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Volume II

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Editor

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Preface

Perinatal medicine, which is concerned with the problems of the fetus and newborn, has rapidly developed in the last two decades as an important and challenging specialty. Rapid advances in the field, coupled with technologic advances, now are making possible the survival of infants with weights as low as 500 g. Ventilator care for severe respiratory problems is on the verge of being replaced by surfactant-replacement therapy; on the other hand, development of such technologies as extracorporeal membrane oxygenation and jet ventilation has revolutionized the care of sick infants.

The advances occurring today in the field of perinatal medicine make periodic updates, like the one provided by this volume, a virtual necessity for clinicians and paramedical personnel alike. A distinguished group of specialists in various aspects of perinatal medicine has contributed to this book. Their wide-ranging experience and points of view should make this book a valuable reference for all physicians and allied health personnel involved in the care of the high-risk mother, fetus, and newborn.

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An Introduction to Perinatal Doppler

DEV MAULIK, JAMES P. YOUNGBLOOD,
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Doppler waveform represents the velocity wave of a flow. The shape of a velocity pulse wave is determined by both the up and downstream circulatory states. Analysis of the waveform therefore can potentially yield information on these circulatory states. Strandness, in 1967, explored for the first time the changes in the Doppler waveform in the occlusive disease of the profunda femoris artery and initiated the application of Doppler for circulatory assessment.[1] Since then, a vast array of investigations have been conducted to define the utility and limitations of Doppler in prognosticating peripheral vascular disease. Doppler ultrasound has also been used for studying cardiac hemodynamics, and Doppler echocardiography is now a major modality for noninvasively assessing cardiac output and hemodynamics in congenital and acquired cardiac valvular and outflow tract lesions and other cardiovascular disorders.[2-4] More recently, Doppler velocimetric investigations have also been applied in relation to umbilical, fetal, and uterine circulations. In 1977, Fitzgerald and Drumm[5] were the first to describe the Doppler frequency shift waveform from the umbilical arterial circulation. An immense amount of information on fetal application of the technique has been generated since then. As discussed in this chapter, an association has been established between certain pregnancy complications and the Doppler indices that serve as the simple, normalized descriptors of the Doppler frequency shift waveforms. Furthermore, ample evidence[6,7,8,9] indicates that an abnormal waveform may be associated with an adverse perinatal outcome.

Doppler Effect

When energy travels in waves, the observed frequency of propagating waves changes with movement between the source of the energy emission and an observer. The frequency increases if the source and the observer move closer and decreases if the source and the observer move apart (Fig. 1.1). This physical principle was first stated during the mid-nineteenth century by Johann Christian Doppler, an Austrian physicist and mathematician, and therefore bears his name.[10] As sound is a form of mechanical kinetic energy that travels in waves, the

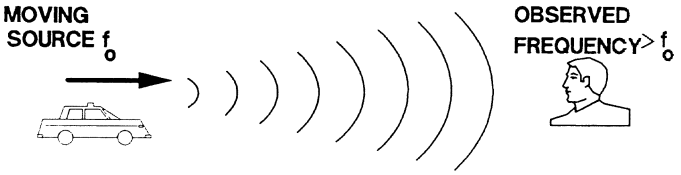

FIGURE 1.1. The Doppler effect. f_0 represents the frequency of the sound emitting from the source, which is the police car in this illustration.

Doppler effect is observed in relation to sound and ultrasound. The effect is also observed when an incident beam of ultrasound is backscattered by moving targets such as red cells in a circulation. Doppler shift waveform is the summation of individual Doppler shift frequencies backscattered by the millions of moving red cells. The summation is achieved by processing the Doppler frequency spectra. The processor is called a *spectral analyzer.* This instrument temporally sorts the

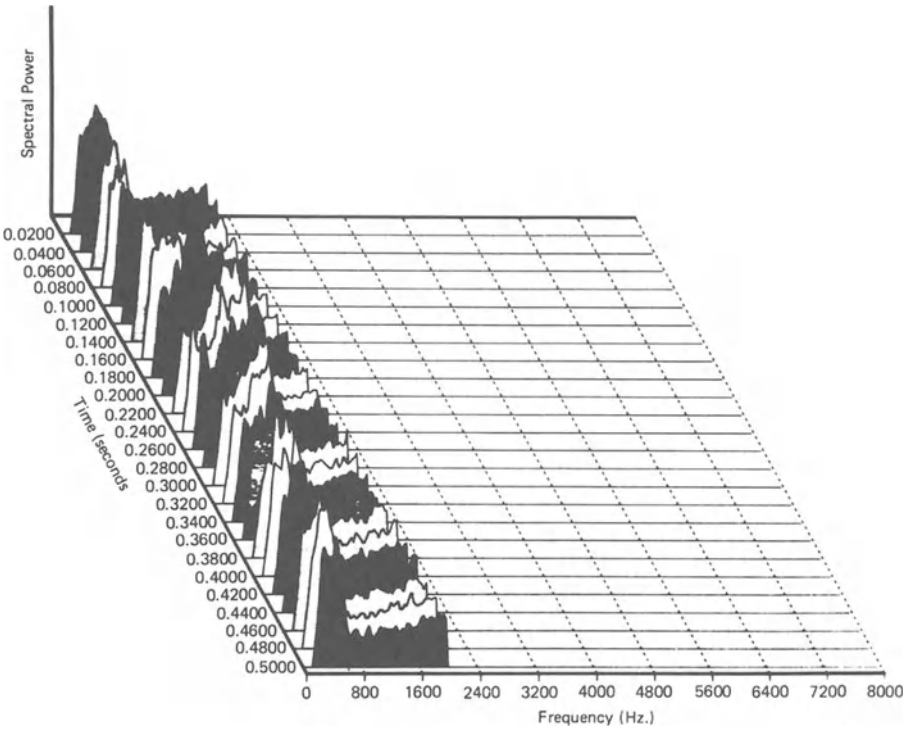

FIGURE 1.2. Doppler frequency shift power spectra as function of the time after coherent averaging. The signal was obtained from the umbilical artery (*Source*: Reprinted with permission from Maulik D, Saini VD, Nanda NC, Rosenzweig MS. Doppler evaluation of fetal hemodynamics. *Ultrasound Med Biol.* 1982;8:705–710, Copyright [1982], Pergamon Press plc.)

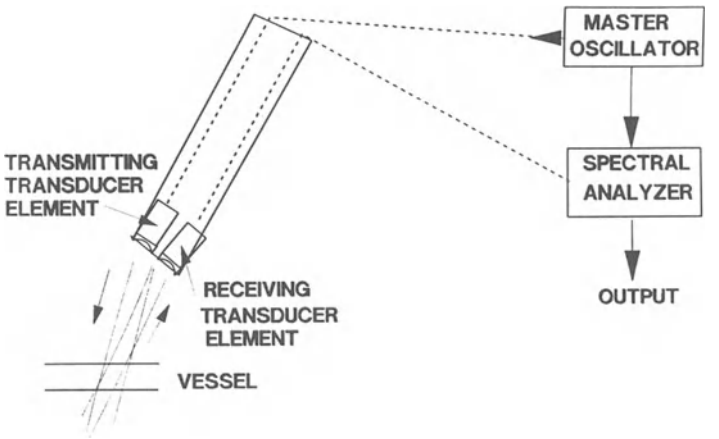

FIGURE 1.3. Schematic depiction of a continuous-wave Doppler system.

spectra according to the magnitude of frequency and power. Although many spectral analyzing methods are available, the current standard is the Fast Fourier Transform (FFT) (Fig. 1.2). In recent instruments, FFT processing is implemented in real time by dedicated microprocessors and allows bidirectional flow assessment. More recently, Kierney and Zimmerman[11] have described an autoregression method of spectral analysis. Obstetric applications of this technique, however, remains to be developed.

