is largely via the kidneys, although some 20% is eliminated via the large bowel. Only 0.1% of the drug can be detected in the urine in its original form after 8 h. On the other hand, metabolites I and II appear in much higher concentrations up to 20-fold.

4. Experimental Studies in Ischemia

Studies in the pig show that when coronary blood flow is reduced to 20%–30% of control, mechanical action of the underperfused region of the heart all but ceases. Yet, if that area is reperfused soon enough, it will contract again normally. When reperfusion with blood is begun after 30 min of coronary occlusion, the contraction of the myocardial wall returns to only half the preocclusion level. However, when intravenous nifedipine infusion ($1\ \mu g\ kg^{-1}\ min^{-1}$) is started just before reperfusion, myocardial thickening returns to 75% of the preocclusion level. This protective effect, presumably against reperfusion damage, as detailed long ago by ZIMMERMAN et al. (1976) and HEARSE et al. (1978), can also be shown in the same animal preparation after complete occlusion of the coronary artery near its origin. While most animals die of ventricular fibrillation within the first few minutes after such ligation, VERDOUW et al. (1983) found, in stark contrast, that animals in whom high doses of nifedipine or a combination of nifedipine and propanolol was administered in the coronary artery just before ligation, survived three consecutive 10-min periods of complete occlusion. Furthermore in other studies, serious arrhythmias were not seen during reperfusion (FAGBEMI and PARRATT 1981). In other words, nifedipine given immediately before reperfusion, or better still, before ischemia is induced, preserves or restores the heart's contractile properties much better than reoxygenation by itself can achieve (VERDOUW et al. 1981). Nifedipine also increases capillary blood flow in nonischemic tissue of animals in whom one of the coronary arteries has been partially occluded for 30 min. This is probably because overall resistance in the coronary vascular circuit is reduced further. However, even in the experimentally induced ischemic area, where little flow remains, perfusion increases, even favoring the capillary flow to the endocardium. This augmentation of capillary flow, possibly via collaterals that have opened, may well play an important factor in the treatment of ischemic states associated with clinical angina pectoris and in the suppression of reperfusion ventricular arrhythmias. In fact, for this reason in our patients submitted for percutaneous transluminal coronary angioplasty or streptokinase desobstruction, ni-

fedipine is now given as a routine prophylaxis. In over 300 patients so treated, ventricular fibrillation occurred only twice. FAGBEMI and PARRAT (1981) have also shown that under these circumstances reperfusion arrhythmias can be completely suppressed by nifedipine as well as by some of its newer derivatives such as nimodipine.

Many authors have observed that sudden reperfusion of ischemic myocardial tissue may cause an extension of myocardial damage, while HEARSE et al. (1978) as well as others showed that such reperfusion damage in fact may be caused by sudden oxygen-induced transmembrane calcium fluxes. It is therefore now clear that reperfusion with oxygen-rich blood may have a detrimental effect on the ischemic left ventricle, whether it is reperfused after a bout of angina based on vasoconstriction, such as after dissolving a platelet aggregate, during exercise in stable angina, or after coronary artery bypass grafting upon coming off the pump. Our data provide direct evidence that, during acute ischemic conditions, the addition of nifedipine preserves local mechanical function and increases capillary blood flow, even within the core of the ischemic area. Let us now see how these observations in the intact animal can be explained by measurements in the isolated heart, in which high energy phosphate metabolism can be better studied in detail.

It has been shown by a number of authors that various calcium antagonists can reduce high energy phosphate breakdown during hypoxia. Although slow channel blockers vary in their mode of action on the cardiac cells, as shown by OPIE (1980), HENRY (1980), and FLECKENSTEIN and FLECKENSTEIN-GRÜN (1980), nifedipine certainly acts under normoxic conditions by virtually arresting all mechanical activity, thus limiting phosphate utilization. However, there are only limited data supporting this view, mainly those published by NAYLER et al. (1980) and HIGGINS et al. (1980), although ICHIHARA et al. (1979) had not found these effects of either nifedipine or verapamil. It was decided therefore to study the effect of nifedipine on the myocardial release of the AMP catabolites adenosine, inosine, xanthine, and hypoxanthine during ischemia.

It was found by DE JONG et al. (1982a, b) that breakdown of adenine nucleotides was indeed prevented by nifedipine. This evidence is based on measurements of purine nucleotides and oxypurines, in coronary flow, and apex displacement (Table 1) as well as of the adenylate energy charge (Table 2). Nifedipine at 10 μg/l concentration increased the control flow from 40 to 100 ml/min per gram dry weight ($P<0.001$). When the perfusion pressure was lowered from 72 to 17 mmHg, coronary flow in the untreated hearts decreased by 60% ($P<0.001$). During ischemia, flow in the presence and absence of nifedipine was comparable, about 15 ml/min per gram dry weight, while during reperfusion, flow increased again to control levels. Ischemia, induced with a pump, diminished coronary flow in treated and untreated hearts by 75% ($P<0.001$). While nifedipine at a concentration of 10 μg/l decreased apex displacement by 35% ($P<0.01$) at 100 μg/l, it diminished contractility during the preischemic perfusion to 10% of the control values observed with its solvent only ($P<0.001$). Since during ischemia, apex displacement was already reduced to about 25% of perfusion values ($P<0.001$), both in treated and untreated hearts, the heart could deliver a threefold *increase* ($P<0.02$) in apex displacement, when the high dose of nifedipine (100 μg/l) had

Table 1. Dose-dependent effect of nifedipine on coronary flow and apex displacement[a]

Nifedipine (μg/l)	Coronary flow (ml/10 min)		Apex displacement (%)	
	Control	Ischemia	Control	Ischemia
0	103±10 (15)	26±2.2 (9)**	86±4 (14)	27±5 (8)**
3	125± 5 (9)	23±0.3 (6)**	101±6 (9)*	19±6 (6)**
10	174± 8 (11)*	25±2.4 (8)**	71±3 (10)*	28±6 (7)**
30	182±11 (9)*	25±1.0 (6)**	41±4 (9)*	26±9 (6)
100	146±10 (9)*	24±0.3 (5)**	7±2 (9)*	23±6 (5)**

[a] Means±standard error; * $P<0.05$ vs 0 μg/l (unpaired t-test); ** $P<0.05$ vs control (paired t-test). Addition of solvent alone to the perfusion fluid had no significant influence on flow and contractility. Apex displacement before the addition of drug was taken as 100%. Heart rate was 360 beats/min. After a control period of 10 min, flow was reduced with a pump for the same period of time. DE JONG et al. (1982a)

been added to the perfusate prior to ischemia (Table 1). Purine release during the control period was 10±5 nmol/min per gram dry weight. At the end of the ischemic period, purine release was 46±nmol/min per gram dry weight ($P<0.05$ vs control), while nifedipine in as low a dose as 10 μg/l reduced this release by 75% ($P<0.05$). These relatively mild ischemic conditions resulted in a lactate release which was 2.6 times higher than the control value ($P<0.02$). This, too was completely abolished by 10 μg/l nifedipine ($P<0.05$). During reperfusion, purine and lactate production, after an initial sharp rise, decreased again, but the hearts released more of these compounds in the untreated group than in the treated group.

When ischemia was made more severe by reducing flow to a larger extent while increasing heart rate, only the highest dose of nifedipine, 100 μg/l could prevent adenosine release during 10 min of ischemia by more than 90% ($P<0.05$). In these experiments the solvent itself also had an effect on purine production during the control period as the release of adenosine rose from levels of 1 mmol/10 min to 7–11 nmol/10 min. Differences in lactate release during the control period were only observed with 3 μg/l nifedipine: this induced a 42% decrease ($P<0.005$). The nifedipine dose had to be increased to levels ten times as high to prevent lactate release ($P<0.001$). The best results, in terms of restricting adenosine release altogether, was obtained when nifedipine (30 μg/l) was combined with propranolol (30 μg/l) (Fig. 6). A significant decrease in myocardial ATP content could not be detected, even when flow was restricted to as little as 2.5 ml/min with a heart rate of 360 beats/min. However, adenylate energy charge decreased by about 15% owing to ischemia ($P<0.02$, Table 2). Again this decrease was prevented by 100 μg/l nifedipine ($P<0.05$ vs solvent). These protective effects are not primarily due to the negative inotropic action of nifedipine, since it was found that the drug did not affect contractility further when, as a result of ischemia, mechanical action had already been reduced. Similarly, PEREZ et al. (1980) and WEINTRAUB et al. (1982) have found that at these doses neither nifedipine nor diltiazem induced further depression of the mechanical activity of ischemic canine heart, but instead, observed a significant enhancement of its performance, just as in our experiments. In fact, with the highest dose of nifedipine an actual increase

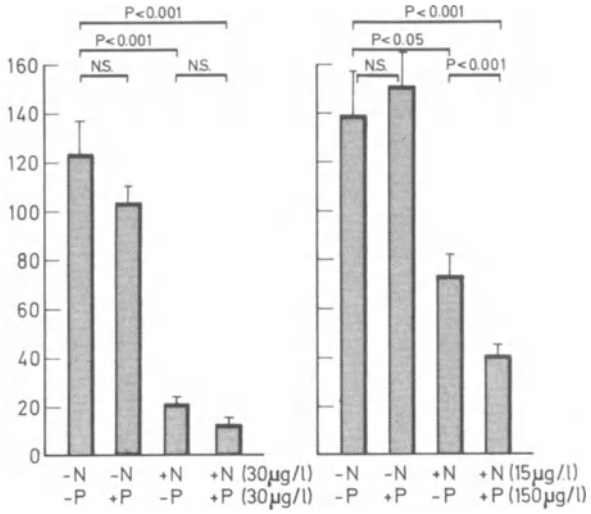

Fig. 6. In rat hearts, perfused according to the Langendorff method, ischemia was caused by reducing coronary flow to ±25% of control valves. In the efflux from the preparation, adenosine was measured as an indicator of breakdown of high energy phosphates which are released through the cell membrane. It can be seen that nifedipine (N) in a dose of 30 µg/l, combined with 30 µg/l propranolol (P), doses that are readily achievable in the clinical situation, leads to a near complete protection of the cell. In another heart in the same series of experiments, it could be demonstrated that the high energy phosphates were indeed present in near normal concentration inside the cell membrane. Note that propranolol alone does not have a major protective effect in this experimental design, but that the efficacy of nifedipine is enhanced by propranolol. DE JONG et al. (1982 a, b)

in apex displacement was found (Table 1), concomitant with a decrease in purine release.

ATKINSON (1977) has reviewed the activities of important regulatory enzymes in vitro as a function of energy charge. With an increase in energy charge from 0 to 1 (see Table 2), the regulatory enzymes in ATP-utilizing sequences increase in activity and those which regenerate ATP decrease in activity. Nifedipine appears capable of increasing the energy charge to levels necessary for the proper functioning of the heart (Table 2) even when under ischemic conditions less oxygen is available. Perhaps its beneficial intracellular action is primarily related to this regulatory function, which has provided a basis for speculations in the past by DE JONG (1982 a) and MAGUIRE et al. (1972). More recently, ABIKO et al. (1981) reviewed the possible mechanisms of action of nifedipine on the cell membrane and in the mitrochondria themselves and concluded with CHURCH and ZSOTER (1980) that the drug also (or mainly) acts via inhibition of release of Ca^{2+} from the intracellular pool, which may help to explain the strong influence on cellular lipid metabolism.

NAYLER et al. (1980) were among the first to show that hearts from rabbits pretreated with nifedipine, verapamil, or propanolol were protected against the ischemia-induced decline in the ATP-generating and O_2-utilizing capacity of the

Table 2. Ischemia-induced decrease of adenylate energy charge and its prevention by nifedipine[a]

Addition	Control	Ischemia	
		$P<0.001$	
None	0.890 ± 0.007 (5)	0.798 ± 0.014 (6)	
		$P<0.02$	
Vehicle	0.896 ± 0.004 (3)	0.761 ± 0.029 (6)	$P<0.05$
			$P<0.05$
Nifedipine (100 µg/l)	0.897 ± 0.007 (4)	0.864 ± 0.024 (4)	

[a] Mean ± standard error; (ATP + 0.5 ADP)/(ATP + ADP + AMP). P calculated with an unpaired t-test. DE JONG et al. (1982a)

mitochondria. According to NAYLER and POOLE-WILSON (1981), at that time no simple explanation for the protection afforded by calcium antagonists to hypoxic and ischemic heart muscle could be given. However, from our experiments we now conclude that nifedipine prevents myocardial adenine nucleotide breakdown in ischemic rat heart, and presumably, as we will see later, in the ischemic intact pig and human heart, by an energy regulatory action over and above its negative inotropic action. The precise mechanism remains to be solved, but little doubt can remain of its beneficial action and further investigation in the human heart appears in order.

II. Pharmacodynamics in Humans

1. Intracoronary Administration

To demonstrate the direct effect of nifedipine on the human heart, the intracoronary route of administration was used by KALTENBACH et al. (1979b). While 0.1 mg intravenously administered nifedipine had shown no effect on systemic hemodynamics or coronary sinus oxygen saturation, intracoronary injection of the same dose caused a significant increase of coronary sinus oxygen saturation, which terminated 5 min after infusion. During exercise, 15 min after administration of 0.1 mg intracoronary nifedipine an anti-ischemic effect, documented by a reduction in exercise-induced increase in LVEDP and exercise-induced ST-T segment depression also became apparent. The authors stated that this effect could not be entirely explained by the effects on the coronary arteriolar resistance because it persisted after coronary flow had returned to normal. The evidence for a central effect of the drug on cardiac metabolism and/or contractility was further studied by SERRUYS et al. (1981a). By measuring the distances between metal markers which had been sutured onto the epicardium during prior surgery, epicardial wall motion was shown to be decreased up to 30% and delayed. Simulta-

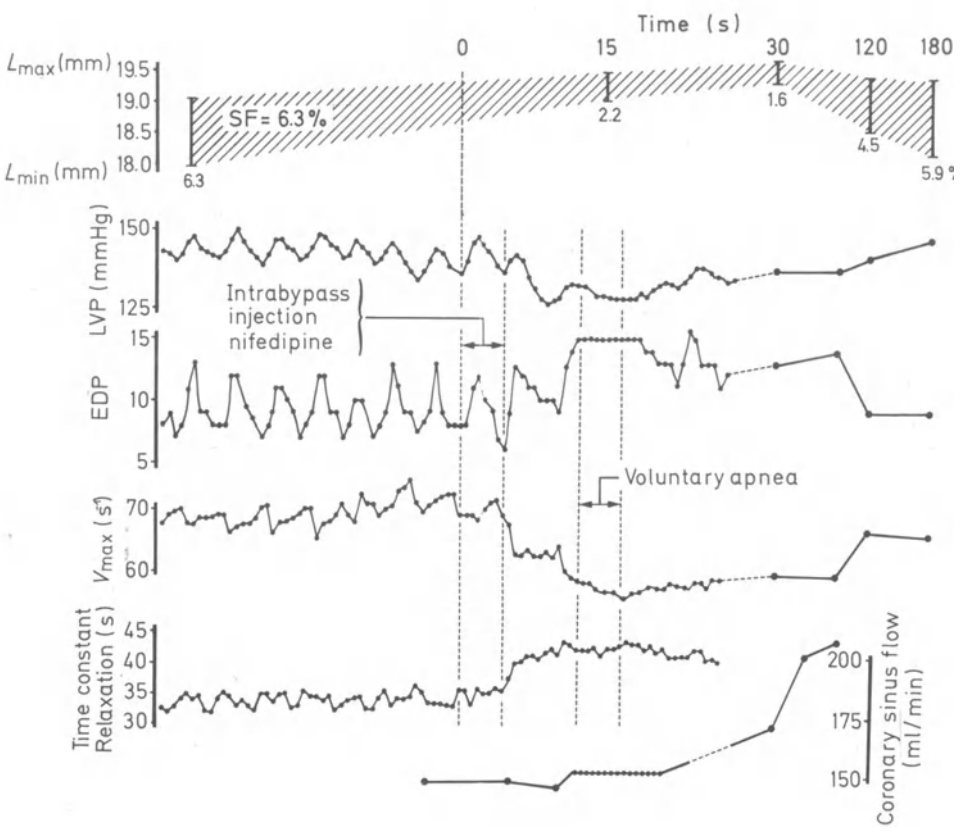

Fig. 7. Beat-to-beat analysis of human myocardial function after a single injection of 0.2 mg nifedipine into the bypass surgically placed on the anterior descending coronary artery. Note that immediately afterwards there is decreased contractility, indicated by the declining V_{max}, a decreased left ventricular pressure, and a marked reduction in the distance between the metal markers sewn onto the epicardium during the previous cardiovascular surgery. L_{max} denotes maximal marker separation, i.e., the situation in diastole and L_{min}, minimal marker separation, i.e., the situation in systole. SF (shortening fraction) is gradually reduced and reaches its maximum reduction at 1.6%, 30 s after injection of the drug. Near complete regional cardiac arrest is associated with a gradual, but steady, increase in coronary sinus flow; 3 min after the injection, the situation has reverted to control circumstances. SERRUYS et al. (1981 a)

neously measured pressure-derived variables demonstrated a direct negative inotropic effect after an injection into the coronary artery bypass graft of 0.1 mg nifedipine with a decrease in left ventricular pressure of 141 of 124 mmHg, a decrease of maximal velocity from 55 to 43 s^{-1}, dP/dt_{max} from 1,855 to 1,521 mmHg s^{-1}, and an increase in left ventricular end-diastolic pressure from 16 to 26 mmHg. No changes in wall motion were seen in the areas not perfused by the artery in which the nifedipine had been injected. It is clear that asynchrony of contraction was induced by nifedipine and is responsible for the slowed overall isovolumic contraction (Fig. 7).

Relaxation of the ventricle as a whole was also impaired as evidenced by a prolonged time constant of relaxation (by 38%) and a diminished peak negative dP/dt, by 26%. All these changes in left ventricular wall motion lasted less than 5 min. The same transient negative inotropic effect was demonstrated by SERRUYS et al. (1981 b) in another group of patients after injection of 0.2 mg nifedipine in the left main coronary artery. Here, frame-to-frame analysis of left ventricular angiograms again showed that intracoronary nifedipine delays, prolongs, and depresses the wall motion. An impaired left ventricular relaxation pattern after intracoronary injection of 0.1 mg nifedipine was also demonstrated by ROUSSEAU et al. (1980 a), both in patients and normal subjects, although abnormalities induced by pacing could be prevented by pretreatment with nifedipine.

Several authors, such as LICHTLEN (1975), BERTRAND et al. (1980), SERRUYS et al. (1980), and RAFFLENBEUL and LICHTLEN (1983) as well as many others have demonstrated a powerful spasmolytic and vasodilating effect after intracoronary administration of nifedipine. This effect was confirmed by RAFFLENBEUL and LICHTLEN (1983) to occur in normal, stenotic as well as poststenotic segments of the injected coronary artery. Shortly after intracoronary injection, coronary blood flow increases and myocardial oxygen consumption ($M\dot{V}O_2$) decreases over a 5-min period. However, the increase in vascular diameter persists after $M\dot{V}O_2$ and coronary sinus blood flow have returned to normal.

The duration of the effect of intracoronary nifedipine on cardiac metabolism was studied by SERRUYS et al. (1981 a, b, 1983) during atrial pacing with heart rates up to 140 beats/min. The pacing-induced angina pectoris threshold was not

Table 3. Effect of pacing on hypoxanthine and lactate release[a]

Parameters studied	Placebo		Nifedipine	
	P1	P2	P1	P2
HR (beats/min)	144± 15	144± 17	149±15	149± 16
LVP (mm Hg)	137± 14	137± 11	142± 17	140± 17
$Pk+dP/dt$ (mm Hg)	2,472±516	2,438±432	2,372±570	2,279±508
V_{max} (s^{-1})	70± 14	70± 14	68± 24	67± 2
CBF (ml/min)	189± 46	186± 54	198± 71	161± 46**
HX (nmol/min)	74.3± 33	26.0± 17	159.1± 39	36.8± 7*
LC (μmol/min)	23.4± 8	13.8] 8**	23.4± 8	0.9± 7*

[a] Mean ± standard deviation; * $P<0.02$ vs P2; ** $P<0.05$ vs P1. The direct effect of nifedipine on cardiac cell metabolism was studied in 20 patients with coronary heart disease during induced ischemia. Left ventricular pressure (LVP) and derived indices (V_{max}, $Pk+dP/dt$), coronary blood flow (CBF), heart rate (HR), and efflux of hypoxanthine (HX) and lactate (LC) were measured during sequential pacing-induced angina (P1 and P2). After P1 ten patients received 0.1 mg nifedipine in both coronary arteries, while the others were injected with the solvent. P2 was carried out 25 min later. Anginal threshold remained *unchanged* in both groups during P2. Despite the recurrence of angina during P2, appreciably less hypoxanthine and lactate were released in both groups compared with their controls (P1). Most important was the suppression of lactate release after nifedipine administration, an observation not made in the placebo-treated group. SERRUYS et al. (1983)

affected 25 min after administration of 0.1 mg intracoronary nifedipine, but at that time the efflux of catabolites of ATP remained significantly reduced (Table 3). Recently, SERRUYS et al. (1983) were able to show that, during complete occlusion of the coronary artery by inflation of a balloon catheter, lactate production, which had markedly increased during the induced ischemia, could be completely suppressed when intracoronary nifedipine was given prior to the occlusion (Fig. 8). All these data indicate a marked O_2-sparing effect and also that the cause of induced anginal pain is not necessarily the release of high energy phosphate catabolites. As originally postulated by FLECKENSTEIN (1983) and seen by KALTENBACH et al. (1979 b) in humans, a prolonged effect of nifedipine on cardiac metabolism is therefore likely. NAYLER (1980), HENRY (1980), and DE JONG et al. (1982 a, b) have all shown this drug to have a powerful effect on myocardial adenine nucleotide metabolism, possibly by increasing the efficiency of oxygen utilization, independent of its influence on the vascular wall itself.

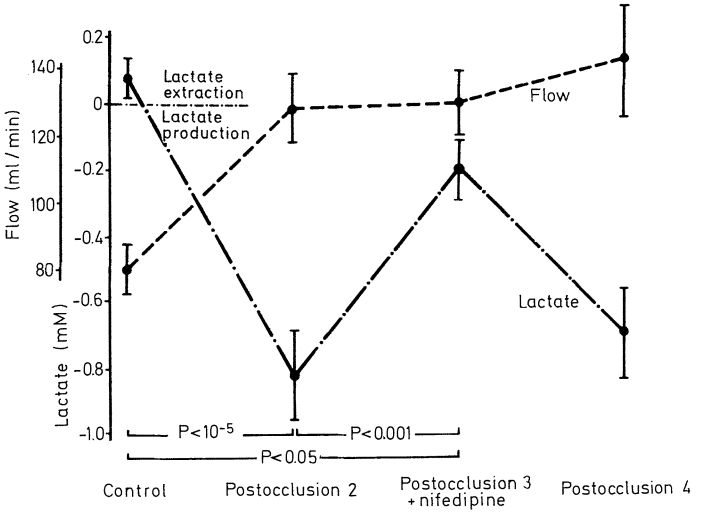

Fig. 8. This schematic display depicts the degree of lactate extraction and production, as well as the measurement of flow in the great cardiac vein (which contains most of the coronary system efflux) at various points during a percutaneous transluminal angioplasty procedure. At control, the vessel is 70% obstructed by an atheroma, but coronary flow is normal at 80 ml/min. There is no lactate production. Immediately after the first inflation of the dilating balloon and its subsequent deflation, coronary sinus flow has increased, but extensive lactate production reflects the preceding episode of ischemia. During the distending procedure, coronary flow is totally obstructed, leading to distal ischemia. When nifedipine is given prior to a second occlusion episode, note that there is virtually no lactate production, although coronary artery flow has not changed. This demonstrates the cardioprotective effect of nifedipine in avoiding ischemia and production of lactate, although flow was actually interrupted for the same length of time, with the second balloon dilatation. After the fourth occluding and distending episode, this time without nifedipine administration, there is again lactate production. Mean $\pm$ standard error; $N = 14$. SERRUYS et al. (1983)

2. Intravascular Administration

ROBINSON et al. (1980) studied the effect of intra-arterial administration of nifedipine on peripheral blood vessels in healthy volunteers. Nifedipine in the forearm caused an increase in blood flow over the dose range a 4–6.4 μg/min. On a molar basis, nifedipine appeared to be three times as potent as verapamil. Local infusion of nifedipine proved to be without effect on the norepinephrine-constricted vein at concentrations 100 times greater than threshold concentration for arterial resistance vessels. It was, however, effective in preventing contraction of veins depolarized by high concentrations of potassium, when the noradrenergic mechanisms was inhibited with phentolamine.

MOSTBECK et al. (1976) showed, after intravenous administration of nifedipine, a shift in blood volume from the limbs toward the trunk. Regional blood volume decreased in arms and legs, again indicating an absence of a dilating effect on the peripheral venous reservoir. After intravenous administration of nifedipine, LYDTIN et al. (1975) measured with plethysmography an increase in peripheral blood flow. These data clearly demonstrate that nifedipine acts mainly on the arterial resistance vessels and has no venous pooling effect as is so clearly the case with the nitrate compounds.

LYDTIN et al. (1975) showed with 0.0075 mg/kg in healthy volunteers, an increase in heart rate by 25 beats/min, while systolic and diastolic blood pressures decreased. The cardiac output increased from 8.3 to 12.0 l/min. These authors concluded that an increase in contractility takes place after intravenous administration of nifedipine, which can be explained by β-sympathomimetic stimulation related to the decrease in peripheral resistance. In five patients with coronary artery disease, KALTENBACH et al. (1979 b) found no changes in coronary sinus oxygen saturation of various hemodynamic parameters after 0.1 mg nifedipine administered intravenously, although after 1 mg a significant decrease in aortic and left ventricular end-diastolic pressure was observed, with increased coronary sinus oxygen saturation. Here the dose is clearly of significance. During exercise, with the same intravenous dose, the rise in left ventricular end-diastolic pressure was less, together with a lower aortic mean pressure when compared with control exercise data. SERRUYS et al. (1981 a) also studied the effect of 1 mg intravenous nifedipine on cardiac function in 11 patients with coronary artery disease. Again, peak left ventricular pressure was lowered from 152 to 128 mmHg, while basal heart rate rose from 71 to 87 beats/min. During atrial pacing to a level which in the control state had led to angina pectoris, there was a reduction in peak left ventricular pressure at all pacing rates. Regional shortening fraction, measured from pairs of radiopaque markers, increased over the entire pacing range. At the highest pacing rate, an increase of the maximal velocity of the contractile elements was also present. There was therefore no evidence of a negative inotropic effect, but rather of an increase in regional function. These difference between the intrinsic negative inotropic effect of nifedipine shown after direct intracoronary injection of the drug in humans and its absence after intravenous administration of nifedipine, can be explained by the reflex sympathetic drive, due to baroreceptor stimulation after the reduction in peripheral vascular resistance. The lesser amounts of the drug, which after intravenous administration still reach the myo-

cardium itself, do not lead to cardiac depression as the peripheral effects predominate.

During angina pectoris induced by atrial pacing, ENGEL et al. (1980) had also observed a tendency toward higher blood flow in poststenotic areas and a decrease in normal areas after administration of nifedipine. Thus, blood distribution or redistribution during atrial pacing appeared to become more homogeneous. As the xenon washout technique can not differentiate between flow of subendocardial, medial, or subepicardial layers and only measures transmural flow, there, remains the possibility that flow after nifedipine administration is only increased in the nonischemic subepicardium. However, the animal data from our laboratory, VERDOUW et al. (1982) would mitigate against this as they demonstrate, by the microsphere technique, an augmentation of the capillary flow in the ischemic subendocardium.

The effects of nifedipine on coronary sinus blood flow have been investigated by several other authors. KOHLER (1975) observed in six patients with mitral stenosis, a rise in coronary sinus blood flow (CSBF) by 40% after 15 min while a maximal increase of 70% was present after 30 min. MERILLON et al. (1978) observed an increase in CSBF and a decrease in coronary vascular resistance (CVR) in 20 patients with coronary artery disease. Almost identical changes in CSBF (+16%) and CVR (−18%) were seen by SIMONSEN et al. (1978) 15 min after oral administration of nifedipine. Neither MERILLON et al. (1978), SIMONSEN and NITTER-HAUGE (1978), nor SCHAEFER et al. (1975) could, however, confirm a significant increase in flow during atrial pacing-induced tachycardia. These latter authors suggested that coronary artery disease in their patients was too severe and that vessels were therefore already maximally dilated, preventing an additional effct of nifedipine. Such an explanation would also fit some of our clinical observations in stable and unstable angina pectoris.

3. Oral vs Sublingual Administration

ROBINSON et al. (1980) found in healthy volunteers that 10 mg sublingual nifedipine induced dilation of the forearm resistance vessels, but that it did not prevent venoconstriction in response to exercise. In hypertensive subjects, 10–20 mg nifedipine caused a rapid dose-related decrease in blood pressure, although no significant reduction in blood pressure had been observed in the volunteers. Since forearm vascular resistance decreased more in the hypertensive (31%) than in the control subjects (17%), PEDERSEN et al. (1980 a, b) postulated an intact baroreflex mechanism to maintain the blood pressure in the normotensive subjects while in the hypertensive patients this baroreflex mechanism appeared impaired. An increase in peripheral blood flow had earlier been demonstrated by LYDTIN et al. (1975) and by MERILLON et al. (1978). The latter author also found no change in venous tone by plethysmographic studies.

JOSHI et al. (1981), at a constant atrial pacing rate, administered 10 mg nifedipine sublingually to ten coronary artery disease patients already pretreated with atenolol (400 mg/day). He observed a significant decrease of dP/dt and $dP/P_{max}dt$ which suggested that the negative inotropic effect of the drug was more evident after β-blockade. In his experiments, cardiac output remained un-

changed, however. KOCH (1980) gave 10 mg nifedipine sublingually to patients with coronary artery disease pretreated with metoprolol. An increase of epinephrine and norepinephrine plasma levels was observed after nifedipine treatment. Stroke volume increased and the left ventricular filling pressure, which had increased after treatment with metoprolol alone, was again reduced. These studies indicate that the stimulation of the sympathetic nervous system after nifedipine administration, can be blocked by β-receptor antagonists. Thus, the intrinsic negative inotropic effect of the drug may become more apparent after β-blockade. Yet the vasodilating effect of nifedipine appears to predominate and thus, for these reasons alone, a combination of the drugs appears attractive, as at a lower heart rate and afterload, cardiac output is maintained.

These data would support the thesis that β-blockade should be added to nifedipine treatment in coronary artery disease patients to counteract its unwanted β-adrenergic stimulation. The clinical relevance of this will be shown later. In their investigation, LICHTLEN et al. (1976) observed no changes in end-diastolic and end-systolic volume in 7 patients with coronary artery disease measured by quantitative angiography. More recently (1980), they showed that sublingual nifedipine is accompanied by a fall in left ventricular relaxation rate and a slight increase in diastolic volume and muscle stiffness. The interpreted this as an early depressant action of nifedipine on diastolic left ventricular function. To characterize the acute effects of nifedipine on left ventricular systolic and diastolic function, LUDBROOK et al. (1982) studied 32 patients stratified with respect to baseline left ventricular function before and 30 min after administration nifedipine (20 mg sublingually). Striking differences were seen in patients with enlarged end-diastolic volumes >90 ml/m^2 and elevated end-diastolic pressure >20 mmHg versus a second group with normal end-diastolic volume <90 ml/m^2, and end-diastolic pressure <20 mmHg as improvement in systolic and diastolic performance was substantially more prominent in patients with impaired baseline function.

Thus, the common hemodynamic changes after oral and intravenous nifedipine administration in patients with coronary artery disease under resting conditions can be summarized as follows:

Reduction of systemic vascular resistance

Reduction of systolic and diastolic blood pressure, most pronounced when the basal blood pressure is elevated

Increase in heart rate, usually very slight, and probably secondary

Increased cardiac output

Unchanged left ventricular end-diastolic pressure

Slight changes in cardiac dimensions or, in some cases an increase in end-diastolic volume

Unchanged contractility indices such as dP/dt_{max} or maximal velocity.

III. Clinical Experience

1. Vasospastic (Prinzmetal's) Angina

There is now considerable evidence from the literature which shows that major coronary arteries can approximately double their luminal diameter from their most constricted to their most dilated state. When partial vasocontriction takes

place around an already preexisting fixed, often eccentric, obstruction, critical reduction in flow may occur much earlier. In fact, when such increased vasomotor tone of the coronary vascular wall is evoked by very strong stimuli, a sudden reduction in flow may lead to irreversible ischemia within minutes. This must be the current understanding of the mechanisms lying behind unstable angina and, often the next step, impending infarction or even sudden death, of which ventricular fibrillation may only be a final manifestation. The best evidence of the spasm-relieving properties of nifedipine is found in the treatment of Prinzmetal' syndrome.

A survey of experience with Prinzmetal's angina would be incomplete without recollection of the first publication by PRINZMETAL et al. which appeared in September 1959. This report on 20 observed cases begins with a classic case report:

H.B., a physician, age 42, awoke one morning with a rhythmic precordial pressure pain. The pain lasted about 45 s and recurred at strikingly consistent intervals of about 5 min. According to the physician's description, approximately 40 distinct cyclic episodes of pressure pain occurred during one attack. The attacks lasted a total of about 2 h. They set in early in the morning every 24 h and sometimes also occurred in the late afternoon, always at approximately the same time of day.

Although the patient experienced severe pain under conditions of rest, he was able to play 18 to 36 holes of golf or to go skiing for 4–6 h without having any symptoms. Two days after the first attack the first ECG recorded during an attack showed a marked ST segment elevation in leads II and III and a slight reciprocal ST depression in lead I. Surprisingly, the ST segments returned to an isoelectric level within 1–2 minutes after abatement of the pain.

This case shows several important features:

1. The pain occurred under conditions of rest.
2. The patient suffered no pain even during strenuous physical activity.
3. The ECG was normal during pain-free intervals. The clinical findings and exercise tests were within normal limits.
4. The attacks set in at approximately the same time of day every 24 h.
5. Each attack consisted of about 40 rhythmically recurring bouts of pain; the attacks had a decidedly cyclic character.
6. Some clinicians attributed them to psychogenic causes.
7. During the painful attacks the ECG showed a marked ST segment elevation and a reciprocal ST depression in the standard leads.
8. The ECG returned to normal within 1–2 min after abatement of the pain.
9. Nitroglycerin suppressed the recurrence of pain and the associated ECG changes.
10. The patient suffered a myocardial infarction 6 months after the onset of the attacks.
11. The ECG showed that the infarction was localised at same site as the preceding ischaemic attacks.
12. The pain at rest ceased immediately after the myocardial infarction.

The first 8 of the 12 features cited by Prinzmetal remain characteristic of this syndrome today. As early as 1768, HEBERDEN in his treatise "Disorders of the Breast" not only described the condition which we today look upon as classic angina pectoris, but also briefly mentioned the form of this disease which arises in the absence of prior stress. However, his description of it was rather vague and not as graphic as that of the classic picture painted by Prinzmetal. Ober 100 years later in 1876 LATHAM and again in 1910, OSLER sketched the syndrome which is today called variant angina. Acceptance of the variant causes of angina pectoris has varied over the years, and only quite recently has it been generally accepted that the spectrum of angina pectoris can indeed extend from the exertional form classically described by Heberden to the form equally characteristically described

by Prinzmetal, in fact at times within the same patient. In the former case, the pathophysiologic mechanism involves a fixed stenosis which at a time of increased oxygen demand, e.g., during exercise, can cause a disparity between oxygen demand and oxygen supply in the coronary vessels; in the second form of the disease, factors which remain to be fully clarified, produce a primary coronary artery spasm and consequent ischemia, even under conditions of rest, e.g., during sleep.