Three types of Doppler ultrasound implementations have been developed: continuous-wave Doppler, pulsed wave Doppler, and the two-dimensional Doppler color-flow mapping system. A continuous-wave Doppler transducer uses two elements: one for transmitting the ultrasound beam and a second for receiving the backscattered echo (Fig. 1.3). Because any target motion within the sensitive region of the beam path causes the Doppler shift, the system is devoid of any range resolution. In a pulsed wave Doppler system, a single transducer element sends out pulses of ultrasound and acts as the receiving transducer during the interpulse interval after a variable time delay (Fig. 1.4). The depth of the location from which the echoes are received can be controlled by varying the time delay. To select the target location, the pulsed wave Doppler is usually incorporated within an imaging system, and such a device is called a *duplex ultrasound system*. In a Doppler color-flow mapping device, a mean frequency shift-based, color-coded, two-dimensional flow pattern is superimposed on the structural images.

Doppler Waveform Analysis

Doppler frequency power spectrum can be used to assess the velocity profile and the volumetric flow rate. Accurate flow estimation, however, involves integration of time-averaged mean velocity and the vascular cross-sectional area and

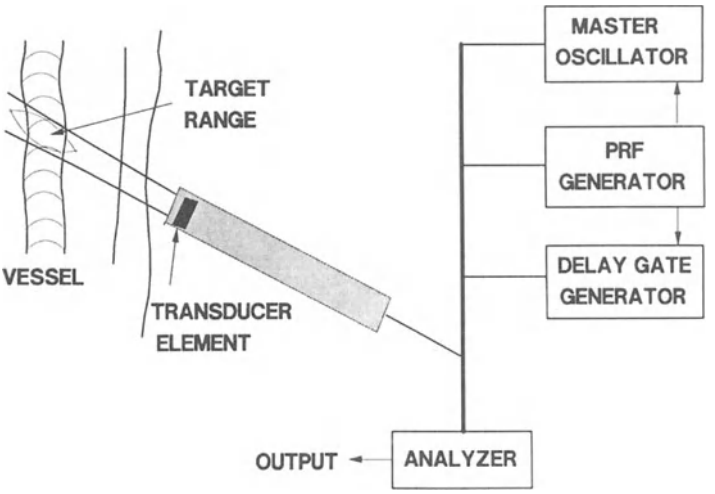

FIGURE 1.4. Schematic depiction of a pulsed Doppler system. (PRF, pulse repetition frequency.)

therefore requires determination of the angle of beam incidence, the vessel diameter, and the insonation characteristics. In umbilical and uteroplacental circulations, most of these factors are difficult to measure. Waveform analysis is therefore the method of choice for most perinatal Doppler applications. The waveform can be derived in three different modes: maximum frequency shift, mean frequency shift, and the first moment.[12] Of these, the maximum frequency envelope remains the current choice. The envelope can be defined by computer algorithm or by manual digitization. This technique, obviously, can be a potential source of error in these measurements.

For perinatal Doppler, the indices characterize two principal, interdependent features of the waveform in an angle-independent manner. These are the pulsatility, which is the difference between the peak systolic and the end-diastolic frequency shifts, and the end-diastolic component itself (Fig. 1.5). In peripheral

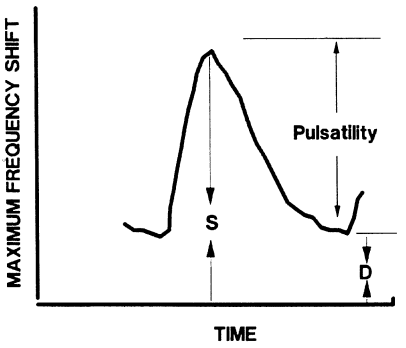

FIGURE 1.5. Schematic representation of the Doppler waveform. S represents the peak systolic and D, the end-diastolic components of the maximum frequency shift envelope.

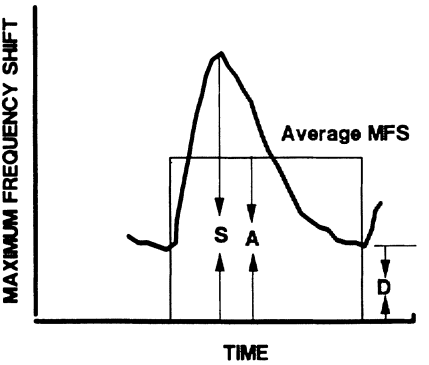

FIGURE 1.6. Doppler indices estimated from the maximum frequency shift envelope. RI = (S-D)/S (Pourcelot, 1974); PI = (S-D)/A (Gosling, 1976); S/D ratio (Stuart and Drum, 1980); D/A ratio (Maulik et al., 1982). (D/A, diastolic/average ratio; PI, pulsatility index; RI, resistance index; SD, systolic/diastolic ratio.) (*Source*: Reprinted with permission from Yarlagadda P, Willoughby L, Maulik D. Effect of fetal heart rate on umbilical arterial Doppler indices. *J Ultrasound Med.* 1989;8:215–218. Copyright 1989 by the American Institute of Ultrasound in Medicine.)

vascular work, pulsatility has been the major characteristic under investigation, as continuing forward flow in diastole does not occur in the peripheral vascular systems such as the femoral or the popliteal arteries. Gosling and co-workers were one of the first groups to report on a descriptor index of the Doppler waveform.[13] The Fourier pulsatility index was later replaced with a simpler version called the *peak-to-peak pulsatility index*, better known as *the Gosling pulsatility index* (PI) (Fig. 1.6). At the same time, Pourcelot's group reported another descriptor of pulsatility and named it the *resistance index* (RI), also known as *the Pourcelot index* (Fig. 1.6).

In 1980, Stuart et al.[14] described an even simpler index of pulsatility, the A/B ratio where A represents the peak systolic value and B represents the end-diastolic value of the Doppler waveform. This is also known as *the systolic/diastolic (S/D) ratio.* This appears to be the most widely used Doppler index (Fig. 1.6). Because one of the major points of interest in the analysis of the umbilical arterial waveform is the assessment of end-diastolic velocity, Maulik et al.[15] proposed the use of normalized end-diastolic velocity, or diastolic/average (D/A) ratio, in 1982 (Fig. 1.6). The main advantage of these indices is that they reflect the pulsatility and end-diastolic velocity with the need for measuring the beam angle or vessel cross-sectional area. More comprehensive waveform analytic techniques also have been described. In 1982, Maulik et al.[15] described a 10-parameter feature characterization of a coherently averaged waveform (Fig. 1.7). This included a normalized measure of the rising systolic slope, the pulsatility, and the end-diastolic velocity. In 1983, Campbell and co-workers[16] described the frequency index profile, in which they normalized the maximum frequency envelope. The profile was specifically developed for the uteroplacental arteries. In 1985, Thompson and others[17] described a four-parameter

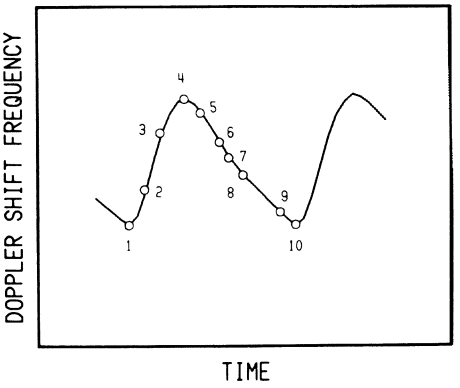

FIGURE 1.7. Reference points in a typical velocity envelope waveform obtained in the umbilical arteries. (1) Trough. (2,3) Ascending slope. (4) Peak. (5,6) Initial descending slope. (7) Inflexion point. (8,9) Final descending slope. (10) Trough. (*Source*: Reprinted with permission from Maulik D, Saini VD, Nanda NC, Rosenzweig MS. Doppler evaluation of fetal hemodynamics. *Ultrasound Med Biol.* 1982;8:705–710, Copyright [1982], Pergamon Press plc.)

curve-fitting analysis of an averaged waveform. More recently, Marsal and his group (1987)[18] have proposed an approach that combines the PI and the characteristics of diastolic flow into a system of evaluation called the blood flow classes (BFC). In these investigators' experience, the BFC appeared to be superior to other flow variables in predicting fetal distress and operative delivery resulting from fetal distress. None of these approaches is in general use, and with the exception of BFC, whether they offer any improvement over the simpler indices is not yet clear. Our own experience by and large corroborates this. Obviously, further investigation is required in this area.

Doppler Assessment of Fetal Circulation

In the obstetric area, the Doppler velciometric method has been used to investigate circulatory dynamics in the umbilical artery, the aorta, and the internal carotid artery. The technique also has been employed in investigating fetal central circulation including the ascending aortic, main pulmonic, mitral, tricuspid, and interatrial flows. Furthermore, the uterine and uteroplacental circulations have also been investigated. Of these, umbilical arterial Doppler investigation appears to be the simplest and most widely used technique. In contrast to aortic or carotid circulations, which need the use of a duplex Doppler system to obtain targeted hemodynamic information, a continuous-wave Doppler is adequate for the umbilical circulatory investigation. The continuous-wave instrumentation is simpler and has a low acoustic power output. Furthermore, the ease of learning and the ease of use are excellent, making it an eminently suitable screening and

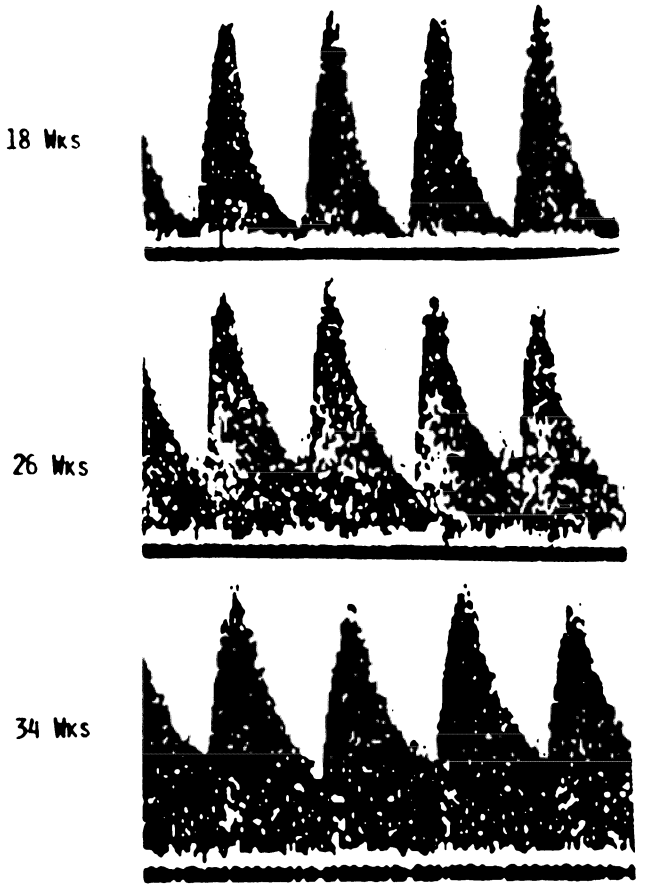

FIGURE 1.8. Changes in the umbilical arterial Doppler frequency shift waveforms with the progression of gestation. (*Source*: Reprinted with permission from Maulik D, Yarlagadda P, Willoughby L. Doppler assessment of feto-placental circulation. *Troph Res.* 1988;3:293.)

monitoring device. Following is a brief review of the current state of the Doppler hemodynamic assessment of the umbilical circulation.

Factors Affecting the Umbilical Arterial Doppler Indices

During pregnancy, the umbilical circulation experiences a continuous increase in the end-diastolic velocity and a concomitant decrease in the pulsatility (Fig. 1.8). This is probably caused by a progressive fall in the fetoplacental impedance to flow and is reflected by a progressive increase in the D/A ratio,[19] as well as a decrease in the S/D ratio,[10] PI.[19,20] Table 1.1 summarizes the longitudinal values

TABLE 1.1. Variation in Doppler indices at different stages of gestation.

Doppler indices		Gestation (weeks)										
		18	20	22	24	26	28	30	32	34	36	38
RI	Mean	0.78	0.77	0.74	0.69	0.70	0.70	0.51	0.65	0.63	0.63	0.62
	SEM	0.01	0.01	0.02	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.01
PI	Mean	1.31	1.27	1.18	1.12	1.11	1.12	1.02	0.99	0.95	0.92	0.92
	SEM	0.03	0.03	0.03	0.05	0.03	0.03	0.04	0.03	0.04	0.02	0.03
S/D	Mean	4.62	4.70	4.00	3.48	3.59	3.60	3.16	3.04	2.91	2.90	2.70
	SEM	0.26	0.26	0.15	0.16	0.15	0.18	0.17	0.13	0.22	0.08	0.08
D/A	Mean	0.38	0.37	0.41	0.44	0.46	0.46	0.51	0.52	0.53	0.56	0.55
	SEM	0.03	0.02	0.01	0.01	0.02	0.02	0.03	0.02	0.02	0.01	0.01

(D/A, diastolic/average ratio; PI, pulsatility index; RI, resistance index; SEM, standard error of the mean; S/D, systolic/diastolic ratio.)

Source: Reprinted with permission from Maulik D, Yerlagadda P, Willoughby L. Doppler assessment of feto-placental circulation. *Troph Res.* 1988;3:293.)

of the Doppler indices from 18 weeks to term gestation measured in 350 uncomplicated singleton pregnancies.[21] Statistical analysis using Duncan multiple-range test demonstrated significant differences in the mean values of the indices at 18, 28, and 38 weeks of gestation. Other investigators reported similar gestational age-related effects in relation to some of these indices, although there were discrepancies in the detailed characteristics of these changes.

Umbilical arterial Doppler indices also are influenced by the fetal heart rate and breathing. Earlier studies failed to note any significant effect of the heart rate on the indices, especially when the rate was within the normal range (120 to 160).[17] More recently, however, numerous investigators[22,23] have noted heart-rate induced statistically significant alterations in the indices. A slower heart rate increases the diastolic time and reduces the magnitude of the end-diastolic velocity; this increases the pulsatility and therefore those indices that reflect this characteristic of the Doppler waveform. As to be expected, the D/A ratio declines with bradycardia. A higher heart rate has an opposite effect on the indices. From 15% to 18% of the variance of the Doppler indices have been shown to be attributable to the changes in the fetal heart rate.[23] Furthermore, when the umbilical arterial Doppler indices were standardized for a fetal heart rate of 140 beats per minute (bpm) and a gestational age of 34 weeks, using a multiple-regression equation, the 95% limits were reduced by 32%, 34%, 26%, and 32% for D/A ratio, S/D ratio, PI, and resistance index (RI), respectively.[23] However, whether such a correction procedure improves the clinical efficacy or not remains to be demonstrated. The indices are also affected by fetal breathing; the effect is exerted by its influence on the mean and maximum velocities and on the duration of the cardiac cycle. Both the peak systolic and end-diastolic components of the waveform are altered. Therefore, umbilical arterial Doppler waveforms should be assessed only during fetal apnea. The location of the Doppler measure-

ment in the umbilical cord can contribute up to 46% of the variance of the Doppler indices.[24]