We can now readily understand that many syndromes to which names such as cardiac neurosis, soldier's heart, silent myocardial infarction, unexpected serious arrhythmia, and even sudden cardiac death, have been applied may in fact result from a mild organic coronary stenosis with superimposed spasm; the latter may conceivably be a transitory mechanism which frequently cannot be demonstrated at autopsy. While the varied manifestations of intermittent spasm associated with atherosclerotic arterial narrowing of moderate degree still need to be thoroughly investigated, as is being done today at many centers, we can now safely proceed on the assumption that spasm, unpredictable as it may be, plays a major role. Our own observations in 23 patients covering a period of 8 years, during which period 7,201 patients with various other heart diseases were admitted to the coronary care unit of the Rotterdam Thorax Centre, confirm the classic description, although its occurrence is rare. Therapy has changed substantially in the course of the 8 years during which we treated the 23 Prinzmetal patients. At follow up of all surviving patients in January 1980, TAAMS et al. (1981) demonstrated interesting differences between of the therapeutic results obtained in 10 patients who where treated with drugs, compared with the 13 who were operated upon.

Ten patients were entirely asymptomatic after the surgical intervention, two had an infarction perioperatively, and one patient died immediately after the operation. Drug treatment proved necessary after the operation in two cases. All ten conservatively treated patients survived – a remarkable result given the mortality figures of untreated patients in the literature (5%–20%). They have been virtually free of symptoms since then. One is now without treatment, one is being treated with β-blockers, the rest are being treated with calcium antagonists, mostly nifedipine, which we first used in 1976, and which has been successful in nearly all the cases in which it has been administered. We initially advised surgery to patients with Prinzmetal's angina who also showed a severe organic obstruction of the coronary arteries; However, in view of the high postoperative mortality and the possibility of perioperative myocardial infarction, we now give this advice less freely. Our results agree with data published by GRONDIN and RAYMOND (1977). They cite incidence rates of 8.6% for postoperative mortality and of 14.1% for postoperative myocardial infarction, forbidding statistics! Given current experience, and that of others (BERTRAND et al. 1981 a, b), treatment with calcium antagonists without β-blockade (HUGENHOLTZ 1982) would be preferable over surgery.

Treating 127 patients with symptoms of myocardial ischemia associated with electrocardiographic or angiographic evidence of coronary artery spasm (CAS), ANTMAN et al. (1980) demonstrated complete control of anginal attacks in 63% of all patients and marked relief in 89% with the use of nifedipine. Earlier, ENDO et al. (1975) had observed the beneficial effects of the drug. Similar positive results

were obtained by HEUPLER and PROUDFIT (1979), PREVITALI et al. (1980), and BERTRAND et al. (1981 a, b) in patients with a positive ergonovine maleate provocation test. Nifedipine also appears to prevent CAS induced by α-adrenergic stimulation such as by the cold pressor (CP) test. It decreased the coronary vascular resistance enhanced by the CP test in coronary artery disease patients as shown by GOLDBERG et al. (1979) and DE SERVI et al. (1980). Coronary resistance, usually elevated during handgrip isometric exercise, also decreases after treatment with nifedipine. With the ^{133}Xe clearance technique at rest, HEEGER et al. (1975) and ENGEL et al. (1980) observed an increase in coronary blood flow after administration of nifedipine in these patients. According to the Hannover group and our own findings (HUGENHOLTZ et al. 1981), this increase is present in the normal as well as the stenotic and the poststenotic areas of coronary arteries. Increases in regional myocardial blood flow in poststenotic areas were confirmed by MALACOFF et al. (1982) although they observed a decrease in flow in regions with normal coronary arteries.

Thus, our observations confirm or supplement the findings of other authors. There is now wide agreement regarding the clinical manifestations of the classic Prinzmetal syndrome and its cause. The role played by coronary spasm, in the strict sense of the word, is generally accepted. The question remains whether patients who show induced spasm by ergonovine or CP test, without the classic Prinzmetal symptoms as shown by coronary arteriography are in a precursory stage of this syndrome, or whether there are many other manifestations of coronary artery disease due to spasm which cannot be characterized as a true Prinzmetal's syndrome. We incline to the latter presumption and believe that the term Prinzmetal should be used only, when the entire syndrome is clinically present. This should, insofar as possible, be substantiated by evidence of spasm which may coincide with a preexisting fixed stenosis or by a dramatic therapeutic response to a calcium antagonist. All these facts indicate that there must be a functional (possibly central nervous system) component which is the primary cause of the spasm, which can be superimposed on the fixed stenosis, and is possibly induced or aggravated by platelet aggregation. Several such theories have been advanced. YASUE et al. (1978, 1979 a) talked of dysregulation of the autonomic nervous system as the principal cause; SCHWARTZ (1982) suggested a strong causal role for the central nervous system.

2. Unstable or Crescendo Angina

This syndrome, much akin to Prinzmetal's, lies between it and classic exercise-induced angina. It is also much more prevalent. During a 1-year period, of 1,263 admissions to our coronary care unit, 73 patients were identified with unstable angina (HUGENHOLTZ et al. 1981). Each of these individuals had persistent chest pain during bedrest, coincident with changes in the ECG, with elevation or depression of the ST segment and changes in the T waves, without any evidence of myocardial necrosis such as the development of new Q waves or an elevation of the various cardiac enzymes. Of these 73, 21 became asymptomatic within 8 h on β-blockers and nitrates alone. In the 52 remaining patients, 60 mg nifedipine, in divided doses of 10 mg, was added to the treatment. Of the 52 patients, 42 then

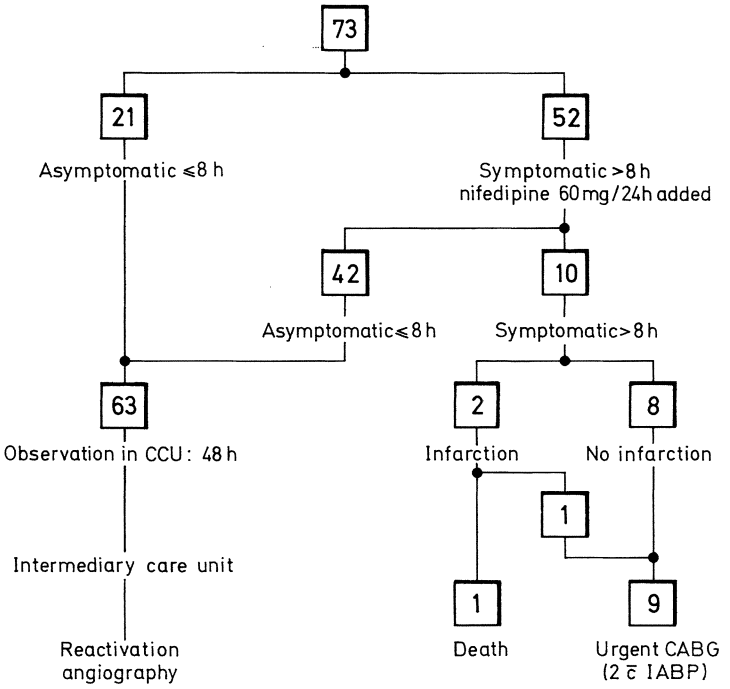

Fig. 9. It is seen that in 73 patients, all with unstable angina, observed over a 1-year period out of 1,263 admissions to the coronary care unit in the University Hospital, Rotterdam, 21 became asymptomatic within 8 h with conventional therapy consisting of bedrest, nitrates (oral of intravenous) and β-blockade. Of the 52 who remained symptomatic during the first 8 h of such treatment, nifedipine was added in doses of 60 mg/day. In 42 of 52, usually when the second dose had been administered orally, symptoms were completely relieved. In 10 other patients, who did not experience such relief, the subsequent arteriograms showed far advanced coronary artery disease. It is argued that the relief of increased vasomotor tone in patients with unstable angina is the deciding factor in explaining the clinical efficacy of nifedipine. CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pumping. HUGENHOLTZ et al. (1981)

became asymptomatic, usually after the second dose; 10 patients remained symptomatic, 9 of whom required urgent bypass grafting. Two patients with persistent pain received intra-aortic balloon pumping with immediate relief of their symptoms. After 1 year, all were alive as are patients who were placed on nifedipine (Fig. 9).

The extent of coronary artery obstructive disease as seen at cardiac catheterization has been detailed before (HUGENHOLTZ et al. 1981). Of the total group of 73 patients, 55 underwent coronary angiography during their initial hospital stay. The severity of coronary artery disease was not unlike that found in stable angina, but the incidence of advanced obstructive coronary artery disease was clearly higher in the ten who remained symptomatic despite all pharmacologic interventions. On the other hand, there was a slight predominance of one- and two-vessel disease in those who responded to nifedipine. The general hemodynamic response to nifedipine was also analyzed in 18 of the 73 patients in whom invasive

baseline data were available from indwelling catheters. No significant peripheral hemodynamic changes could be demonstrated, so that a marked peripheral unloading effect appeared to be absent.

Recently, GERSTENBLITH et al. (1982) have published a prospective, randomized, placebo-controlled study, in which nifedipine and conventional treatment were compared. Of 138 patients with unstable angina, 38 of 68 patients given nifedipine showed success after treatment against 27 of 70 in the control group. Success of medical treatment was defined as absence of sudden death, nonoccurrence of myocardial infarction, or lack of need for bypass surgery within 4 months. These data provide a welcome substantiation of our observations, but how are theirs and ours to be interpreted and explained?

In stable exertional angina pectoris, BROUSTEST et al. (1980) had shown that when nifedipine is used in conjunction with atenolol, the suppression of symptoms induced during exercise testing may become maximal as a function of peripheral unloading and relative bradycardia. SCHMUTZLER (1981) had shown similar data for the combination of metoprolol and nifedipine. The explanation for this increased efficacy of the combination in stable angina is readily at hand: the reduction in heart rate together with the postulated decrease in afterload appear to be the main factors responsible for increased exercise tolerance, decreased incidence of angina pectoris attacks during exertion, and of diminished nitroglycerin usage.

In unstable angina pectoris, however, there is relatively little definite information in the literature regarding the exact mechanisms of action. This is readily explicable because of the uncertainties surrounding the causes of unstable angina pectoris. Despite emphasis on the role of coronary artery spasm, a good example of which can be found incidentally as far back as 1935 in the pathological studies of LEARY, a role which was recently reemphasized by MASERI et al. (1978), and in the detailed knowledge related in previous pages, it has still not been generally accepted that such spasms occur more than in relatively few cases. The general clinical assumption is still that fixed organic stenosis through atherosclerotic involvement of the arterial wall is the usual cause of angina pectoris. While it is now known that obstruction is not always concentric and indeed, frequently eccentric, the concept of fixed stenosis has remained. In the majority of patients with unstable angina, however, the anatomic situation probably lies in between (Fig. 10).

Particularly when eccentric lesions are present which leave part of the circumference of the vascular wall intact, vasoconstrictive stimuli may cause marked changes in the tone of that part of the vessel wall which is unaffected and thus influence the coronary blood flow. Several authors have now demonstrated spontaneous changes in coronary vascular resistance, independent of identifiable stimuli which change myocardial metabolic demand. Others have seen this luminal reduction, up to complete spastic obstruction after total plexectomy or even cardiac transplantation (BERTRAND et al. 1981 b), situations in which supposedly all nervous system connections have been severed. Primary myogenic control of coronary resistance was originally proposed by BAYLISS in 1902, when he described the intrinsic ability of blood vessels to respond to changes in transmural pressure. This mechanism is not generally considered to have a dominant role, but it must be pointed out that is has been difficult up to now to formulate studies capable

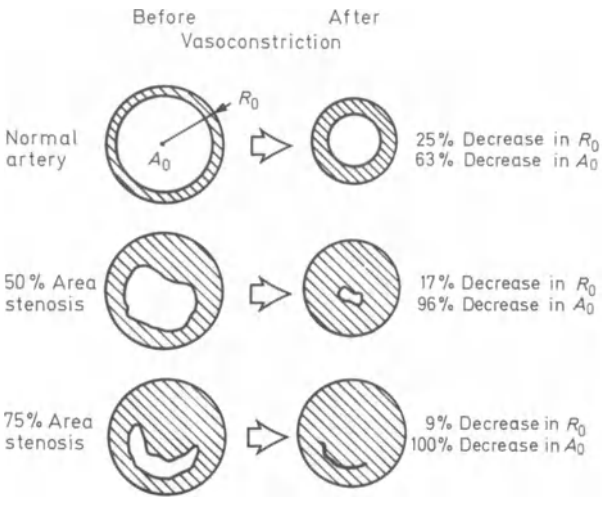

Fig. 10. Effect of changes in vasomotor tone. Note that in the second example an eccentric endothelial lesion with a relatively mild 50% area stenosis can turn into a critical 96% stenosis with only a minor reduction in the external diameter. In other words, moderate changes in vasomotor tone can change an insignificant obstruction into a critical one. A_0, area; R_0, radius. HUGENHOLTZ (1982), modified from MCALPIN

of defining the importance of this mechanism in atherosclerotic blood vessels. BERNE et al. (1980) have tested different vasoactive agents such as adenosine, nitroglycerin, and calcium antagonists for their ability to affect the induced action potential of isolated large and small coronary arteries. Adenosine blocked the calcium-dependent action potential in small coronary arteries, but had no effect on the action potential in large arteries. In contrast, nitroglycerin blocked the action potential in large coronary arteries, but not in small ones, while calcium antagonists blocked the action potential irrespective of the size of the vessel. Indeed, nifedipine is capable of interfering completely with the autoregulation of the renal vascular bed, whereas nitroglycerin fails to affect this regional system.

Autoregulation of blood flow is defined as the intrinsic regulatory mechanism of a vascular bed to maintain its blood flow at a constant rate, regardless of the changes in perfusion pressure. In the syndrome of unstable angina in which the combination exists of an eccentric fixed endothelial lesion with a hypersensitive, but otherwise healthy, vascular wall opposite, the influence of nifedipine is such that it can promptly relax this excessive vascular tone. In keeping with this concept are the observations of the rapid and persistent relief of pain in the majority of our patients with unstable angina pectoris (HUGENHOLTZ et al. 1981), and the striking results in Prinzmetal's angina, reported by ANTMAN et al. in their large series of patients in 1980. The specific action of nifedipine in autoregulation of the major epicardial and the smaller coronary arteries, stabilized what had been a very brittle condition. The fact that in 42 of our 52 patients such relief persisted for the entire period of observation is a further strong argument in favor of this mechanism. The hypothesis has also been put forward that there is a subset of patients with inappropiate vasoconstriction or suspected CAS, who may worsen

with β-adrenergic blockade as with the CP test or indeed exercise or excessive emotion. In fact, YASUE et al., as far back as 1976, have specifically argued against the use of β-blockers in these individuals, as they showed that β-blockade may induce vasoconstriction. Since in our series of patients, who had remained unresponsive during 8 h of β-blockade, the response to nifedipine was so consistent (and just as effective as had been pain relief by intra-aortic balloon pumping via increased coronary flow in our previous experience with the same kind of patients; MICHELS et al. 1980), there is little doubt that nifedipine in these unstable angina patients was the sole agent which tipped and kept the balance in their favor.

More recently, BRAUNWALD (1980, 1982) has reviewed current clinical evidence and stated that there now might very well be a preference for the use of calcium antagonists over β-blockade in patients suspected of having abnormally increased coronary vasomotor tone, such as is the case in unstable angina and Prinzmetal's syndrome. Such an opinion is supported by several reports in the literature (YASUE et al. 1979 a, b; ROBERTSON et al. 1979 a, b; HUGENHOLTZ 1982), which indicate that angina pectoris occurring in Prinzmetal's syndrome may be worsened by treatment with β-blockers, particularly propanolol. The first observation by YASUE et al. appeared in 1976 postulating that in Prinzmetal's syndrome, β-blockade could potentially lead to further vasoconstriction and thus worsen symptoms. In a more recent report, YASUE et al. (1979 b), observed four cases in whom periodic attacks during rest were relieved by nitroglycerin, but were made more severe by propranolol. In fact, the combination of propranolol and isoproterenol infusion induced "Prinzmetal" attacks very similar to spontaneous attacks, while infusion of isoproterenol alone did not do so. Coronary arteriography at the time showed severe spasm of the coronary arteries. These observations are similar to those described by FLECKENSTEIN and FLECKENSTEIN-GRÜN in 1980 on an isolated vascular system. In these experiments, they showed conclusively that the addition of β-blockade caused severe vasoconstriction of the coronary arteriolar wall, which could be relieved, however, by calcium antagonists.

FULLER et al. (1980) studied with thallium scintigraphy the response to nitrates, β-adrenergic blockade, calcium flux blockade, and prostaglandin inhibition. The exercise-induced spasm with pain episodes could be prevented by oral nitrates, but not totally eliminated by the other drugs, while β-adrenergic blockade appeared to be detrimental. A 69-year-old man treated by CARILE and CIVERRA (1980) with pindolol, had his attacks of angina worsen with further ECG signs of anterior ischemia. Replacement by nifedipine led to total relief. This was also the conclusion of MARX (1980), who reviewed the subject for the nonmedical literature in 1980. He concluded: "in spasm induced angina propranolol may exacerbate symptoms while calcium antagonists of various kinds would appear to be the drug of choice." This concept of dynamic coronary obstruction in the presence of "normal" or diseased coronary arteries implies a direct role for coronary vasodilators in patients with any form of angina pectoris, even when frank coronary spasm is absent. Also implicit in this hypothesis is the concept that dynamic and fixed components of obstruction may variably contribute to the degree of obstruction in different patients. It should therefore not be surprising that in

patients with largely fixed obstructions benefit will mainly come from attempts to lower $M\dot{V}O_2$ with nitrates and β-blocking agents, while in extreme cases only the balloon catheter dilation of the coronary artery or bypass surgery can provide adequate relief. On the other hand, patients with varying degrees of constriction will do better on nifedipine, which as was shown earlier, also has a direct cardioprotective effect on the cardiac cell, thus lending added weight to the use of this drug in attacks of angina pectoris which may lead to ischemic areas of myocardium, distal to the obstruction (see Figs. 8–10).