Umbilical Arterial Doppler Velocimetric and Intrauterine Growth Retardation

One of the first clinical evaluations of the Doppler velocimetry was in relation to the demonstration of its association with intrauterine growth retardation (IUGR). IUGR is a problem of multiple or unknown etiologies. One of the major known mechanisms involves uteroplacental circulatory insufficiency. It has also been demonstrated that in IUGR one of the first changes in fetal homeostasis is fetal and fetoplacental hemodynamic compromise. Initial Doppler investigations of the umbilical circulation indicated a significant association between an elevated S/D ratio or the PI and small for gestational age (SGA) infants.[25-27] Furthermore, abnormal Doppler indices in the umbilical circulation were found to correlate well with abnormalities of the fetoplacental microvasculature.[28] This observation has been supported by Jimenez et al.[29] but refuted by Nessman et al.[30]

Many investigators have studied the clinical potential of Doppler velocimetry of the umbilical artery as a predicting tool for IUGR.[31-33] For the abnormal S/D ratio, Fleisher et al.,[31] in one of the first such reports, noted a sensitivity of 78%, a specificity of 83%, and a positive predictive value of 49%; in the presence of hypertension, the last parameter increased to 66%. van Vugt et al.[32] investigated the diagnostic efficacy of the PI, RI, and A/B (S/D) ratio and found a sensitivity of 77.8%, 77.8%, and 66.7%, respectively; a specificity of 88.5%, 88.5%, and 77.5%, respectively; and a positive predictive value of 58.3%, 58.3%, and 50.0%, respectively. Benson and Doubilet[33] comprehensively reviewed the published reports on the efficacy of fetal and uteroplacental Doppler investigation for predicting IUGR. Only those papers that fulfilled certain criteria were included in this study: published explicit criteria for antenatal diagnosis of IUGR; strict application of the criteria; adequacy of the data for determining directly the diagnostic efficacy parameters such as sensitivity. Twelve papers fulfilled these selection criteria for umbilical arterial Doppler indices. Of the different descriptors used for the Doppler waveform analysis, an absent end-diastolic velocity had the highest specificity (93%), the lowest sensitivity (37%), and medium positive predictive value (39%). The PI (>2 standard deviations) demonstrated the highest sensitivity (93%) and positive predictive value (54%) and the second-best specificity (91%). The most common descriptor used was the S/D ratio. When a value of greater than 3 was used as the diagnostic index, a sensitivity of 78%, a specificity of 83%, and a positive predictive value of only 34% were encountered. The results were slightly different when the criterion for an abnormal ratio was a value greater than the 95th percentile limit. Benson and Doubilet[33] concluded that these results did not demonstrate the diagnostic superiority of these Doppler descriptors over the existing sonographic anthropometric parameters.

More recent studies, however, which were not included in the previous review, did not conform with the conclusion of Benson and Doubilet.[33] Gaziano et al.[34]

performed duplex pulsed Doppler investigations in 256 high-risk patients and compared the umbilical arterial S/D ratio with the sonographic weight-estimation method based on biparietal diameter and abdominal circumference. An S/D ratio ≥ 4 identified 79% of the SGA infants, whereas only 43% of such infants were identified by the sonographic criterion. Berkowitz et al.[35] used a continuous-wave Doppler system to measure the umbilical arterial S/D ratios in 160 patients at risk for IUGR between 30 and 42 weeks of pregnancy. Fetal weight was sonographically estimated from abdominal circumference and femur length or from the formula of Shepard et al.[36] An S/D ratio ≥ 3 demonstrated a sensitivity of 55%, a specificity of 92%, and a positive predictive value of 73%. Corresponding values for the sonographic weight estimation were 76%, 80%, and 58%, respectively. Clearly, although sonographic weight estimation offered a higher sensitivity, a greater diagnostic accuracy was obtained from the Doppler technique. Furthermore, the latter appeared to be capable of identifying IUGR at a significantly earlier stage of pregnancy than the sonographically recognizable manifestation of growth compromise. Obviously, further prospective studies are needed to resolve this controversy regarding the efficacy of Doppler velocimetry of the umbilical artery as a predictor of IUGR. In any such investigations, care should be taken to distinguish between the infants who are constitutionally small but otherwise normal and those who are deprived in utero. Furthermore, Doppler velocimetry and sonographic anthropometry should not be regarded as mutually exclusive investigative tools for assessing IUGR. As mentioned previously, preliminary results indicate that a combined protocol using the two modalities may prove to extend our diagnostic capability.

Umbilical Arterial Velocimetry as a Fetal Surveillance Tool

Cumulative experience indicates that the Doppler indices can be powerful predictors of fetal compromise. Several preliminary studies have compared fetal heart-rate monitoring techniques with the umbilical arterial Doppler velocimetry. Trudinger et al.[37] compared umbilical arterial A/B ratio with fetal heart-rate assessment based on reactivity and a modified Fischer score in 170 high-risk patients. A birth weight below the 10th percentile or an Apgar score less than 7 at 5 minutes were considered the indicators of fetal compromise. The Doppler technique demonstrated a sensitivity of 60%, a specificity of 85%, a positive predictive value of 64%, and a negative predictive value of 83%. The corresponding values for the two techniques of fetal heart-rate assessment were 17% and 36%, 97% and 88%, 69% and 58%, and 72% and 75%, respectively. The authors also noted that an abnormal A/B ratio preceded any abnormalities in the fetal heart rate in these patients. Farmakides et al.[38] compared the nonstress test (NST) with the umbilical arterial S/D ratio in 140 women. In the circumstance where both the tests were abnormal, 50% of fetuses were growth regarded, 62.5% demonstrated fetal distress, 75% needed cesarean section for fetal distress, and 63% of patients were admitted to the neonatal intensive care unit (NICU). In comparison, in fetuses with an abnormal NST but normal S/D ratio and a normal NST

with an abnormal S/D ratio, 2% and 19% were SGA, 32% and 35% demonstrated fetal distress, 32% and 28% needed cesarean deliveries, and 7% and 29% were admitted to the NICU, respectively. Other investigators observed similar prognostication of an adverse outcome when the S/D ratio was abnormal.[39,40]

One feature of the umbilical arterial Doppler waveform that has been associated with a remarkably poor perinatal outcome is the absent or reversed end-diastolic flow.[41,42] Various investigators have shown that absent or reversed end-diastolic flow in the umbilical artery (Fig. 1.3) is associated with very high perinatal mortality (50% to 88%) and with fetal anomalies including lethal chromosomal aberrations such as trisomy 18. It should be reemphasized that the high-pass filter should be discontinued or used at the lowest setting to avoid any erroneous diagnosis of this condition.

In spite of these encouraging reports, the transformation of Doppler velocimetry into the standard of practice depends on the demonstration that its use in perinatal management improves the outcome. There has been a paucity of studies of such nature. So far, only one randomized controlled trial involving umbilical arterial Doppler has been reported.[43] In this study involving 300 patients at high risk for fetal compromise, the control group demonstrated a higher incidence of fetal distress in labor, a more frequent rate of emergency cesarean sections, and longer stays in the NICU. The study did not clarify how the Doppler information was integrated in the management protocol. Furthermore, the number of patients was insufficient to demonstrate other relevant aspects of clinical efficacy. Nevertheless, this pioneering study did indicate that Doppler velocimetry may improve obstetric management. Obviously, further similar expanded studies are needed to define the clinical usefulness of this technique.

Umbilical Arterial Velocimetry in Miscellaneous Complications of Pregnancy

One of the remarkable findings in relation to the umbilical arterial Doppler ultrasound is the high incidence of abnormal waveforms in fetuses with congenital malformations. Trudinger and Cook[44] reported a 50% (13 of 26) incidence of high umbilical arterial S/D ratio in fetuses with major anomalies. Most of these fetuses had a birth weight above the 10th percentile. Furthermore, the incidence of chromosomal aberrations was much higher in the group with abnormal waveform. Hsieh et al.[45] noted absent or reversed end-diastolic flow in umbilical arterial Doppler waveform in eight fetuses with major anomalies. All the fetuses died in utero. Many other investigators have noted similar findings. Such malformations seem to be associated with profound alterations in the fetoplacental circulatory system.

Several workers have used Doppler velocimetry in investigating umbilical arterial hemodynamics in twin gestation. Giles et al.[46] observed that in 33 out of 65 twin pregnancies, one or both twins were SGA; in these SGA infants, the A/B ratio was increased in at least one twin. In this study, continuous-wave Doppler

was used. Farmakides et al.[47] investigated umbilical arterial S/D ratio using continuous-wave Doppler in 43 twin gestations. They noted that an S/D ratio difference between fetuses averaging 0.4 or more was predictive of a weight difference greater than 349 g, with a sensitivity of 73% and a specificity of 82%. Using pulsed Doppler ultrasound, Nimrod et al.[48] observed in 30 twin pregnancies that the sensitivity and specificity of the umbilical arterial S/D ratio were 50% and 82%, respectively. In comparison, the sonographic estimation of the biparietal diameter and abdominal circumference differential demonstrated a sensitivity and specificity of 45% and 84%, and 22% and 74%, respectively.

The utility of umbilical arterial S/D ratio has been investigated by Bracero et al.[49] in 43 diabetic pregnancies. They noted a significant positive correlation between the Doppler index and serum glucose level ($P < .001$). The study also suggested an increased risk of stillbirths and neonatal morbidity in diabetic pregnancies with elevated S/D ratios. In a preliminary report, Landon et al.[50] observed a significant negative correlation between birth weight and mean third-trimester S/D ratio and no correlation between the mean second- or third-trimester S/D ratio and the glycosylated hemoglobin. The authors also noted that in patients with class F and R diabetes or chronic hypertension, early Doppler investigation showed the potential of identifying fetuses at high risk. These studies demonstrate the potential utility of Doppler velocimetry in managing diabetic pregnancies. Further investigations, however, are needed to define this utility.

Conclusion

This chapter briefly reviewed the role of Doppler velocimetry in perinatal practice with special emphasis on its application for assessing umbilical hemodynamics in managing certain categories of high-risk pregnancy. Obviously, not all the potential perinatal applications can be covered in a review of this nature. Cumulative experience demonstrates that the umbilical arterial Doppler velocimetry represents a significant advance in fetal investigation. Caution must be exercised, however, in introducing the use of this technique as a generic standard of practice. Although a preliminary randomized trial with a limited number of patients demonstrated the clinical efficacy of umbilical arterial S/D ratio,[43] further prospective randomized investigation is needed to clarify the various factors that contribute to the observed changes in the indices and to define the role of the indices in the obstetric decision-making process and intervention and in improving the perinatal outcome.

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2
Doppler Echocardiography of the Human Fetus: A Review

DEV MAULIK, NAVIN C. NANDA, CURTIS L. LOWERY, AND JAMES P. YOUNGBLOOD

Advances in Doppler ultrasound technology have immensely changed the practice of medical imaging in recent years. This is particularly noticeable in noninvasive cardiologic diagnosis, for which the rapidly developing technique of Doppler echocardiography has proved extremely useful. The technologic advances essential for this development include the following:

1. Two-dimensional (2-D) echocardiography-directed pulsed wave (PW) Doppler echocardiography: The PW Doppler echocardiography can measure blood-flow velocity bidirectionally in specific intracardiac locations and outflow tracts. This capability of assessing normal and abnormal cardiac hemodynamics has enhanced the diagnostic efficacy of the 2-D and M-mode echocardiographic methods.

2. Two-dimensional Doppler color-flow mapping (DCFM), in which color-coded flow patterns are superimposed on images of the anatomic structures: Recently, the DCFM technique, by depicting color-coded flow distribution in cardiac chambers and great vessels, has significantly enhanced our ability to investigate cardiac circulatory dynamics.

Current literature illustrates the clinical applications and confirms the utility of these techniques in cardiologic practice.[1-3] More recently, Doppler ultrasound has been successfully applied for studying cardiac hemodynamics in the human fetus.[4-6] The importance of this development can be appreciated from the fact that, until recently, fetal cardiovascular investigation has been limited to real-time 2-D ultrasound and fetal heart-rate–monitoring techniques. Obviously, the introduction of Doppler echocardiography has significantly supplemented the existing techniques for fetal cardiac assessment. In this chapter, we present a brief review of the applications of PW Doppler echocardiography and 2-D DCFM in the human fetus.

Methods

Pulsed-Wave Doppler Echocardiography

In 1984, Maulik et al.[4] were the first to describe the procedure for fetal pulsed Doppler echocardiography and reported the measurement of right ventricular output. Since then, several reports have elaborated on the assessment of flow-velocity characteristics in the various cardiac chambers and outflow tracts.[5-10] In this chap-

ter, we present a brief description of the method. The essential instrumental requirement consists of a duplex Doppler ultrasound system. The latter is composed of a single-transducer assembly incorporating the 2-D real-time cardiac-imaging capability along with the PW Doppler mode. This allows determining the target location and collecting Doppler shift information from this location. Initially, a general imaging scan of the fetus is performed, during which fetal orientation is determined, and the fetal heart is located. A detailed, 2-D echocardiographic imaging is then performed to identify various components of fetal cardiac anatomy, including the atrial and ventricular chambers, valvular orifices, and outflow tracts. During this examination, standard echocardiographic planes are used whenever possible. Frequently, however, it is necessary to employ modified echocardiographic planes when fetal orientation may not allow the use of standard planes. Once a detailed anatomic examination of the heart has been performed, the Doppler cursor is moved across the 2-D cardiac image, and the Doppler sample volume (DSV) is then placed at the desired intracardiac or outflow locations. The Doppler sample volume is the teardrop-shaped three-dimensional area in the ultrasound beam path from which Doppler frequency shift signals are obtained by range gating. This is achieved at this point by changing the ultrasound mode from the 2-D imaging to the PW Doppler. Fine manipulations of the transducer in a systematic manner allow imaging of the various components of fetal cardiac anatomy, and Doppler signals are obtained from the desired intracardiac or intravascular target area. As the fetus moves, it is necessary to verify repeatedly the location of the DSV. This is achieved by frequently switching between the Doppler and the 2-D imaging modes. Certain current ultrasound devices with mechanical sector scanning transducers aid this procedure by automatically showing the DSV location in a 2-D image displayed in an inset on the screen at predetermined intervals. Alternative approaches include electronic array transducers, which can perform simultaneous imaging and Doppler interrogation. (This is achieved in numerous ways—a detailed discussion of which is beyond the scope of this review.) To select the optimal transducer frequency, a balance must be reached between the quality of resolution, which is favored by a higher transducer frequency, and the depth of penetration, which is favored by a lower frequency. For fetal scanning, we recommend the use of a 3-MHz transducer, as this offers the desired trade-off between the depth of penetration and an adequate image resolution. In some circumstances when the fetal heart is superficially located because of favorable fetal location, a 5-MHz transducer may be used, thus offering a higher resolution.