3. Stable, Exercise-Induced Angina

After all the arguments advanced in the previous pages, in favor of the use of calcium antagonists in conditions where the tone of the vascular system is altered, what can be the rationale of its use in stable, exercise-induced angina where fixed sclerotic lesions in the coronary arteries abound? This is a vexing question indeed, as despite the overwhelming clinical evidence from at least 50 double-blind, randomized studies, between 1974 and May 1982, involving at least 1,129 patients, with doses of nifedipine ranging between 10 and 60 mg, all of which show nifedipine to be very effective therapy when compared with placebo, there is yet to appear a study which convincingly shows the exact mechanism of action. Indeed, when nifedipine in the treatment for stable angina pectoris is compared with placebo or other proven effective agents such as propranolol, nitroglycerin, diltiazem, or verapamil, or for that matter other β-blockers, there is as yet no generally accepted explanation for its proven efficacy. An even more extensive list of references testifying to this point is available upon request from the author.

SOBEL (1981), in a review, indicated that 4 million patients had by then been treated by nifedipine. Yet he, too, was unable to propose a final hypothesis of the various proposed mechanisms, such as peripheral arterial vasodilation, with reduced work of the heart as a consequence and/or selective decreases in the coronary vascular resistance which enhance coronary blood flow, as was shown by ENGEL and LICHTLEN (1981). The last hypothesis, in combination with the delay in or suppression of the injurious effects of calcium under temporary ischemic conditions, are the most likely to be ultimately proven to play the major role.

BRAUNWALD (1982), in his excellent review of the mechanisms of action of calcium channel blocking agents, also indicates that the reasons for beneficial action in stable angina pectoris must be multifactorial. He, in particular, emphasized the data obtained by GUNTHER et al. (1981 a, b) who, having noted that patients with coronary atherosclerosis and stable angina exhibit coronary vasoconstriction during the CP test, found that nifedipine could abolish this coronary vasoconstrictor response. These observations suggest that neurogenic vasoconstrictive mechanisms contribute much more to the imbalance between myocardial oxygen supply and demand than has been hitherto accepted. MASERI et al. (1978) have repeatedly emphasized that neurogenic vasoconstrictor mechanisms are the prime source of such imbalance and that coronary vasodilation induced by calcium channel blockers could play a major role in this respect. In this regard it must be reemphasized that nifedipine contrasts in its action with propranolol which, as

was argued by YASUE et al. (1976), can augment coronary vasoconstriction. It was in fact shown to be the cause of cold-induced coronary vasoconstriction, presumably by blockade via β_2-mediated vasodilation.

BRAUNWALD (1982), like ROUSSEAU et al. (1980 b, 1981), pointed to yet another mechanism by which calcium antagonists and in particular nifedipine may help relieve symptoms common in patients with coronary artery disease. Dyspnea or other symptoms of pulmonary congestion, secondary to decreased ventricular compliance, are often misinterpreted as "pressure on the chest." The following mechanism is postulated: in patients with critical obstruction of the coronary arteries, moderate increases in heart rate may lead to early ischemia thereby reducing mitochondrial ATP production. The resultant lower energy charge of the cardiac cell (DE JONG et al. 1982 a, b) interferes with the uptake of Ca^{2+} by the sarcoplasmic reticulum or with the extrusion of Ca^{2+} from the cell, both of which are energy-requiring processes. As a consequence, myoplasmic Ca^{2+} rises, the relaxation of the myocardial wall becomes incomplete, and the ventricle as a whole becomes less compliant. Thus, the Ca^{2+} channel blockers by interference with entry of excess calcium into the cell, restore myoplasmic Ca^{2+} to normal, thereby enhancing diastolic relaxation and lowering ventricular diastolic pressure. This, in turn, is reflected in a decrease of the symptoms of pulmonary congestion, which since it may coexist with typical anginal pain, may be experienced by the patient as relief. This attractive theory, which has also been postulated by us to occur in acute ischemic circumstances such as during unstable angina at rest (HUGENHOLTZ et al. 1981) leaves unchallenged the original concept that in some patients, particularly those with a moderate degree of increased peripheral vascular resistance, the drug acts through a lowering of cardiac work and thus of myocardial oxygen demand.

Although many trials on patients with stable angina had been reported in the years between 1976 and 1980, when HUGENHOLTZ (1982), with certain criteria, such as: double-blind design, placebo control, more than 24 patients, random assignment to the study group, and reasonably convincing evidence of stable angina pectoris, assessed these studies, he could identify only 15 which proved conclusively that there was a decrease in the frequency and severity of symptoms and increase in exercise tolerance with a reduction in the degree of ST segment changes when the patients were treated with the active compound. These selected studies were carried out by various workers, including DARGIE et al. (1981 a), in 524 patients. MOSKOWITZ et al. (1981, personal communication) in a small series of 10 patients also showed that nifedipine in a randomized, single-blind, crossover study reduced the consumption of nitroglycerin and increased the duration of treadmill exercise from 426 s on placebo to 523 s on nifedipine.

The largest collectively reported experience comes from MÜLLER and CHAHINE (1981) who reported on 67 patients from various American centers in whom a dose of 3×10 or 3×20 mg was given over a period of at least 2 months and compared in a random fashion with placebo. They, too, could confirm the high degree of efficacy of nifedipine in chronic, stable, exercise-induced angina, although certainly not all patients became symptom free. Some of these trials already indicated the beneficial effect of a combination of nifedipine plus a β-blocker, usually propranolol. DALE et al. (1982) evaluated the effect of adding ni-

fedipine to chronic β-blocking therapy in ten patients with angiographically proven coronary artery disease, in whom angina pectoris could also be provoked by atrial pacing. Nifedipine prolonged the atrial pacing time until the onset of angina from 285 to 421 s, a significant observation together with a demonstration of increased lactate extraction. These data have subsequently been confirmed in our laboratory by SERRUYS et al. (1983) and point to the interesting phenomenon that, under this type of stress, nifedipine can delay the onset of angina.

DARGIE et al. (1981 b) in a double-blind comparison of propranolol, nifedipine, and their combination, found that there was less widespread exercise-induced ST depression on the ECG after nifedipine administration and also that

Table 4. Reasons for discontinuation of nifedipine treatment[a]

	Number of patients	
Headache, congestion in the head	29	
Retching, nausea, queasiness	21	
Feeling of warmth, heat sensation	20	
Reddening, flush	12	
Gastrointesting, disorders	11	
Allergy	7	
Dizziness	7	
Edema of the leg	6	
Hypotension	6	
Local pain, site of injection	6	
Dysopia	5	
Exanthema	4	
Trembling	4	
Tingling sensation	4	
Hemorrhagic tendency	3	
Vomiting	3	
Palpitation	3	
Weakness	3	
Sweat secretion	3	
Dyspnea	2	
Giddiness	2	
Tiredness	2	
Tinnitus	2	
Restlessness	2	
Anorexia	1	
Pain in the leg	1	
Diarrhea	1	
Itching	1	
Cardiovascular disorder	1	
Psoriasis	1	
Tachycardia	1	
Thrombophlebitis	1	
Discontinuation due to side effects	175	238 of 5,008 (4.75%)
No data	63	

[a] From an extensive series collected by EBNER (personal communication) for 5,008 patients. It can be seen that treatment had to be discontinued for a large variety of symptoms, but in only a small number of patients

Table 5. Summary of comparative pharmacokinetics[a]

	Nifedipine	Verapamil	Diltiazem
Dose:			
Oral: (mg/8 h)	10–20	80–160	60–90
Intravenous (μg/kg)	5–15	150	75–150
Onset of action:			
Sublingual (min)	3	⩽	⩽
Oral (min)	<20	<30	<30
Absorption, oral (%)	>90	>90	>90
Bioavailability, oral (%)	65–70	19–24 (single dose) 38–48 (chronic treatment)	<20
t_{max}, oral (h)	1–2	1–2	0.5
Protein binding (%)	90	90	77–80
Therapeutic plasma concentration (ng/ml)	25–100	15–100	30–130
Metabolism	Metabolized to an acid or lactone in liver (both inactive)	Extensively dealkylated in liver; 8% first-pass metabolism after oral dose	Deacetylated with subsequent glucuronidation in liver;about 50% firstpass metabolism (may be saturable)
Elimination half-life (h)	3–5	5 (3–8)	2–6
Recovered in urine (%)	80	70	30–40
Recovered in feces (%)	15	15	60

[a] After HENRY (1980) and PIEPHO et al. (1982)

there were fewer episodes of ST segment depression noted on a 48-h ambulatory cardiogram. Again the combination of nifedipine 60 mg/day and propranolol (240 mg/day) proved to be the most efficacious of the regimens that were examined. Side effects leading to discontinuation of treatment with nifedipine, already rare (Table 4) are even further reduced with this combination therapy. Table 5 summarizes the pharmacokinetics of nifedipine, verapamil, and diltiazem.

D. Diltiazem

I. Chemistry and Pharmacokinetics

1. Absorption and Bioavailability

Diltiazem (Fig. 11) was originally developed in Japan and introduced by SATO in 1971. Diltiazem (D-*cis*-3-acetoxy-2,3-dihydro-5(-2-(dimethylamino)ethyl)-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one hydrochloride, CRD-401) is rapidly and almost completely absorbed from the digestive tract, the half-life for ab-

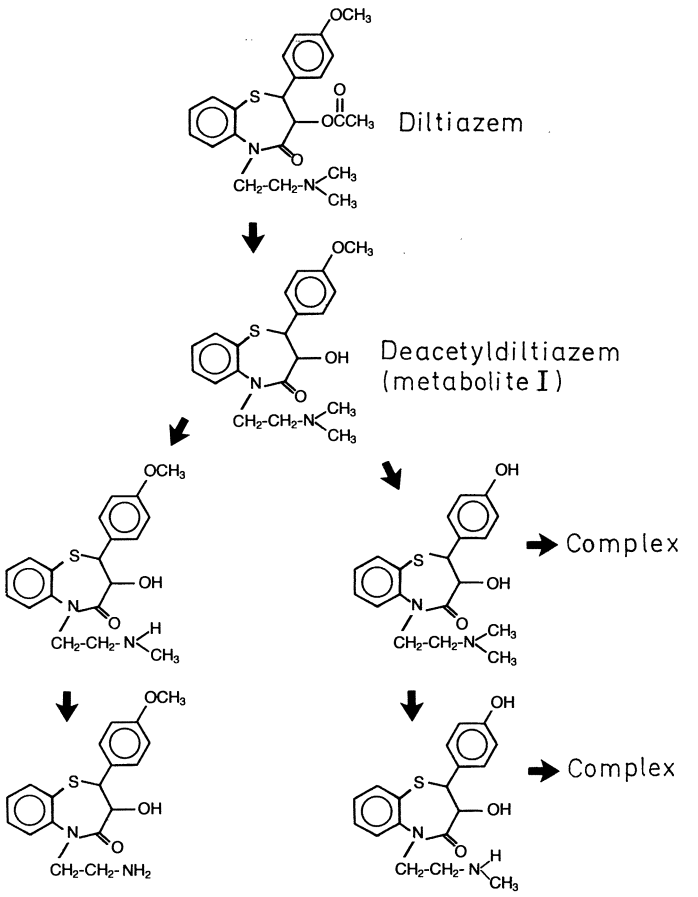

Fig. 11. Diltiazem and its various breakdown products. For details, see text

sorption being 26 min (MESHI et al. 1971). Peak plasma levels are attained within 1 h in most cases following administration of gelatin capsules (MORSELLI et al. 1978). The complete absorption from the gastrointestinal tract was demonstrated by MESHI et al. (1971) using ^{14}C-labeled substance in rats. The half-life of absorption was 26 min.

Oral formulations on the market are sustained-release preparations leading to maximum plasma levels after 3–4 h on average (MORSELLI et al. 1978; BIGHLEY et al. 1980; KOIWAYA et al. 1981 a, b; KINNEY et al. 1981; ZELIS and KINNEY 1982; HERMANN et al. 1983). KOIWAYA et al. (1981 b) found mean peak plasma concentrations of 93.3 ± 12.6 ng/ml within 3 h after administration of 90 mg diltiazem to nine volunteers. Decreases in heart rate and blood pressure occurred proportional to the plasma level of diltiazem. The data are reproduced in Fig. 12. Owing to the first-pass metabolism, the absolute bioavailability is approximately 40%. There are three papers comparing areas under the concentration–time curves (AUC) after intravenous and oral administration of diltiazem. Bioavailability

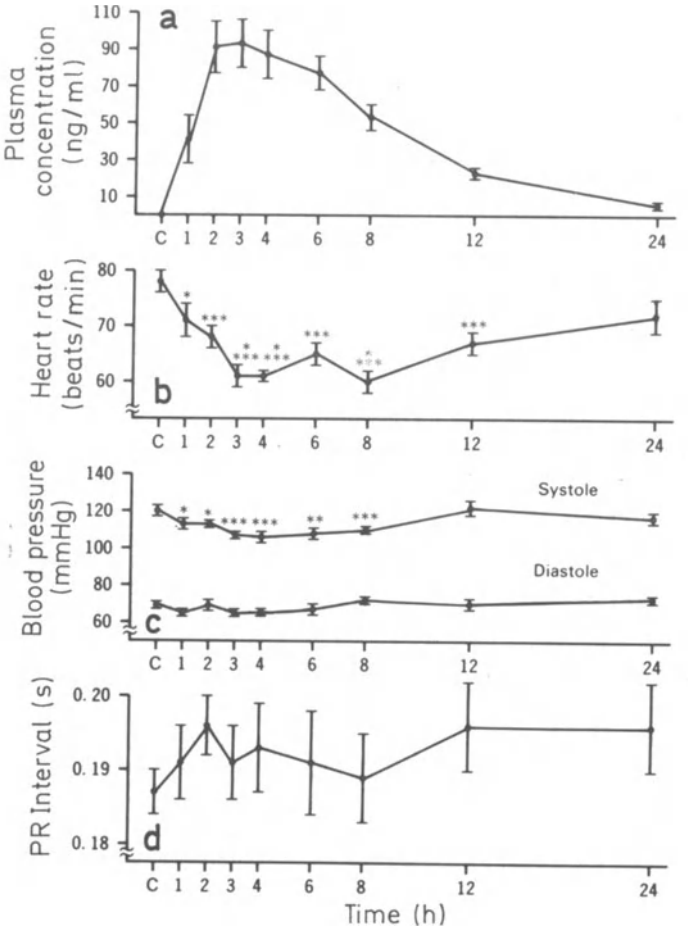

Fig. 12. Plasma concentration **a**; heart rate **b**; blood pressure **c**; and PR interval **d** after single-dose administration of 90 mg oral diltiazem in nine normal volunteers. Peak plasma concentration was attained within 3 h, and mean peak plasma concentration was 93.3 ± 12.6 ng/ml. Decrease of heart rate and depression of blood pressure occurred in inverse proportion to the plasma level of diltiazem. No significant prolongation of PR interval was demonstrated after diltiazem administration. The values are expressed as mean $\pm$ standard error. Statistical significance: * $P<0.05$, ** $P<0.001$, *** $P<0.005$, **** $P<0.001$. KOIWAYA et al. (1981 b)

was determined by OCHS and KÖLLE (1982) $44\% \pm 10\%$, $N=6$; HERMANN et al. (1983) $42\% \pm 18\%$, $N=12$; and SMITH et al. (1983) $37.8\% \pm 10.6\%$, $N=8$.

Of the various metabolites, only the primary metabolite deacetyldiltiazem has been found to be pharmacologically active. Its activity is about 40%–50% of that of the parent compound. Considering the lower levels of deacetyldiltiazem both after single and repeated dosing, its contribution to the effect of diltiazem is very likely to be minimal (ROVEI et al. 1977, 1980; MORSELLI et al. 1979).

2. Distribution

SAKUMA et al. (1971) studied the distribution of diltiazem ^{14}C in mice by means of whole body autoradiography. Immediately after intravenous injection, the radioactivity disappeared from the blood and accumulated in the heart muscle, lung adrenal cortex, kidney, skeletal muscle, and brain. Using a microautoradiographic technique, TSUCHIYA et al. (1978) studied the distribution of diltiazem ^{14}C in the dog kidney after renal arterial injection. The highest densities were found in the proximal and distal tubules and the ascending loop of Henle. The accumulations seem to be compatible with the observation that diltiazem affects these segments directly, thus causing the diuretic action.

More recently, GARTHOFF et al. (1982) demonstrated the marked diuretic effect of a new calcium antagonist, nitrendipine, in acutely saline-loaded rats. They saw a dramatic renal effect which was different from that observed after administration of standard vasodilators such as hydralazine. These limited observations require further substantiation, but they are interesting since these newer calcium antagonists would seem to enable the kidney to excrete sodium despite the rather marked drop in peripheral blood pressure. OCHS and KÖLLE (1982) determined the disposition characteristics, based on plasma levels in humans following intravenous and oral administration of diltiazem. The volume of distribution V_{ss} was 5.2 l/kg and the disposition half-lives were 0.1 h for the α-phase, 2.1 h for the β-phase, and 9.8 h for the terminal γ-phase.

Protein binding was determined by MORSELLI et al. (1978) and BLOEDOW et al. (1982). Over a great concentration range, approximately 80% of the diltiazem was bound to serum proteins. Binding to albumin was only 35%–40%, the rest probably binds to acidic glycoproteins as described for many basic drugs. The percentage of unbound diltiazem was not influenced by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin.

Although Japanese studies had also shown that 90 mg/day appeared an effective oral dose for the treatment of angina in the Japanese population, ZELIS and KINNEY (1982) found in 13 healthy American men that, after administration of 60, 90, and 120 mg, the peak plasma concentrations were 72, 117, and 152 ng/ml, while times to peak concentrations were 3.9, 3.3, and 4.0 h respectively. However, there was wide variability among patients after the administration of a single dose. They concluded that a 30-mg dose produced such different plasma values that some were below the sensitivity of the measurement techniques and also that their data on the 120-mg dose were obtained in too few patients to be meaningful. Therefore, they recommended a dose above 60 mg every 6 h to achieve therapeutic plasma concentrations.

These data are at variance with the doses reported from Japan, which may, in part, be explained by the difference in the populations, inasmuch as Japanese subjects had generally smaller body weights, as well as by intersubject variability. This had earlier also been noted by MORSELLI et al. (1978) who found tenfold interpatient differences. ZELIS and KINNEY (1982) postulate that this variability is not due to differences in absorption, as diltiazem is well absorbed, but may be related to the extensive deacetylation, a microsomal biotransformation which may

be saturable at larger doses. These workers also found a rather high incidence of adverse effects consisting of headaches, dizziness, nausea, vomiting, and fatigue which mainly occurred with the higher doses at which time there were effective plasma concentrations of at least 50 ng/ml.

3. Elimination

Diltiazem undergoes intense biotransformation. The following reactions were observed: deacetylation to the primary metabolite I; oxidative *O*- nd *N*-demethylations; and conjugation of the phenolic metabolites (MESHI et al. 1971). MORSELLI et al. (1978) identified five metabolites in human urine by means of mass spectroscopy. The biotransformation oathways are outlined in Fig. 11. Only 0.1%–4% of the administered drug was excreted as unchanged diltiazem in human urine (ROVEI et al. 1980). Thus, diltiazem is subjected to a nearly complete metabolic clearance. Following intravenous and oral administration of diltiazem to humans, KÖLLE et al. (1983) determined the mean hepatic extraction ratio to be 54%, the total clearance Cl_{tot} was 11.5 ml min^{-1} kg^{-1}.

Varying information is to be found in the literature regarding the elimination half-life. The following values have been reported: 2 h (OYAMA 1979); 3.1 h (HERMANN et al. 1983); 4 h (TAEYMANS et al. 1982); 4.45 and 4.85 h (SMITH et al. 1983); 4.1, 5.1, and 5.6 h (ZELIS and KINNEY 1982); 4–7 h (ROVEI et al. 1980); and 4–8 h (MORSELLI et al. 1978). The shorter half-lives are possibly due to limited assay sensitivity or too short measurement periods and should mainly reflect distribution phases.

KÖLLE et al. (1983) described the plasma level time courses by an open three-compartment model. Compared with the β-phase, the terminal γ-phase with a mean half-life of 9.8 h represented a smaller contribution to the total AUC (approximately 30% after intravenous infusion). This model seems to be in accordance with plasma levels after repeated oral administration (MORSELLI et al. 1978; KÖLLE et al. 1983; J. J. HANNIGAN and J.E. MCCLURG 1980, unpublished work).

4. Experimental Studies

SAIKAWA et al. (1977) studied the electrophysiologic effects of diltiazem as did MITCHELL et al. (1982 a, b) and TRITTHART and KOID (1983), to name but a few of these investigations. They showed that diltiazem lowers the plateau of the action potential and shortens the duration of the monophasic action potential of canine Purkinje fibers. At the same time, it depresses the contractility of the cardiac cell in these high concentrations (2.2×10^{-5} *M*). Although voltage clamp experiments with diltiazem have not been reported, the findings suggest that the drug may block the slow current at relatively low concentrations and exert fast channel inhibitory effects at high concentrations.

SUTTON and MORAD (1982) looked at the mechanism of action of diltiazem on isolated human myocardium. They saw a voltage-dependent reduction in tension and found the negative inotropic effect of diltiazem to be accompanied by a suppression of the slow inward current. The data from MITCHELL et al. (1982 a, b) showed in patients that after intravenous administration of diltiazem at two

different dose levels, sinus cycle length was prolonged and atrio-His (AH) conduction time lengthened (+22%), with an increase in the effective refractory reduction of mean arterial pressure of 8%. When subsequently digoxin was given, additive effects on the sinoatrial (SA) and atrioventricular (AV) node function were seen without significant adverse overall effects. These electrophysiologic measurements explain the decrease in cardiac frequency observed in most clinical studies. The data also indicate that the electrophysiologic effects both in the animal and in the human, although incompletely studied, differ from those for nifedipine and verapamil in the usual doses.

Relatively little work has been carried out in the isolated heart or the intact animal to elucidate the exact mechanisms of action. FLAIM and ZELIS (1982) have studied the cardiovascular dynamics, in particular the cardiac output distribution in the conscious rat. They were able to show a marked decrease in cardiovascular resistance of 45% with a increasing cardiac output in most animals. The major effect of diltiazem, however, was to reduce vascular resistance in the coronary circulation with an attendant increase in coronary blood flow from ± 400 ml per 100 g cardiac weight per minute to roughly triple that value at the highest dose of the drug (equivalent to 10 mg kg^{-1} h^{-1}). Their article also provides further details on the regional distribution of total cardiac output after intravenous infusion. Particularly striking again is the increase in blood flow to the kidneys, digestive apparatus and, up to a point, but less so than for some other calcium antagonists, to the brain. A significant decrease in left ventricular peak systolic pressure concomitant with an increase in end-diastolic pressure was only achieved at the higher infusion rate of 10 mg kg^{-1} h^{-1}. There was also a significant drop in systolic and diastolic pressure although heart rate remained unchanged. Their data raise the possibility that diltiazem may be a vasodilator rather specific to the coronary circulation yet lacking significant negative inotropic effect on the myocardium.

Similar findings which earlier have been reported by NAGAO et al. (1972, 1975) and by FRANKLIN et al. (1980), postulated not only a dilation of the coronary collateral vessels, but also a redistribution of intramyocardial blood flow. This question led BACHE and DYMEK (1982) to study the effects of diltiazem on the transmural myocardial blood flow in the presence of an induced stenosis of a coronary artery up to total acute coronary artery occlusion. When the induced proximal coronary stenosis prevented reactive hyperemia, ischemic coronary vasodilation after a 10-s total arterial occlusion caused a transmural redistribution of blood flow toward the subendocardium, leading to underperfusion of some regions. Although diltiazem did not increase coronary collateral flow during the acute arterial occlusion, it blunted the vasodilation that occurred in response to the 10-s total occlusion. Similar observations had been made by VERDOUW et al. (1980) for nifedipine. It also partially corrected the subendocardial underperfusion that had occurred with the experimentally induced, flow limiting, coronary stenosis. Thus, they conclude that this might be a mechanism leading to therapeutic benefit as it reduced the mismatch between myocardial oxygen demand and regional blood supply. Other mechanisms which they postulate are the traditional ones such as a direct reduction of myocardial oxygen consumption via reduced cardiac work and an influence on collateral flow in the so-called ischemic border zone. Their

findings certainly support the use of this particular drug in patients with coronary artery stenosis and suspected ischemia.

BUSH et al. (1982) studied the effect of diltiazem on myocardial injury after complete occlusion of the coronary artery. They found in dogs that the infarct size appeared to be smaller although there had been no increase in blood flow to the ischemic myocardium. These are unlike findings reported from our laboratory (VERDOUW et al. 1980) in which an increase in microsphere-measured capillary flow was demonstrated after administration of nifedipine, even within the core of the ischemic area. With diltiazem there was a decrease in mortality and in the occurrence of ventricular arrhythmia when compared with placebo-treated animals. The heart rate and blood pressure were both lower in diltiazem-treated dogs so that their conclusion was that the drug worked indirectly via a decrease in myocardial oxygen demand and directly by limiting the transmembrane calcium flux both during ischemia and reperfusion. Findings pointing in the same direction were reported by VOUHE et al. (1982) when they compared in dogs the effects of cold cardioplegia and potassium chloride with diltiazem. They found that overall left ventricular function appeared to be better preserved with diltiazem, regardless of whether or not flow was reduced experimentally in the circumflex artery. The direct effect of diltiazem on the myocardial cells was most conclusively demonstrated by HENRY and WAHL (1983, personal communication) in experiments in ischemic hearts in which they excluded the factors of afterload and augmentation of myocardial perfusion, which usually confound the interpretation of the mechanisms by which the drug may act. They compared diltiazem and the new calcium antagonist, nitrendipine on unperfused myocardium subjected to hypoxia. They were able to demonstrate that the onset of hypoxic contracture was significantly delayed in muscle strips treated with diltiazem (31 ± 3 min) and nitrendipine (23 ± 2 min) while contraction was significantly inhibited when compared with controls. It is argued conclusively that these drugs act directly on cardiac muscle since the effects occurred under hypoxia and in the absence of any rhythmic electrical and mechanical activity. A recent review by BING and BING-LO (1983) further elucidates these actions of diltiazem, while SCHWARTZ (1983) has provided a nice review of his and other work, identifying the possible mechanisms of preservation of the myocardium by this compound.

II. Pharmacodynamics in Humans

1. Intracoronary Administration

Although there appears to be relatively little information on the pharmacokinetics, there is even less known about the effects of the drug after intracoronary injection into the human heart. The extensive review article written by HENRY (1980) on the comparative pharmacology of the calcium antagonists, nifedipine, verapamil, and diltiazem, mentions no data of the effects after direct intracoronary injection. He did find in comparing diltiazem with verapamil and nifedipine that the greatest percentage increase in spontaneous frequency of the isolated guinea pig atrium with the smallest percentage decrease in the first derivative of force development (dF/dt) occurred with diltiazem while nifedipine showed the largest percentage decrease in dF/dt and the least change in spontaneous frequen-

cy. Even in the extensive analysis of SCHROEDER et al. (1982b) or the report on the multiclinic trial of diltiazem on Prinzmetal's angina by SCHROEDER et al. (1982a) no mention is made of any observations after direct intracoronary administration. However, the effect of intracoronary administered diltiazem was analyzed by BERTRAND et al. (1981c) in ten patients with coronary artery disease. A dose of 150 μg/kg in five patients increased coronary sinus blood flow by 20%–25%; its action lasted less than 10 min. Coronary resistance was lowered during the same time by about 40%, with 50 μg/kg there was hardly any effect. The influence of intracoronary injection of 1 mg diltiazem on left ventricular pressures, echocardiographic fractional shortening, and coronary sinus saturation was studied by KOBER et al. in 1982 and compared with the effect of 10 mg diltiazem administered intravenously. Systolic and end-diastolic pressures were not affected by intracoronary administration whereas the systolic pressure was transiently reduced by intravenous administration. This latter hemodynamic effect was accompanied by a transient increase in heart rate. Peak positive dP/dt remained unchanged while peak negative dP/dt decreased transiently after either intravenous or intracoronary administration. The ejection parameters were not influenced by the drug, but a pronounced, short (5 min), increase of coronary sinus saturation was observed.

2. Intravascular Administration

TAEYMANS et al. (1982) studied the hemodynamic response to diltiazem after intravenous administration of a single dose of 20 mg in six patients. The only hemodynamic change observed was the transient fall in systolic blood pressure between 2 and 5 min from 146 ± 19 to 119 ± 15 mmHg. Heart rate, cardiac output, pulmonary pressure, and systemic vascular resistance remained unchanged for the 10-h observation period. The half-life of the drug was found to be 4 h. On the other hand, after oral administration of 120 mg, the drop in systolic blood pressure was from 144 ± 28 to 123 ± 22 mmHg while the heart rate decreased from 68 ± 9 to 64 ± 8 beats/min. HOSSACK et al. (1982c) analyzed the effect of 0.25 mg/kg intravenous diltiazem followed by an infusion of 0.003 mg kg^{-1} min^{-1} on coronary artery segments filmed at rest and during the fourth minute of sustained 25% maximal handgrip, a form of isometric exercise. It was demonstrated that small and medium sized coronary vessels showed a reduction of 23% at rest and 29% during handgrip, a reduction in lumen which could be completely prevented by the administration of diltiazem. These data directly prove the efficacy of diltiazem in terms of suppressing handgrip-induced vasoreactivity. Following infusion of 30 μg/kg^{-1} min^{-1} diltiazem intravenously in patients with coronary artery disease, BOURASSA et al. (1980) observed a slight but nonsignificant reduction of aortic pressure. Systemic vascular resistance however decreased by 20%. After 15 min, the fall in the blood pressure persisted and heart rate, which had remained unchanged during the infusion, began to decrease. Left ventricular end-diastolic pressure and cardiac index were unchanged, but there was a fall in coronary vascular resistance and CSBF tended to increase (BOURASSA et al. 1980). Also, a dose-related reduction in oxygen uptake was observed.

Total myocardial oxygen consumption on the other hand was not altered significantly since the product of coronary blood flow and left ventricular oxygen extraction did not change. At the end of an infusion of 5 min of 300 μg/kg, BIAMINO et al. (1982) observed an increase in heart rate and cardiac output together with a sharp decrease in blood pressure and total peripheral resistance. Concomitantly, the filling pressures increased and dP/Pdt was reduced. After the initial rise, the heart rate decreased below the baseline values.

Although the reduction in blood pressure and peripheral resistance remained present over a 15-min period, there was a slight decrease in coronary blood flow which, combined with a narrowed aortocoronary sinus oxygen difference, resulted in a significant reduction in myocardial oxygen consumption. These authors concluded that the temporary increase in filling pressures reflected a negative inotropic effect of the drug. BERTRAND et al. (1981 c) had administered 0.15 mg/kg diltiazem over 2 min followed by 0.05 mg/kg over 8 min. This increased coronary sinus blood flow significantly by 12% with a fall of 18% in coronary artery resistance. When a bolus dose of 0.15 mg/kg, was given, coronary blood flow increased by more than 20% together with a reduction in coronary resistance of 40%.

More recently, diltiazem was administered intravenously in five patients with precapillary pulmonary hypertension. In four of them, CREVEY et al. (1982) found hemodynamic pressure and total pulmonary resistance at rest as well as during exercise. Unlike some other vasodilators, diltiazem did not worsen pulmonary gas exchange or ventilation–perfusion distribution.

3. Oral vs. Sublingual Administration

The hemodynamic effects of oral diltiazem (210 mg) were investigated by MAGOMETSCHNIGG et al. (1981) in six volunteers at rest, under psychologic stress, and in various orthostatic conditions. Under all conditions, diltiazem showed a vasodilating property, which was more pronounced on the arterial resistance vessels than on the pulmonary vessels. KUSUKAWA et al. (1972) had already shown that three doses of 30 mg/day led to a significant decrease in stroke volume, cardiac output, and stroke work in patients with coronary artery disease. Because the decrease in end-diastolic volume concurred with a decrease in stroke volume, they concluded that a decrease in venous return was responsible. In patients with coronary artery disease, ROSENTHAL (1982) observed a decrease in diastolic blood pressure of only 9 mmHg 180 min after a dose of 120 mg.

HOSSACK et al. (1982 a, b) administered diltiazem to ten patients with coronary artery disease. A dose of 240 mg/day was effective in increasing the total duration of exercise and the time to the first onset of angina during exercise. Again there was a reduction in diastolic blood pressure during submaximal exercise, but not at maximal exercise. Similar effects of diltiazem on exercise performance were reported by LOW et al. (1981). However, these authors did not observe changes in heart rate, blood pressure, or pressure–rate product. BOURASSA et al. (1980) as well as THEROUX et al. (1980) evaluated the effect of 120 mg diltiazem in patients after a myocardial infarction. Cardiac index and systemic vascular resistance remained unchanged, while heart rate decreased by 11% and the pressure–rate

product by 20%. In the same patients, lesser changes were seen with nifedipine and verapamil while heart rate increased by 6% with nifedipine. The authors conclude that all three drugs can safely be given under these circumstances. While after intravenous and intracoronary administration, diltiazem has been shown to lower coronary vascular resistance and augment coronary blood flow, oral administration, judging by its clinical responses, seem to have similar efficacy. On the other hand, the effects on heart rate, peripheral resistance, and systemic blood pressure are inconsistent and rather less after oral dosing.

III. Clinical Experience

1. Vasospastic (Prinzmetal's) Angina

PEPINE et al. (1981 b) reported a randomized double-blind trial on the effect of diltiazem in 12 patients with variant angina. Over 10 weeks, diltiazem in dosages of 120 or 240 mg/day was compared with placebo. Significant decreases in angina frequency and nitroglycerin consumption were observed when the patients were on diltiazem. Given the small number of patients in that study, it was gratifying to read the results of a multiclinic controlled trial of diltiazem in Prinzmetal's angina. In a randomized multiple crossover study on 48 patients, SCHROEDER et al. (1982 a) found with 120 and 240 mg/day that with the lower dose angina was reduced by 41% from the run-in placebo period while treatment with the higher dose reduced angina frequency by 68% from the run-in placebo period and by 43% from the paired placebo period. There were similar reductions in oral nitroglycerin consumption. Adverse reactions to the medication were seen in only 5%. It was notable that there were no alterations in the arterial pressure or heart rate, although the PR interval increased slightly.