Finally, in selecting duplex devices for fetal usage, caution should be exercised regarding the acoustic energy output consistent with the biosafety recommendations developed by the Center for Devices and Radiological Health of the FDA[11] and the American Institute of Ultrasound in Medicine.[12]

Doppler Color Echocardiography

The introduction of DCFM-based echocardiographic technique represents one of the major advances in noninvasive cardiac diagnosis.[13,14] The system essentially is based on a multigated, multisample, pulsed, Doppler-phased array-transducer

system. This technique consists of Doppler-phase or angular frequency-shift analyses and uses signal-processing techniques called *autocorrelation* and *moving target indicator.* Autocorrelation multiplies the direct quadrature output signals by the time-delayed output signals and integrates this output over time to produce the mean frequency shift and variance information from the scan plane. The moving target indicator acts as a filter for the autocorrelator and eliminates the high-amplitude and low-velocity signals from slow-moving targets such as vessel walls. To express the direction, velocity magnitude, and variance of blood flow, the Doppler information is color coded and is spatially superimposed on grey-scale, 2-D echo image or M-mode format. Usually, the flow toward the transducer is displayed in red and the flow away, in blue. The brightness reflects the magnitude of the detected velocity. Green is added to the blue or red to the degree that flow is turbulent or variant. If the mean angular frequency exceeds the Nyquist Limit (+/− 180°), the color changes to that of the opposite flow direction, producing the phenomenon of color aliasing, similar to the aliasing phenomenon in pulsed Doppler. The image is displayed on a video screen. Recently, fetal cardiac hemodynamics have been imaged using the DCFM technique.[15]

Doppler Depiction of Fetal Atrial Hemodynamics

Pulsed Doppler

Atrial flow characterization by the PW Doppler ultrasound demonstrates turbulent flow velocity patterns in both the RA and the LA (Fig. 2.1). Maulik et al.[4] were the first to describe atrial velocity dynamics. They reported that the foramen ovale valve movement was associated with the changes in the Doppler frequency shift in the LA; they observed a higher frequency shift when the valve was open compared to when the valve was closed. They also noted higher Doppler frequency shifts in the right atrium (RA) than the left atrium (LA). Because the RA dimensions appeared greater than those of the LA, Maulik et al. speculated that the higher Doppler frequency shift in the RA possibly reflected a higher volumetric flow in the RA. Obviously, in order to convert the frequency shift data into volumetric flow, one must measure the atrial outflow dimensions and the angle of insonation. It is noteworthy that subsequent pulsed Doppler investigations on atrio-ventricular volumetric flow have demonstrated a larger outflow from the RA into RV across the tricuspid orifice than from the LA into LV across the mitral orifice.

Color Doppler

Doppler flow mapping of atrial circulatory dynamics using a DCFM duplex system offers an impressive depiction of the atrial flow. As illustrated in Figure 2.2A,B (See Color Plate I), the flow returning from the inferior vena cava into the atria can be clearly visualized. As evident, the returning stream divides into

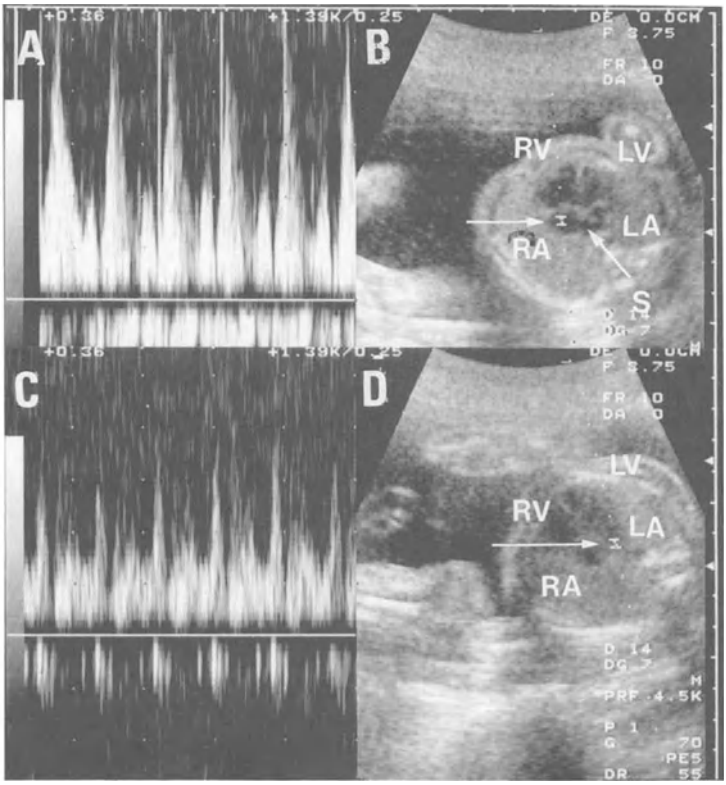


FIGURE 2.1. (A,B): Doppler characterization of right atrial flow in a normal fetus. S indicates the location of the fetal spine. The upper right panel (B) shows the two-dimensional echocardiogram of the right and the left atria (RA,LA) with the foramen ovale demonstrated (oblique arrow) as an echo-free space in the middle of the interatrial septum. The Doppler sample volume, indicated by two short parallel lines next to the horizontal arrow, is located in the right atrial cavity. The right and left ventricles (RV,LV) are also visualized. The Doppler tracings (left panel, A), obtained from the right atrium, demonstrate phasic and turbulent flow patterns with relatively high-magnitude frequency shifts. Panels (C,D): Doppler characterization of left atrial flow in a normal fetus. The two-dimensional echocardiogram (right panel, D) shows the position of the Doppler sample volume (two short parallel lines, horizontal arrow) in the LA. The oblique arrow points to the valve of foramen ovale. The Doppler tracing (left panel, C) shows phasic flow patterns with complex turbulent flow velocity dynamics. Note also the relatively lower magnitude of the Doppler frequency shifts obtained from the LA compared with those from the RA.

two flow components: (1) the larger flow component swirls toward the RA and right ventricle (RV) along the eustachian valve; (2) the smaller flow component enters into the LA through the foramen ovale. Using DCFM technique, the superior vena caval flow entering the RA can be visualized separately from the inferior vena caval return. Eventually, this flow becomes confluent with the inferior vena caval flow jet in the RA cavity.

The Doppler flow characteristics of the atria previously described here conform with the known fetal atrial blood flow patterns as observed during acute radioangiographic studies conducted in previable human fetuses.[16] They are also consistent with the studies involving fetal sheep preparations.[17] These investigations consistently demonstrated a greater flow volume in the RA than in the LA. The Doppler investigations confirmed the preceding experimental findings in the human fetus.

Doppler Depiction of Atrioventricular Hemodynamics

Pulsed Doppler

Flow dynamics across the tricuspid and mitral orifices have been investigated by several groups using the PW Doppler system. The Doppler waveform, thus derived, confirms the PW Doppler findings that the deflection resulting from the contraction of the RA (A wave) is greater than the initial RV inflow deflection resulting from diastole (E wave) (Fig. 2.3A). In the LV, however, the A wave was equal to or only minimally greater than the E wave (Fig. 2.3B). These findings suggest a physiologically lower compliance of the RV in comparison with the LV and are similar to the pulse Doppler echocardiographic observations made in neonates and infants. Takahashi et al.[6] investigated mitral and tricuspid flows using pulsed Doppler and noted (1) that the peak velocity across the mitral orifice was 52.1 +/− 9.9 cm/s (mean +/− standard deviation [SD]), and the peak velocity across the tricuspid orifice was 56.1 +/− 8.7 cm/s (mean +/− SD) and (2) that the velocity patterns of the RV and LV inflow demonstrated two peaks consistent with the rapid filling phase and the atrial contraction phase. Subsequently, Reed et al.[7] reported pulsed Doppler assessment of flow velocities through the tricuspid, mitral, pulmonary outflow, and aortic outflow areas. They reported the mean maximum velocities of 51 +/− 1.2 cm/s (mean +/− standard error [SE]) and 47 +/−1.1 cm/s (mean +/− SE) across the tricuspid and mitral orifices. Quantification of atrioventricular flow in fetuses of 26 to 30 weeks' gestational age showed a tricuspid flow rate of 307 milliliter (ml) +/− 30 kg/min and a mitral flow rate of 232 +/− 25 ml/kg/min. Hata et al.[9] used a duplex system, which allowed the use of both continuous-wave (CW) and PW Doppler systems. They noted that (1) the transmitral and transtricuspid maximum velocities increased progressively with the advance of gestational age and (2) the tricuspid/transmitral velocity ratios were approximately equal in most cases. The latter observation also has been confirmed by Huhta et al.[18]