Earlier, this same group had reported similar data on 36 patients treated at their own hospital. During a mean of 17.5 months of diltiazem therapy, the frequency of anginal attacks was reduced from 21.5 to 1.3 attacks per week. This 94% reduction in pain frequency occurred with a doses of 240 or 360 mg diltiazem. In these patients, too, there were few adverse effects, while only six patients had slight pedal edema. Earlier, WATERS et al. (1981 a, b) had carried out ergonovine testing to evaluate the possibility of spontaneous remissions of variant angina during long-term treatment with calcium antagonist drugs. In 22 patients who clinically had responded to calcium blocker drugs, ergonovine was injected to assess the vasomotor state of the coronary system. Judging by the ECG, in particular the behavior of the ST segment, they concluded that in many patients with variant angina, the ergonovine tests became negative more or less in parallel with the disappearance of symptoms. Thus ergonovine testing, which can help in recognizing patients who should be put on therapy, may equally be employed to identify those in whom therapy can be discontinued. In the assessment of the efficacy of the treatment with diltiazem, and in a comparison with nifedipine and verapamil in variant angina, WATERS et al. (1981 b) found that, during treatment with diltiazem (120 mg every 8 h), the ergonovine test result became negative during the maximal dose of 0.4 mg in 11 of the 27 patients. The test was not improved in 5 patients while it remained positive at a much higher ergonovine dose level than during the control test in the remaining 11. These re-

sults were identical to those obtained with nifedipine. On the other hand, during treatment with verapamil (160 mg every 8 h), the test results became negative in only eight patients, remained positive at two or more ergonovine dose levels, higher than those during control testing in ten, and were positive at a dose similar to that of the control test in the remaining nine patients.

Spontaneous Prinzmetal's angina attacks occurred in none of the drug treatment periods associated with the negative ergonovine tests. These authors concluded that diltiazem and nifedipine more than verapamil, can block ergonovine-induced angina and ST segment elevation in most patients. These data confirm the report by KIMURA and KISHADA in 1981, on the collected case reports in 11 centers in Japan which indicated that diltiazem, like nifedipine, as a marked beneficial effect on Prinzmetal's angina. Similar evidence has been gathered by GINSBURG (1983) at the Stanford Medical Center.

2. Unstable or Crescendo Angina

Only one study is available in the world literature. ANDRE-FOUÈT et al. (1983) were the first to use the drug in patients with unstable angina. In a group of 36 patients unresponsive to β-blockade they found, as HUGENHOLTZ et al. (1981) had done with nifedipine, that the addition of diltiazem in a dose of 180 mg four times daily led to the disappearance of the rest pain with a normalization of the ECG in the majority of their patients. They ascribed the efficacy of diltiazem to its direct vasodilating effect on the coronary artery system.

3. Stable, Exercise-Induced Angina

Early in 1981, two reports appeared in the American literature by HOSSACK and BRUCE (1981) and by KOIWAYA et al. (1981 a), indicating an improved exercise performance with individuals in stable angina pectoris after diltiazem treatment. The first group of authors studied ten patients with chronic stable angina over a period of 7 weeks. The drug was administered in a random, double-blind fashion and evaluated at increasing dose levels of 120, 180, and 240 mg per day. Diltiazem lengthened the total duration of exercise and the time to the first onset of angina as well as the time to the first appearance of 1 mm ST depression in the group treated with diltiazem. These effects were most marked at the highest dose of diltiazem. The heart rate was reduced at rest and during submaximal exercise there was some reduction in diastolic blood pressure without any change in systolic pressure.

In terms of the mechanism of relief, or delay in onset, of angina pectoris during exercise, they suggested, since the heart rate was reduced at rest and at submaximal exertion with a comcomitant reduction in the pressure–rate product, that the mechanism of action of diltiazem was largely based on a reduction in cardiac work. In addition, there was a suggestion that in patients with an increased coronary arterial tone, the drug might work through the relaxation of this tone.

Convincing evidence of the exact mechanism of action however was not demonstrated in this study. KOIWAYA et al. (1981 a) showed in nine patients with coronary disease and effort angina that the duration of exercise before the onset of angina as well as the time to the onset of ischemic ST segment depression, were

increased after 90 mg oral diltiazem compared with the effect after oral administration of placebo or a few minutes after administration of 0.3 mg sublingual nitroglycerin. This clinical antianginal efficacy of diltiazem, persisting for at least 2 h after oral administration, was tentatively ascribed to the various factors described, but the authors emphasized that the exact mechanisms by which diltiazem works against effort angina remain unclear. Again they pointed to the work by YASUE et al. (1979 a) that coronary spasm can be induced by exercise, a factor which might be countermanded by diltiazem as it was shown in patients with proven coronary spasm. In addition, they discussed the speculation that diltiazem might depress myocardial oxygen consumption and decrease extravascular coronary resistance in myocardium already rendered ischemic.

Somewhat later, a study appeared from LOW et al. (1981) with observations on 12 patients with chronic effort angina and angiographically documented, fixed coronary artery stenosis in whom diltiazem was compared with placebo in an 8-week protocol. They observed similar efficacy and postulated a reduction in myocardial oxygen demand and an increase in exercise tolerance without depression of myocardial performance. They, too, indicated that the higher dosages were the more effective. Two further randomized, double-blind, crossover studies were published in 1982. STARLING et al. (1982) studied ten patients with documented fixed coronary artery disease and compared diltiazem in doses of 120, 180, and 240 mg/day with placebo. Only diltiazem at 240 mg/day significantly increased the time to onset of angina pectoris as well as the time to the onset of ST segment depression. In addition, time to maximal exercise was increased and the heart rate at maximal exercise was decreased. They concluded that the higher dose of 240 mg/day significantly improved exercise performance in patients with stable angina pectoris. Again, these authors were not very specific about the reasons for the efficacy of the drug. They indicated that the pressure–rate product was increased only minimally despite a significant improvement in exercise capacity, thus suggesting a probable reduction in myocardial oxygen demand. DE BACKER and VINCKE (1982) studied 24 patients with exercise-induced angina pectoris over a double-blind period of 8 weeks. They, too, reported that the active product was well tolerated and that 180 mg diltiazem increased the anginal threshold and decreased the ST segment depression at an identical submaximal work load when compared with placebo. These authors are quite outspoken in their conclusions that their results are in accordance with others, but the mechanisms whereby these effects occur remain unclear. They suggest, that peripheral effects are not primarily responsible for the drug's efficacy.

These comments are very important inasmuch as further analysis of other literature reports confirm the uncertainty about the reason for the efficacy of the drug. In fact, the majority of the reports seem to indicate that the anti-ischemic effects are not accompanied by a significant reduction in heart rate or blood pressure at submaximal level, so that the antianginal effect must be due to some other mechanism than secondarily reduced myocardial oxygen demand. This returns us to the earlier comments made by the Japanese workers that a primary effect might be related to the decrease in vascular coronary resistance, the prevention of increased coronary arterial tone or spasm during physical effort, or direct effects on cardiac muscle.

In a preliminary report by PETRU et al. (1982, personal communication), the long-term effectiveness of 360 mg/day diltiazem for angina pectoris was analyzed. Eight patients completed a 20-week trial showing improved exercise tolerance and decreasing occurrence of angina pectoris and improved maximal exercise duration over the entire period. At these higher doses however, transient edema was noted in five of the patients during the first 2–3 weeks of therapy.

The long-term increase in exercise tolerance and reduced ST segment changes were also observed after diltiazem treatment in 12 patients with stable angina pectoris by WAGNIART et al. (1982). Many other reports have been published in various journals none of which contain larger numbers of patients, nor longer periods of observations. Thus, even more so than is the case with nifedipine, the exact mechanism or mechanisms by which the drug may exert its beneficial action remains elusive. HENRY (1980) in his extensive comparison between the three major drugs emphasizes these uncertainties. My personal view is that the evidence for a significant decrease in afterload by peripheral arterial vasodilation or, in the case of diltiazem, of a significant decrease in the heart rate, is not sufficient to explain the efficacy of this drug. Rather, a primary reduction in the coronary vascular resistance, which may increase in response to physical activity, or a primary reduction in oxygen consumption by the myocardium, or better relaxation of the ventricular wall, or all these together, will eventually provide the evidence for the clinically evident beneficial action of this drug.

E. Verapamil

I. Chemistry and Pharmacokinetics

1. Absorption and Bioavailability

Verapamil, 2,5-bis(3,4-dimethoxyphenyl)methylamino-2-isopropylvaleronitrile hydrochloride, is a synthetic compound remotely related to papaverine. Verapamil is optically active, the (−) isomer being more potent than the (+) isomer (BAYER et al. 1975). After the first report by HAAS and HÄRTFELDER (1962) describing some of its pharmacologic properties, pharmacokinetic data in humans were not available until the investigations of SCHOMERUS et al. (1976). This was also the only study demonstrating with ^{14}C-labeled verapamil that absorption was rapid and nearly complete (about 90%), whereas bioavailability was low. Extensive presystemic metabolism was shown to be the cause of this low bioavailability. The liver was assessed as the main site of first-pass metabolism (EICHELBAUM et al. 1980 b; SOMOGYI et al. 1981; WOODCOCK et al. 1981 a, b). In subjects with normal hepatic function, mean values of the absolute bioavailability of verapamil were 19%–24% with a total range of 10%–38% (EICHELBAUM et al. 1981 a; KOIKE et al. 1979; FREEDMAN et al. 1981 b; MCALLISTER et al. 1982) independent of the dose administered (MCALLISTER et al. 1982). In patients with atrial fibrillation, a mean bioavailability of 35% with a range of 13%–64% was reported by KATES et al. (1981), however this was not supported by the data of ANDERSON et al. (1982 a). In liver cirrhosis it was 52% with a range of 35%–74% (SOMOGYI et al. 1981). Thus, according to the impairment of liver function, doses of verapamil have to be reduced, more so with oral than with intravenous administration. In-

terestingly, during long-term administration, verapamil accumulation is greater than would be predicted from those single-dose studies (FREEDMAN et al. 1981 b; KATES et al. 1981; SHAND et al. 1981; WAGNER et al. 1982), suggesting saturation of the hepatic first-pass extraction. Mean steady state levels after chronic treatment were 2–2.5 times higher than the predicted level. The suggestion that this increase in systemic availability was due to reduced hepatic first-pass extraction was supported by the findings of a relative decrease in concentration of norverapamil, the major metabolite of verapamil (FREEDMAN et al. 1981 b).

One additional aspect of verapamil absorption kinetics has been proposed by EICHELBAUM et al. (1980 a, b). These authors found that after oral administration, 2–3 times higher plasma levels of verapamil were required in order to produce the same change in the PR interval as after intravenous administration, whereas in patients after portocaval shunt surgery with nearly 100% bioavailability, the oral and intravenous concentration–response curves for verapamil were almost identical. This led to the hypothesis that verapamil undergoes a stereoselective presystemic extraction with preferential clearance of the more active (−) isomer. However, this hypothesis has still to be proved.

2. Distribution and Protein Binding

Owing to differences in the subjects studied and the differences in methodology, a considerable variability exists in the parameters describing distribution of verapamil after intravenous or oral administration. Following intravenous infusion, the volume of the central compartment was estimated between 0.2 l/kg (FREEDMAN et al. 1981 b) and 4.8 l/kg (EICHELBAUM et al. 1979, 1981 b) depending on the use of a two- or three-compartment analysis. Similarly, remarkable differences are reported for the volume of distribution at steady state, ranging from 2.3 to 6.2 l/kg (KOIKE et al. 1979; KATES et al. 1981; FREEDMAN et al. 1981 b; EICHELBAUM et al. 1979, 1981 b) and even 9.2 l/kg in patients with hepatic cirrhosis (SOMOGYI et al. 1981).

REITER et al. (1982) designed and tested an infusion regimen consisting of a loading bolus of 10 mg over 2 min, followed by a rapid loading infusion of 0.375 mg/min over 30 min, yielding an average concentration of 157 ng/ml (range 114–227 ng/ml) and a maintenance infusion of 0.125 mg/min yielding a mean concentration of 122 ng/ml (range 77–174 ng/ml) which produced a stable PR interval prolongation of 27%.

Peak concentrations after single dose administrations of verapamil occurred between 1.1 and 1.8 h (FREEDMAN et al. 1981 b; KOIKE et al. 1979) with no change after chronic ingestion (SCHWARTZ et al. 1982 b). Only in patients with hepatic cirrhosis were earlier peak levels due to shunted blood reported (SOMOGYI et al. 1981). Mean maximum concentrations of 55 ng/ml were found after administration of 80 mg in solution (EICHELBAUM et al. 1981 b); 149 ng/ml after 120 mg (KATES et al. 1981); 38 ng/ml after 80 mg; and 90 ng/ml after 160 mg (MCALLISTER et al. 1982). Owing to large interindividual variations in drug disposition, the same clinically effective through concentrations of about 100 ng/ml (SUNG et al. 1980; FRISHMAN et al. 1982 a) were achieved during chronic oral treatment with verapamil doses varying from 160 to 480 and even 720 mg/day (WOODCOCK et al.

1980; FREEDMAN et al. 1981 b; SCHWARTZ et al. 1982 b). Although not generally recommended, measurement of plasma levels may be helpful in nonresponders.

The concentration–effect relationship of verapamil on AV conduction or on heart rate reduction in patients with chronic atrial fibrillation has been studied by several groups (DOMINIC et al. 1979, 1981; SUNG et al. 1980; JOHNSTON et al. 1981; EICHELBAUM et al. 1980 a; ANDERSON et al. 1982 a, b; MCALLISTER et al. 1982; SCHWARTZ et al. 1982 a). Despite good individual linear or log-linear relationships, the overall correlations were poor. Thus again, general recommendations cannot be drawn from these data.

YONG et al. (1980) and KEEFE et al. (1981) confirmed earlier results by SCHOMERUS et al. (1976) on plasma protein binding of verapamil of 90%, independent of the concentrations used from 50 to 1,500 mg/ml and of different disease states such as renal failure or cardiac surgery. Hepatic cirrhosis was also of no influence (SOMOGYI et al. 1981). Lidocaine, diazepam, disopyramide, salicylate, and propranolol significantly reduced protein binding of verapamil, but to an extent not likely to be of clinical importance (YONG et al. 1980). Their findings of decreased protein binding in the presence of norverapamil and other verapamil metabolites could not be confirmed by KEEFE et al. (1981). The observed displacement of verapamil by heparin (KEEFE et al. 1981) may be explained as an in vitro phenomenon (CHOU and LEVY 1981). Untoward drug interactions due to displacement of verapamil from binding sites in vivo have not yet been reported.

3. Elimination

Total plasma clearance of verapamil following intravenous administration was usually found to lie between 860 and 1,258 ml/min with extreme values of 550 and 1,454 ml/min (EICHELBAUM et al. 1981 a, b; KATES et al. 1981; FREEDMAN et al. 1981 b) and in children between 315 and 888 ml/min (WAGNER et al. 1982). These values are very close to hepatic blood flow. Since only 3%–4% of an intravenous dose is excreted unchanged in the urine (SCHOMERUS et al. 1976), total clearance equals metabolic clearance. Thus, because of its unrestricted high hepatic extraction, verapamil exhibits the characteristics of flow-dependent hepatic clearance (EICHELBAUM et al. 1981). Owing to the low bioavailability, the oral clearance was found to be five times the systemic clearance (EICHELBAUM et al. 1981; FREEDMAN et al. 1981).

In the early studies, mean elimination half-lives ($t_{1/2}$) of 1.8–3.7 h were reported (KOIKE et al. 1979; EICHELBAUM et al. 1981; DOMINIC et al. 1981). Other studies suggested longer $t_{1/2}$ of 5.0–5.7 (intravenous) and 6.3–8.2 h (oral) (FREEDMAN et al. 1981; KATES et al. 1981). Analogous to the saturable presystemic first-pass metabolism noted after chronic oral treatment, a saturation of the systemic clearance was also obvious, indicated by the prolongation of verapamil $t_{1/2}$ (9.6–13.2 h) (FREEDMAN et al. 1981; KATES et al. 1981; SCHWARTZ et al. 1982 b). This suggests that reasonably stable plasma concentrations might be achieved with an 8- or even 12-hourly dosage schedule. About 70% of an intravenous or oral dose of verapamil was excreted in the urine, 3%–4% unchanged. Twelve metabolites have been identified (SCHOMERUS et al. 1976; EICHELBAUM et al. 1979), the major one, norverapamil, having less than 20% of the cardiovascular activity of verapa-

mil (NEUGEBAUER 1978). The preferential metabolic step involves *N*-dealkylation with further metabolism by *O*-demethylation and subsequent conjugation. The cleavage of the C–N–C bond occurs at the carbon atom belonging to the shorter side chain.

Whereas, after intravenous infusion, little or no norverapamil could be measured, following oral administration, the levels of this metabolite were similar to or higher than those of verapamil (KATES et al. 1981; FREEDMAN et al. 1981 b; JOHNSTON et al. 1981; WOODCOCK et al. 1980). Peak concentrations were achieved at approximately 1.4 h, $t_{1/2}$ was estimated to be longer than that of verapamil, but no significantly (FREEDMAN et al. 1981 b; KATES et al. 1981). These authors also found prolongation of norverapamil $t_{1/2}$ by about 50% on chronic oral treatment.

Since verapamil is mainly cleared by the liver, drugs which alter hepatic blood flow might be expected to affect the kinetics of verapamil. This may also apply to drugs known to induce or inhibit hepatic enzymes. However, no interactions concerning these possibilities have been reported in the literature. On the other hand, verapamil itself has been shown to increase digoxin plasma levels by about 60% during concomitant administration of both drugs (KLEIN et al. 1982 a, b; PEDERSEN et al. 1982; SCHWARTZ et al. 1982 a), leading to the recommendation to adjust digoxin doses.

II. Pharmacodynamics

There are four mechanisms by which the hemodynamic effects of verapamil may be explained: (a) peripheral vasodilation as well as (b) a direct influence on the coronary vascular resistance (c) a direct myocardial depressant or protective effect (d), depending on whether the tissue is normoxic or ischemic. ANGUS et al. (1976) had, like ROSS and JORGENSEN (1967), observed that verapamil exerted a notable depressant effect on cardiac performance with a dose-dependent peripheral vasodilation with reflex increases in myocardial contractility and heart rate. These data are similar to those described for nifedipine, although the reflex tachycardia, which is dose dependent, seems to be more pronounced with nifedipine than with verapamil. Regarding the influence of verapamil on the coronary vascular system, NAYLER et al. (1968) demonstrated in dogs that verapamil, while decreasing myocardial oxygen demand consistently, also decreased coronary vascular resistance, even during the hypotensive phase of the drug. This direct effect on the coronary circulation, originally observed by HAAS and HARTFELDER (1962), has been confirmed by numerous other authors such as MELVILLE et al. (1964), and MELVILLE and BENFEY (1965) with myocardial clearance of radioactive rubidium as an index of coronary flow. LUEBS et al. (1966) had already shown that after intravenous administration of verapamil in humans, there was a marked increase in coronary blood flow which, however, was less marked in patients with diseased vessels. FERLINZ and TURBOW (1980) found, however, that in patients with coronary artery disease, intravenous verapamil decreased CSBF without significant changes in CVR. They interpreted their data to indicate that verapamil mainly exerted its influence via a reduction in systemic vascular resistance which secondarily reduced myocardial oxygen consumption. In contrast

with this are observations which indicate that during continuous intravenous verapamil infusion, both systemic and coronary vascular resistance decrease without a change in CSBF. Thus, while there is a direct effect on CVR, the ultimate effects on CSBF are variable, leaving verapamil as only a mild epicardial coronary vasodilator and perhaps the weakest of the three agents. These findings do not negate the proven efficacy of verapamil in classic vasospastic angina, as shown by PARODI et al. (1980).

SINGH and VAUGHAN WILLIAMS (1972) showed that these in vitro depressant effects can be competitively antagonized by calcium and by catecholamines. The direct effect on the myocardium was carefully studied by NAYLER et al. who in 1980 demonstrated a protective effect of pretreatment with verapamil as well as with nifedipine and propranolol on mitochondrial function in the ischemic or reperfused myocardium. They showed in isolated rabbit hearts, which were either perfused aerobically and made totally ischemic for 90 min or made ischemic for 90 min and then reperfused, that the ischemic heart gained Ca^{2+}. In addition the endogenous stores of ATP and creatine phosphate were depleted, the mitochondria accumulated Ca^{2+}, and cardiac oxidative phosphorylating activity was impaired. Hearts from rabbits who were pretreated with verapamil, or the other two drugs, were protected against ischemia- and reperfusion-induced damage, while their systolic tension generating capacity appeared much better maintained. Thus, these studies conclusively show that under these circumstances a main part of their activity is directly on the myocardium. Earlier, REIMER et al. (1977) had shown the protective effect of verapamil on necrosis following temporary coronary artery occlusion in anesthetized dogs. In the first report on clinical efficacy, HOFFMAN (1964, personal communication) already indicates a role for its vasodilating capacity. Although emphasis remained focused on the efficacy of the drug in various cardiac arrhythmias as reported by SCHAMROTH (1971, 1980) and SCHAMROTH et al. (1972), KRIKLER emphasized as early as 1974 the various other roles that verapamil could and should play in clinical cardiology.

Thus, the mechanisms of action of verapamil appear to be primarily a vasodilating influence on the peripheral vascular resistance, a lesser influence on the coronary vascular resistance, and a strong negative inotropic effect when given directly to the myocardium, whilst under ischemic circumstances this mode of administration may exert a protective action. This places verapamil in a different category from nifedipine or diltiazem, with the peripheral unloading the first and foremost principle in addition to its remarkable electrophysiologic efficacy.

1. Experimental Studies

There is a relative paucity of animal studies with two notable exceptions: the excellent series of studies by Fleckenstein and his staff (FLECKENSTEIN 1983) and those by NAYLER (1980) and NAYLER and POOLE-WILSON (1981). In 1978, Fleckenstein reemphazised the main result of calcium antagonism, namely vascular dilation. By that time, these extensive experimental studies had been confirmed by the first clinical data. In addition NAYLER et al. (1980), in their comparative study on the protective effect on the heart itself of pretreatment with verapamil, nifedipine, or propranolol, came to the conclusion that verapamil and ni-

fedipine, and, as has been shown subsequently also diltiazem, exert a negative inotropic effect by inhibition of slow channel transport of the cardiac cells. Thus, ATP reserves are less rapidly depleted during ischemia and this leaves ATP available for the maintenance of intracellular homeostasis. NAYLER (1980) also postulated that sufficient ATP might remain available to ensure the continued functioning of the Na^+, K^+-adenosine triphosphatase enzyme so that intracellular accumulation of Na^+ might also be avoided. A similar influence of nifedipine on the preservation of intracellular energy charge was shown by DE JONG et al. (1982a, b) for nifedipine. Thus, destructive effects such as a too rapid exchange between Na^+ and Ca^{2+} might be avoided during the reperfusion. In contrast, propanolol had smaller effects on preserving the endogenous stores of ATP and creatine phosphate. Its protective effect therefore has to be explained via a blockage of endogenous catecholamines which are usually released during the early stages of oxygen deprivation. Alternatively, the membrane stabilizing properties of the drug might provide an explanation.

At any rate, all three drugs have in common an ability to slow the rate of depletion of ATP reserves, provided they are administered before ischemia is induced. As we know from the studies of VERDOUW et al. (1980, 1981, 1982) even treatment immediately after ischemia has been induced, but before reperfusion begins, may be beneficial. It is of interest to note that HENRY (1980) has found similar protective actions of verapamil and nifedipine, in different experimental preparations. In his review on the mechanism of action of calcium channel blocking agents, BRAUNWALD (1982) concurs that verapamil, like the two other compounds considered in this chapter, requires a multifactorial explanation for its beneficial action in angina. Although all three drugs have a direct influence on CVR, only nifedipine has been demonstrated to produce a preferential dilation of the coronary vessels, while it has also been shown to abolish the reflex coronary vasoconstrictor response which occurs during the CP test and the handgrip test. This efficacy remains to be proven for verapamil.

FLECKENSTEIN (1983) has summarized the most exciting, recent, experimental evidence of the efficacy of verapamil against the development of vascular atherosclerosis. He has shown over a number of years, that arterial senescence is reflected in a progressive deposition of calcium in the vascular wall, particularly in the arterial media. In animal experiments, calcium overload of the smooth muscle in the arterial wall appeared to be a causative principle in the atherosclerotic destruction of the wall rather than a concomitant or subsequent phenomenon. In experimental studies, prophylactic treatment with suitable calcium antagonists prevented such arterial calcium overload and thereby afforded protection against experimental vascular damage. In particular, verapamil contained in the diet of normal Sprague–Dawley rats over a period of 8 months, retarded the arterial Ca accumulation significantly. Also verapamil, as well as diltiazem, proved to be a most efficient antidote against arterial calcinosis induced by excessive administration of vitamin D_3 or dihydrotachysterol. Although in alloxan-induced diabetic rats, verapamil prevents arterial calcinosis and the development of calcinotic eye cataracts, in spontaneously hypertensive rats, chronic treatment with nifedipine was proven particularly effective in terms of the prevention of the blood pressure rise and the avoidance of excess arterial calcium deposition. These exciting data,

which are corroborated by HENRY et al. (1984) in a different animal model in which excessive atheromas are induced, may pave the way for a much wider application for the use of calcium antagonists and may also provide yet another mechanism by which the antianginal action may be explained: the slow but gradual removal of calcium deposits from the arterial wall and the atheromatous lesions in the coronary system, thereby further improving coronary blood flow.

2. Intracoronary Administration

PARODI et al. (1980) studied the effect of an intracoronary injection of 0.5 mg verapamil in patients with coronary artery disease. Vasodilation was consistently produced and could not be enhanced by sublingual nitroglycerin. Furthermore, ergonovine maleate-induced CAS was relieved in all three patients. HOPF et al. (1980) showed, in patients with coronary artery disease, that intracoronary doses caused no systemic effects, although contractility diminished markedly while the left ventricular filling pressure was slightly reduced.

3. Intravascular Administration

ROBINSON et al. (1979) found that, on a molar basis, verapamil was three times less potent than nifedipine on the forearm resistance vessels and on the potassium-constricted vein. On the norepinephrine-constricted vein, the difference between the two drugs was even more marked. Here, verapamil will induce dilation only with concentrations 10 times higher than those already effective in resistance vessels; in contrast, nifedipine had no apparent effct on the norepinephrine-constricted vein at doses 100 times higher than those effective on resistance vessels. It is evident that verapamil has a much more pronounced effect on the arterial resistance vessels than on the venous capacitance vessels. As a result, a marked increase of calf blood flow was observed by BRITTINGER et al. (1970) after intra-arterial injection of verapamil in four healthy men. A decrease in systemic blood pressure of 13 mmHg was seen by BASS and FRIEDEMANN (1971) after administration of a 10-mg bolus. When 5 mg, every 4 min, to 60 mg maximally was given intravenously in ten healthy volunteers, heart rate increased 15%, presumably because of the decrease in peripheral resistance, but returned to basal values in 45 min. Similarly VINCENZI et al. (1976) showed within 4 min after an average intravenous dose of 10 mg in seven healthy control subjects, a significant increase in heart rate and cardiac output, together with a decrease in peripheral resistance and blood pressure. BRITTINGER et al. (1970) had also noted an increase in heart rate by 13%, but without any significant effect on blood pressure after administration of 5 mg intravenously.

During exercise, in eight asymptomatic men, ATTERHOG and EKELUND (1975), after injection of a bolus of 0.1 mg/kg in 2 min followed by continuous infusion of 0.007 mg kg^{-1} min^{-1}, observed a slight decrease in systemic arterial pressure with an increased heart rate. All these data indicate that intravenous verapamil, in control subjects, leads to a decrease in vascular resistance, which by means of the baroreceptor mechanism gives rise to an increase in heart rate, just as was the case with nifedipine. This led SEABRA-GOMES et al. (1976) to study the effect of the administration of intravenous practolol *with* verapamil, all at 0.1 mg/kg in

patients with coronary artery disease. As verapamil prolonged the PR interval at basal heart rates, an effect which became more obvious after adding practolol, heart rate had to be controlled by atrial pacing. The combination of practolol and verapamil did not affect preload or afterload, but caused a reduction in left ventricular dP/dt_{max}. Accordingly, as they were quick to emphasize, one should avoid the combination of these drugs in patients with severely impaired myocardial function.

With 0.145 mg/kg verapamil as an intravenous bolus and 0.005 mg kg^{-1} min^{-1} as infusion rate, CHEW et al. (1980 a, b) found a significant dilation of normal as well as of narrowed segments of coronary arteries in patients with coronary artery disease. A reduction in estimated stenosis, associated with a slight, but significant increase in coronary sinus blood flow, were observed. Myocardial oxygen consumption decreased as well. Maximal atrial pacing under control conditions led to a decrease in myocardial lactate extraction in all patients, whereas no abnormalities of the transmyocardial lactate gradient were produced after verapamil administration. Also, no decrease in ejection fraction was present during atrial pacing while anginal complaints were absent or minimal as compared with control conditions. In 12 patients studied by FERLINZ and TURBOW (1980), myocardial oxygen consumption and lactate metabolism were influenced in the same direction. Anginal complaints diminished after administration of verapamil at a dose of 0.1 mg/kg as a bolus and 0.005 mg kg^{-1} min^{-1} as an infusion, although coronary sinus blood flow at rest, and during pacing, had decreased. ZYGELMAN et al. (1981) observed no change in coronary blood flow at rest, but a decreased flow during atrial pacing with verapamil at 0.10 or 0.17 mg/kg as a bolus and 0.005 mg kg^{-1} min^{-1} as an infusion. $M\dot{V}O_2$ was reduced and coronary arteriovenous oxygen difference decreased at rest and during atrial pacing.

Despite different doses, the data of these authors indicate that verapamil decreases myocardial oxygen consumption with or without a consistent decrease in CSBF. SEABRA-GOMES et al. (1976) observed after administration of verapamil 0.1 mg/kg in patients with coronary artery disease, that left ventricular dP/dt was reduced, even when the heart rate was fixed by atrial pacing, while there were no changes in echocardiographic ventricular dimensions, systemic vascular resistance, or aortic pressure. FERLINZ et al. (1979) demonstrated, in 20 patients with coronary artery disease, that this negative inotropic effect was compensated for by the vasodilating effects of the drug. In fact, several indices of left ventricular performance improved after intravenous administration of verapamil at 0.1 mg/kg bolus injection and 0.005 mg kg^{-1} min^{-1} infusion. Cardiac index, ejection fraction, and mean velocity of circumferential fiber shortening increased, but heart rate remained the same. Left ventricular end-diastolic pressure increased after verapamil infusion, while there was no change in left ventricular end-diastolic volume. This would indicate a verapamil-induced decrease in left ventricular compliance. In the same study, mean aortic pressure and systemic vascular resistance decreased by 12 mmHg and 30% respectively. Of all asynergic segments, 70% improved or remained the same after verapamil treatment, while 30% detoriated further, as judged from the hemiaxial shortening of left ventricular angiograms.

CHEW et al. (1980 a, b) also came to the conclusion that, in patients with a mild to moderate decrease in left ventricular ejection fraction, accompanied by a normal or mildly elevated mean pulmonary capillary wedge pressure, the intrinsic depressant effect of the drug was almost completely offset by its vasodilating properties. CHEW et al. (1981) saw with gated blood pool scanning, no increase in ejection fraction, although in Ferlinz's patients, ejection fraction did increase by 9% as determined by contrast angiography. In another eight patients, HECHT et al. (1981) demonstrated with radionuclide ventriculography, that regional wall motion abnormalities and a reduced ejection fraction which appeared during atrial pacing-induced angina pectoris, normalized after intravenous administration of verapamil. Verapamil also prevented the increase during exercise in pulmonary capillary wedge pressure at intravenous doses of 0.145 mg/kg and an infusion rate of 0.005 mg kg^{-1} min^{-1}. ZYGELMAN et al. (1981), at doses of 0.15 mg/kg and an infusion of 0.005 mg kg^{-1} min^{-1}, found reduced blood pressure and systemic vascular resistance and a diminished dP/dt_{max} during spontaneous rhythm as well as during atrial pacing. End-diastolic pressures became slightly elevated after verapamil administration during sinus rhythm, but remained unchanged during pacing, as did the cardiac output. These data again indicate, as is the case with nifedipine, that the intrinsic negative inotropic effect of these drugs is minimized by decreases in afterload so that overall ventricular performance in patients without heart failure is not impaired or can actually improve.

FERLINZ (1980) also studied the effect of intravenous verapamil in patients with congestive failure at doses of o.1 mg/kg as a bolus and 0.005 mg kg^{-1} min^{-1} infusion rate. Ejection fraction, stroke volume index, and velocity of circumferential fiber shortening increased concomitantly with a decrease in arterial pressure and systemic vascular resistance. At higher doses of verapamil, i.e., 0.145 mg/kg as a bolus and 0.005 mg kg^{-1} min^{-1} infusion rate, CHEW et al. (1981) found in three patients with coronary artery disease, one of whom had an acute myocardial infarction, all with pulmonary capillary wedge pressure >20 mmHg, that the mean arterial pressure decreased markedly together with the stroke volume index and that pulmonary capillary wedge pressure abruptly increased. All three patients developed clinical heart failure. This last observation stresses that higher doses of verapamil must be employed with great caution. Further investigation will have to be performed to see at which dosage verapamil will actually benefit patients with overt congestive heart failure.

Accordingly, caution must be employed when giving verapamil intravenously in myocardial infarction. In seven patients, a bolus of 0.145 mg/kg verapamil, followed by an infusion of 0.005 mg kg^{-1} min^{-1}, lowered mean arterial pressure and reduced systemic vascular resistance (CHEW et al. 1981), yet heart rate and ejection fraction remained the same, while stroke volume and cardiac index increased, the latter by 27%. Pulmonary capillary wedge pressure also increased moderately. One patient, however, with a severely depressed ejection fraction and a high pulmonary capillary wedge pressure developed hypotension and a marked elevation of pulmonary artery pressure with clinical heart failure. BACHOUR et al. (1977) gave 5 mg intravenously in 14 patients with an acute transmural infarction and supraventricular arrhythmias. While normotensive patients had a transient slight blood pressure dip after verapamil injection, those with hypertension

showed a more pronounced fall in blood pressure. Cardiac index and stroke index increased markedly. On the other hand, HAGEMEYER (1978) could not demonstrate any untoward effects in 16 patients with a sustained supraventricular tachycardia treated within 72 h after an acute myocardial infarction. A similar positive result was obtained by WOLF et al. (1977) who administered 7.5 mg verapamil intravenously followed by an infusion of 0.1 mg/min in patients with an acute myocardial infarction within 12 h of admission to hospital. While arterial pressure declined with peripheral vascular resistance, left ventricular stroke work index and left ventricular filling pressure remained the same. These limited experiences seem to indicate that verapamil can be given to most patients with an acute myocardial infarction. One must, however, keep in mind its intrinsic negative inotropic effect since the drug might precipitate subclinical heart failure into overt heart failure, particularly in those who have already depressed left ventricular function, (ejection fraction 30%), a large heart, or who are hypotensive (SINGH et al. 1982; PACKER et al. 1982 a, b).

4. Oral Administration

TAN et al. (1982), in a double-blind study, analyzed the effects of 160 and 320 mg verapamil on left ventricular function by means of radionuclide blood pool imaging. At rest, patients with coronary artery disease had a lower blood pressure, while heart rate was unchanged. All showed an increased exercise tolerance, while ejection fraction was maintained at the same level. In contrast, the placebo-treated group experienced a fall in ejection fraction together with an increase in end-systolic volume. JOSEPHSON et al. (1981) studied, also with radionuclide blood pool imaging, the effects of 480 mg verapamil on left ventricular function. Verapamil reduced the number of exercise-induced regional wall motion abnormalities and the extent of exercise-induced reduction in ejection fraction. This had not been found by LEON et al. who, in 1980, after administration of the same dose of verapamil, had observed a decrease in resting ejection fraction from 48% to 44%, although the placebo-treated patients behaved similarly. The same group looked somewhat later (LEON et al. 1981) at the influence of oral verapamil on left ventricular diastolic filling in patients with coronary artery disease. Heart rate and ejection fraction decreased after verapamil treatment, although peak filling rate increased. They postulate that the improvement in left ventricular diastolic filling may be partly responsible for the symptomatic improvement during verapamil therapy.