Color Plates

Plate I

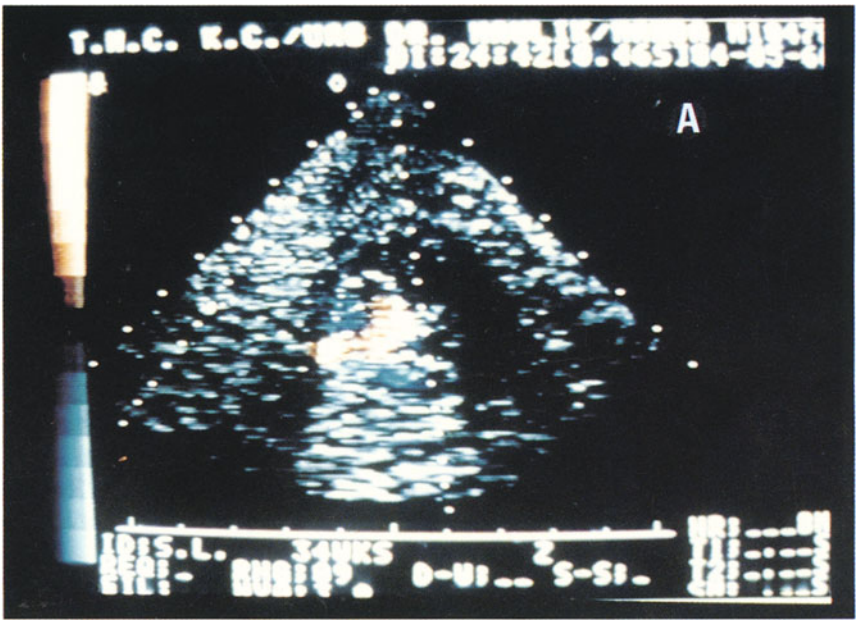


FIGURE 2.2. Fetal Doppler color-flow mapping. (A) Doppler echocardiogram; (B) schematics. Flow toward the transducer is colored red, away from it is blue. Aortic short-axis views; Inferior venal caval (IVC) flow is seen splitting into two components; the larger component is directed into the right atrium (RA) through the eustachian valve (EV), while a significantly smaller component is directed into the left atrium (LA) through the valve of foramen ovale (FOV). Some of the right atrial flow (near the lateral wall) is also seen swirling backward (colored blue). The high velocity produced by the large amount of flow moving through a relatively small vessel results in the inferior vena caval flow taking on a yellowish-white appearance. (AS, atrial septum; AV, aortic valve; MPA, main pulmonary artery; PV, pulmonary valve; RV, right ventricle; TV, tricuspid valve.) (*Source*: From *Angiology, The Journal of Vascular Diseases, Volume 37*:629–631, 1986. Reproduced with permission of the copyright owner; Westminster Publications, Inc., Roslyn, New York, U.S.A. All rights reserved.)

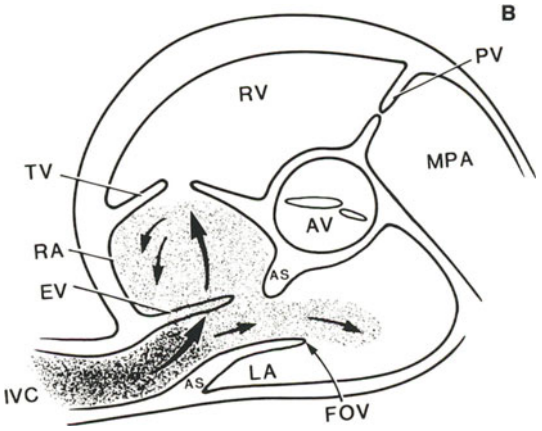


Plate II

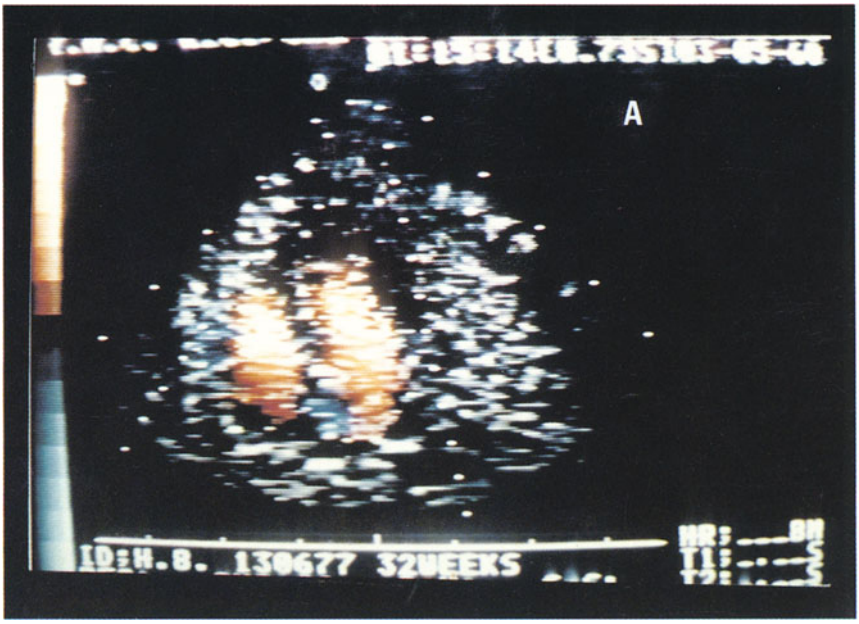


FIGURE 2.4. Fetal Doppler color-flow mapping. Red represents blood flow toward the transducer; blue away from it. (A, B) apical four-chamber view. The red-colored areas represent blood moving from the right atrium (RA) into the right ventricle (RV) and from the left atrium (LA) into the left ventricle (LV) during diastole. The blue-colored area represents blood flowing from the right atrium into the left atrium through the foramen ovale (FO). (MV, mitral valve; TV, tricuspid valve.) (*Source*: From *Angiology, The Journal of Vascular Diseases*, Volume 37:629–631, 1986. Reproduced with permission of the copyright owner; Westminster Publications, Inc., Roslyn, New York, U.S.A. All rights reserved.)