III. Clinical Experience

1. Vasospastic (Prinzmetal's) Angina

After a short-term trial performed in 12 patients in a coronary care unit, PARODI et al. (1980) demonstrated that verapamil drastically reduced the number of anginal attacks, myocardial infarction, and mortality rate in patients in whom spasm was proven to be the cause of the angina. This was later confirmed in a long-term follow-up. KELLY et al. (1980) treated 27 patients with severe Prinzmetal's angina pectoris at rest, documented by the ergonovine maleate test during

angiography or ECG. Relief of the symptoms occurred in most of the patients within 36 h after starting verapamil therapy (240–320 mg/day). In six patients, who had documented coronary spasm, and coronary artery obstruction of less than 50%, FREEDMAN et al. (1981 a) were able to prevent exercise-induced CAS by verapamil in a dose of 160–480 mg. Other authors such as HANSEN and SANDOE (1978) and FREEMAN et al. (1981 a) have also reported on the effective relief of Prinzmetal' angina, particularly when refractory to nitrates. In the article by PARODI et al. (1980), the vasospastic origin of ischemic heart disease was demonstrated by continuous hemodynamic and ECG monitoring as well as by ^{201}Tl scintigraphy and coronary arteriography during ischemic episodes. The follow-up of their 200 patients with documented vasospastic unstable angina at rest demonstrated conclusively that verapamil drastically reduced the number of ischemic anginal attacks as well as the incidence of the subsequent myocardial infarction and mortality. Their direct observations suggest that the main pharmacologic mechanism of the drug in patients with this type of vasospastic angina is the prevention of spasm or the relaxation of coronary smooth muscle. Verapamil in doses of 320–400 mg orally is usually well tolerated and appears to be effective in the majority of these patients. PARODI et al. (1980) emphasize, however, that this may not be the only mechanism of action since it is still unknown what the causes of vasospasm are. In this respect, the subsequent studies by JOHNSON et al. (1981 a) are of importance since they also showed a 86% reduction in the incidence of anginal attacks in Prinzmetal's disorder although it should be remarked that 14 of the 19 patients also received nitroglycerin. JOHNSON et al. (1981 b, c) compared the action of verapamil with that of nifedipine in the treatment of variant angina pectoris. In ten patients who were treated for an average of 2 months, either with 240–480 mg/day (average 400 mg/day) verapamil or 40–160 mg/day nifedipine (average 82 mg/day), or placebo, they found both drugs to be equally effective in the suppression of symptoms as well as the signs of ischemia, monitored on ambulatory ECG, although nifedipine appeared to be associated with more adverse effects than either placebo or verapamil.

In a 9-month, double-blind, crossover trial, WINNIFORD et al. (1982) demonstrated the effectiveness of verapamil in patients with variant angina, most of whom had normal coronary arteries. In two patients, placebo and verapamil were administered in a randomized, double-blind study of 9 months duration in which it was shown that verapamil reduced the frequency of angina, as well as the use of nitroglycerin, and the incidence of transient episodes of ST segment deviation. Subsequently, 23 patients were treated with nifedipine in a non-blind version for 2 months and it was confirmed that this agent exerted a beneficial effect similar to that of verapamil. Scintigraphy in ten patients did not show any deterioration of left ventricular performance. These authors conclude that long-term oral verapamil and nifedipine are each superior to placebo and that neither agent adversely influences left ventricular performance. WATERS et al. (1981 a, b) have advocated ergonovine testing to evaluate spontaneous remission of variant angina when patients, during long-term treatment, become asymptomatic on calcium antagonists drugs. As was discussed earlier in the section on diltiazem, their conclusion, that in many patients with variant angina, symptoms will disappear spontaneously, is a significant observation. If it is to be proved subsequently that a negative

response to a repeated provocation by ergonovine is indeed equivalent to the identification of patients who no longer require treatment, this would be an important message (WATERS et al. 1981 a, b). The fact that in 12 of their 22 patients in whom no angina nor ST segment shifts recurred during the second ergonovine test to a maximal dose of 0.4 mg, and that all these 12 patients remained free of variant anginal attacks up to 13 months later, would seem to support their position. On the other hand, the relative absence of side effects of verapamil or any of the other calcium antagonists would suggest prolonged treatment with these drugs in patients who have been symptomatic for a long time.

2. Unstable Angina

MEHTA and CONTI (1982) reviewed several double-blind, placebo-controlled, randomized clinical trials in patients with unstable angina pectoris. The studies by PARODI et al. (1979, 1980) were referred to earlier and have shown verapamil to be superior to placebo in abolishing symptomatic as well as asymptomatic ischemic episodes. From 127 ischemic events during placebo treatment, there were only 27 episodes during therapy with verapamil. In the second study by MEHTA et al. (1981), the double-blind, randomized, parallel design allowed choice of drug to be altered and the dose of the drug to be increased according to individual responses. It was shown again that verapamil reduced anginal atacks in 12 of 13 patients, whereas placebo was effective in only 1 of 6. They conclude that verapamil therapy is markedly beneficial for the short-term prophylaxis and management of symptomatic as well as asymptomatic ischemia in patients with severe obstructive coronary artery disease and unstable angina at rest. They emphasized that the drug can produce a rapid stabilization of symptoms, rather than that which can be obtained by hospitalization, sedation, intensive observation, and bedrest alone. Finally, PARODI et al. (1982) in reviewing their previous experience with three clinical trials comparing the effectiveness of verapamil and propranolol in patients with angina at rest, confirm that verapamil is far more effective than propranolol in the treatment of resting angina. In fact, they conclude that the effectiveness of propanolol in this syndrome appears comparable to that of placebo. In Sect. C, dealing with nifedipine, similar conclusions have been reached, while some authors like ROBERTSON et al. (1979 a, b) in fact believe that propranolol may worsen the symptoms in that syndrome.

3. Stable, Exercise-Induced Angina

When verapamil was first used as an antianginal agent by PHEAR (1968) and by LIVESLEY et al. (1973), it was employed in low doses (40–80 mg t.i.d.) and was not found to relieve angina significantly more than placebo. In a double-blind comparison of verapamil and propranolol FAGHER et al. (1977) showed that larger doses, up to 120 mg t.i.d. were effective not only in reducing angina attack rate and nitroglycerin consumption, but also in prolonging exercise tolerance. SANDLER et al. (1968) found that 120 mg t.i.d. had a favorable effect on the amount and duration of the ST segment depression. This was subsequently confirmed by BALA-SUBRAMANIAN et al. (1981 a, b). PARISI (1982) assigns to verapamil an efficacy which is equal to that of diltiazem and points to the fact that neither vera-

pamil nor diltiazem produce a cardioacceleratory response, whereas nifedipine does; the latter drug also lowers the resting systolic blood pressure slightly more than does verapamil, a fact which may be beneficial in blunting the usual exercise-induced hypertensive response.

In 1981, LEON et al. published a comparison of verapamil alone and its combination with propranolol in 11 patients with chronic angina pectoris. They, too, reported that at 480 mg/day, exercise time was improved by an average of 3.4 min and that it was more effective than propranolol 160–320 mg/day, with a mean increment of only 1.3 min. However, the combination of verapamil and propranolol further increased exercise time to an average of 4.7 min, while 9 of the 11 patients became pain free during exercise. The attentive reader will remember there are similar observations for the combination of nifedipine and β-blockers (Sect. C.III.2). An added advantage is that the combination further decreases heart rate as well as the pressure–rate product. In this small series, however, there were some adverse effects such as PR interval prolongation in most of the patients, with transient atrioventricular nodal or Wenckebach block and exertional dyspnea as well as pedal edema. FRISHMAN et al. (1982 d) compared oral verapamil and propranolol in 20 patients with stable angina pectoris, again in a placebo-controlled, double-blind, randomized, crossover protocol. They came to the conclusion that the frequency of anginal attacks and the amount of nitroglycerin consumed was most reduced with verapamil at 480 mg/day, but not with placebo or propranolol. Although propranolol reduced the exercise pressure–rate product more than did verapamil alone, they conclude that verapamil has a slight advantage over propranolol in terms of clinical efficacy. Similar findings were reported by TAN et al. (1982) in a study from Australia performed in a double-blind, placebo-controlled manner in 12 patients. In addition to confirming the earlier results, they also showed that during exercise the ejection fraction determined by radionuclide ventriculography did not decrease (44% vs 45%), thus indicating that the expected decrease in left ventricular ejection fraction due to exercise-induced ischemia was avoided.

The report on a symposium on the efficacy of therapy with verapamil for stable angina pectoris appeared in November 1982. WEINER and KLEIN (1982) carried out a double-blind, placebo-controlled, crossover study in 26 patients with 480 mg/day verapamil. This dose reduced the frequency of angina attacks from 5.6 to 2.2 per week, with a concomitant reduction in nitroglycerin consumption. These changes were significantly better than those seen with placebo. These authors ascribe the beneficial effects of verapamil to a significant reduction in the pressure–rate product during exercise. They also reported on 193 patients who had been entered in 6 independent clinical trials, showing similar results. In this larger series, adverse effects were reported to be infrequent except for one study (PINE et al. 1982), in which more frequent adverse reactions were observed when a dose of 480 mg/day was employed. BALA-SUBRAMANIAN et al. (1982 a) carried out a double-blind, randomized, placebo-controlled, crossover study in which the double-blind phase was preceded by a 2-week single-blind placebo period followed by a randomization to either 4 weeks therapy with verapamil at 360 mg/day or propranolol 240 mg/day, followed by crossover to the other drug. Both verapamil and propranolol increased exercise tolerance from 5.5 min with place-

bo to 7.8 min with propranolol and 9.1 min with verapamil with concomitant reduction in ECG abnormalities. Their study, along with eight similar double-blind, placebo-controlled investigations, some of which have already been mentioned, and all of which are consistent, lead to the conclusion that verapamil produces subjective as well as objective relief of effort-related anginal symptoms to a degree which is comparable to or higher than that seen with β-blocking agents.

Since, in these studies, some patients clearly preferred or benefited from one drug more than the other, their preference or benefit will be dictated by considerations other than drug effectiveness alone. In other words, contraindications before therapy or adverse reaction after therapy will usually dictate which choice is made. In a small study in 12 patients with stable angina pectoris and moderate systemic hypertension, FRISHMAN et al. (1982d) showed verapamil to be a safe and effective treatment alternative to propranolol for relieving anginal symptoms and improving exercise tolerance while having a greater influence on standing diastolic blood pressure. Thus, as was the case in the discussion on nifedipine, coexisting hypertension may argue strongly in favor of either combining an existing β-blocker treatment with a calcium antagonist, or even switching completely to the calcium antagonist. In a second article in the symposium, BALA-SUBRAMANIAN et al. (1982c) provided a rationale for the choice between calcium antagonists in chronic stable angina. They do this on the basis of a double-blind, placebo-controlled comparison of verapamil and nifedipine in a series of 24 patients. A similar comparative study was done between nifedipine and diltiazem by BROUSTET et al. (1981) in 16 patients. Both series are small in number, but show that in terms of exercise duration, at the doses given, there are minor differences in efficacy in chronic stable angina between these drugs. BALA-SUBRAMANIAN et al. (1982c) also come to the conclusion that since seven patients during exercise had increasing angina with nifedipine, whereas none did so with verapamil, and since there were slightly longer exercise durations with verapamil, coincident with slower heart rates, verapamil would seem to be the more effective and better tolerated drug. Also, the conclusion by BROUSTET et al. (1981) that diltiazem was slightly favored over nifedipine points in the same direction. On the other hand DAWSON et al. (1981) could not find any significant differences favoring one over the other. It should be pointed out, however, that the biologic half-life of nifedipine is shorter than those of the other two drugs, which may require a different dosage from what was given. In addition, there are the obvious interindividual variations in tolerance and there remains the uncertainty about the exact mechanism by which any of these three drugs works in a given individual. For example, if in a patient the reflex sympathetic stimulation is not affected by nifedipine, but attenuated by verapamil, it is understandable that under those circumstances verapamil is more effective. The same ipso facto would go for diltiazem. If, on the other hand, peripheral unloading is not the major mechanism by which the drug acts, but the relief of excessive coronary vascular tone is, nifedipine might be the drug of choice since it is the strongest of the three in these terms.

Finally, in the symposium referred to, there is an extensive study by SCHEIDT et al. (1982) on the long-term effectiveness of verapamil in stable and unstable angina pectoris, based on a 1-year follow-up of patients treated in placebo-controlled, double-blind, randomized trials. These investigators, each of whom has

extensive experience with this drug, come to the conclusion that the improvement in stable angina is continuous over the full year, while in unstable angina the initial reduction of anginal symptoms, which was sustained in most patients for longer than 1 year, did not seem to affect the high subsequent incidence of death or myocardial infarction. They come to the important conclusion that, while calcium channel antagonists may decrease the number of patients requiring coronary bypass surgery or at least delay the time when such interventions are necessary, they do not appear to alter the natural history of the disease in this time span. An interesting observation was made by FRISHMAN et al. (1982c) on the effect after abrupt withdrawal of verapamil compared with propranolol. There appeared to be no evidence of a rebound increase in frequency of anginal attacks or changes in blood pressure or hearts rates after verapamil withdrawal, whereas these were observed in patients suddenly withdrawn from propranolol. It was of interest to note that the plasma catecholamines during exercise were significantly higher with propranolol than with verapamil!

A final section might be devoted to the description of studies in which the effect of adding verapamil to patients already receiving a β-blocker is again analyzed. In a study, published in 1981, LEON et al. demonstrated the clinical efficacy of verapamil alone and in combination with propranolol in chronic stable angina pectoris. With the usual protocol and with bicycle ergometry, they proved that verapamil by itself was a more effective antianginal agent than propranolol, but that the combination provided additional improvement in exercise capacity over either drug alone. They ascribed this to a lower pressure–rate product, mainly because of a significant decrease in heart rate. In a slightly different protocol BASSAN et al. (1982a, b) demonstrated in ten men with stable angina pectoris, who had not been fully relieved by optimal doses of propranolol at 210 mg/day, that a single oral dose of 120 mg verapamil significantly improved their symptoms. Exercise tolerance increased and verapamil was also able to reduce resting systolic pressure further. They also conclude that verapamil is a highly effective antianginal supplement to propranolol. Earlier that year, BALA-SUBRAMANIAN et al. (1982c), in yet another study, comparing verapamil and propranolol, came to the same conclusion, although they warned that patients need to be carefully monitored for adverse effects, mainly on the conduction system. Also in 1982, KIEVAL et al. studied the effect of intravenous verapamil on the hemodynamic status of patients with coronary artery disease who were already on propranolol. In 20 such patients who were on chronic propranolol therapy, intravenous verapamil in varying doses led to a further reduction in mean arterial pressure by 22%, with a dose of 0.1 mg/kg, as well as a decrease in systemic vascular resistance by 24%, effects which were also seen in the pulmonary circuit. Concomitant increases in cardiac index or in ejection fraction were not observed. They note that the combined negative inotropic effects of verapamil and propranolol are of negligible importance, although it should be pointed out that these patients did not have a significant depression of myocardial performance at the outset. The warning to monitor carefully all patients with depressed left ventricular function who are given verapamil must therefore be maintained.

F. Summary

In summary, from the literature which has appeared over the last decade on the topic of calcium antagonists in the therapy of angina pectoris, a selection was made in favor of the three major compounds: nifedipine, verapamil, and diltiazem. These three agents are now more or less routinely used in most developed countries.

In the clinical situation, the net hemodynamic and electrophysiologic effects of these drugs are the result of a complex interaction between their peripheral and their central effects, their mode of administration and their dosages, as well as of their specific profile and pharmacokinetics. The degree of baroceptor stimulation and reflex-mediated β-adrenergic activity, which counteract and influence the intrinsic negative dromotropic, chronotropic, and inotropic effects of the calcium antagonists, are only in part related to the degree of peripheral dilation. Their varying effects on various vascular beds make their clinical assessment even more difficult. Finally, although their effects on vascular and cardiac muscle are somewhat similar, there exist major differences in their antiarrhythmic properties.

All three of these calcium antagonists are effective in treating patients with coronary spasm, variant angina, and unstable angina. In patients with chronic exertional angina pectoris, their effects vary. Often combination therapy with β-blockade is effective. Perhaps nifedipine should more often be combined with a β-blocking agent in order to balance the baroceptor reflex-induced effects and to reduce side effects as lower dosages of the combined drugs prove to be equally effective. On the other hand, the combination of verapamil and diltiazem with a β-blocking agent is less advisable because of the potential adverse electrophysiologic and hemodynamic reactions, particularly in patients with chronic cardiac

Table 6. Therapeutic applications of nifedipine, verapamil and diltiazem in brief

Myocardial ischemia	Nifedipine	Verapamil	Diltiazem
Variant angina	Therapy of choice	Therapy of choice	Therapy of choice
Exertional and unstable angina			
1. Monotherapy	Effective	Effective	Effective
2. Combination with β-blocker	Very effective	Some risk	Probably effective
Infarct size reduction	Not effective	Not effective	No data
Cardioplegia	Promising	Promising	Promising
Heart failure	Beneficial	Caution advised	Caution advised
Hypertension	Effective	Effective	Under investigation
Hypertrophic cardiomyopathy	Promising; under investigation	Recommended in absence of heart failure and/or conduction defects	No data

failure and large hearts. Other therapeutic applications are summarized in Table 6.

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