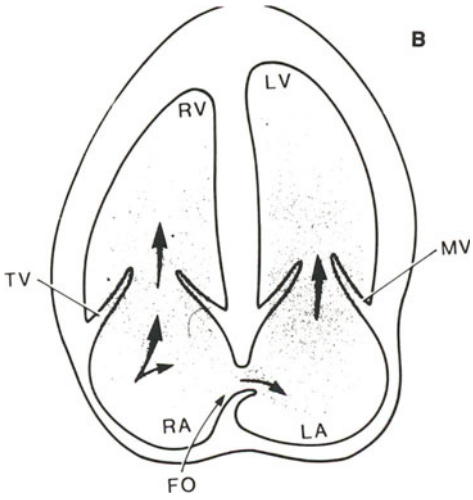


Plate III

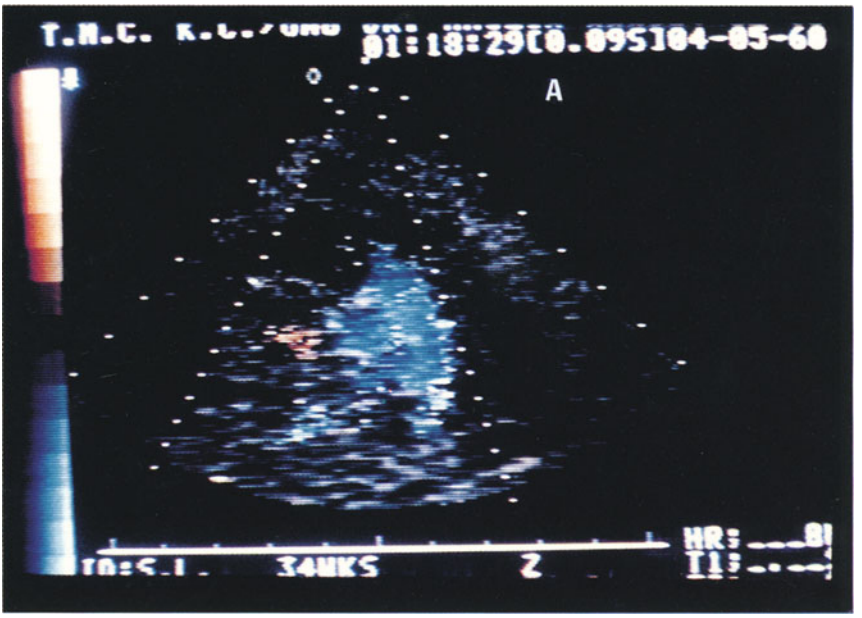
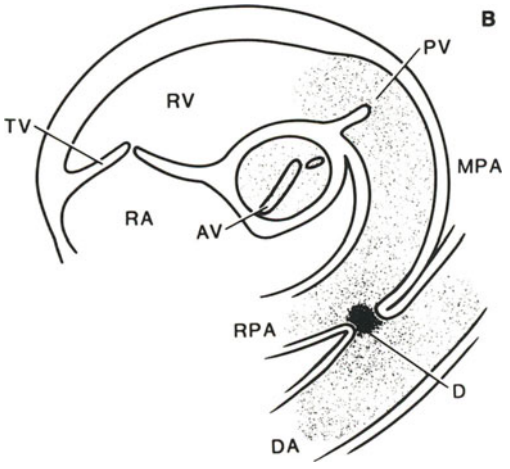


FIGURE 2.7. Fetal Doppler color-flow mapping. (A) Doppler echocardiogram; (B) schematics. Flow toward the transducers is colored red; away from it is blue. Aortic short-axis view ductus arteriosus (D) is identified as a red-colored area between the main pulmonary artery (MPA) and the descending aorta (DA). The red color results from aliasing produced by turbulent flow in the ductus. Note that aortic root and MPA lumens are completely filled with blood flow (blue color). (AV, aortic valve; PV, pulmonary valve; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; TV, tricuspid valve.) (*Source*: From *Angiology, The Journal of Vascular Diseases* Volume 37:629–631, 1986. Reproduced with permission of the copyright owner; Westminster Publications, Inc., Roslyn, New York, U.S.A. All rights reserved.)



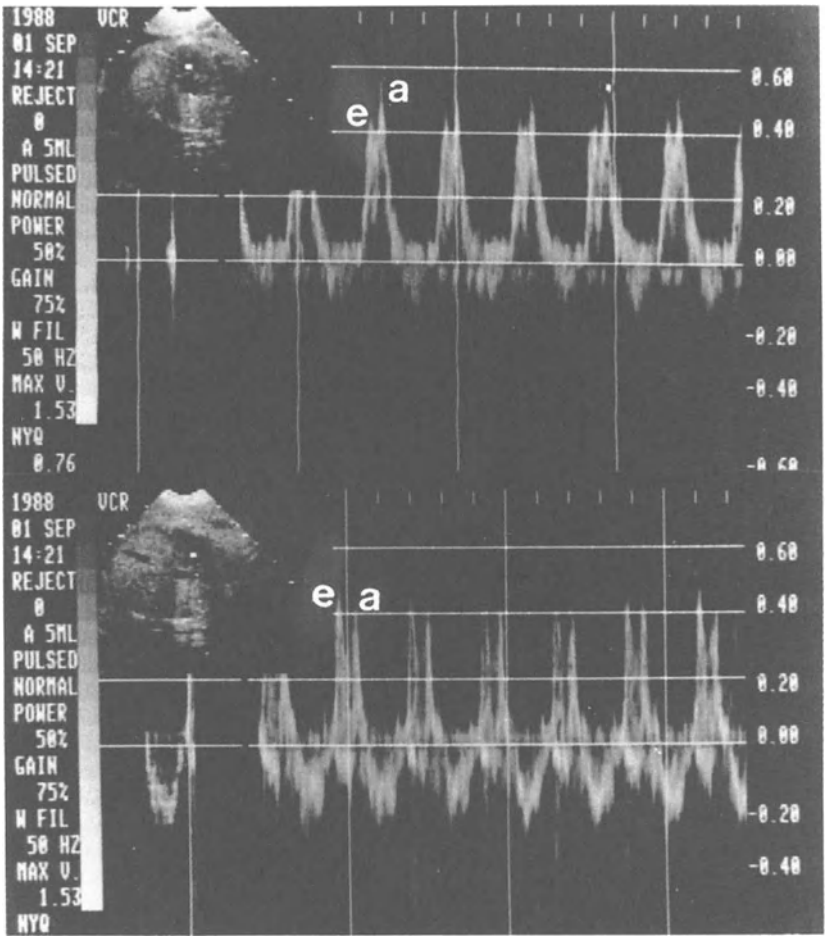


FIGURE 2.3. Doppler echocardiography of the atrioventricular waveform. (A) The right ventricular Doppler waveform. (B) The Doppler waveform from the left ventricle. A indicates flow velocity due to atrial systole; E indicates initial ventricular inflow deflection.

Color Doppler

Although the PW duplex Doppler system allows measurement of Doppler signals across these orifices, color-flow technique vividly portrays the flow patterns across these atrial ventricular flow channels (Fig. 2.4 A,B). (See Color Plate II). Furthermore, color Doppler also facilitates acquisition of the Doppler signals from the different areas of the atrioventricular flow jets. It also allows a more refined alignment with the flow axis, resulting in more confident recordings of the Doppler waveforms.

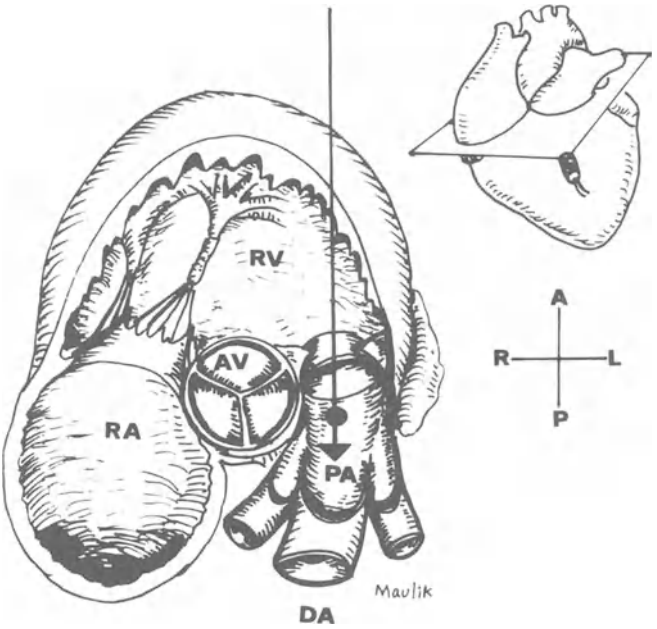


FIGURE 2.5. Schematic of aortic short-axis plane showing placement of the Doppler cursor line parallel to the walls of the main pulmonary artery (PA) to obtain maximal Doppler frequency shifts. (RA, right atrium; AV, aortic valve; RV, right ventricle; DA, ductus arteriosus. Orientation symbols: A, anterior; L, left; P, posterior; R, right.) (*Source*: with permission from Maulik D, Nanda NC, Perry, GJ. Application of Doppler echocardiography in the fetus. In: Maulik D, McNellis D, eds. *Doppler Ultrasound Measurement of Maternal–Fetal Hemodynamics*. Ithaca, NY: Perinatology Press; 1987. p 167–184; and Maulik D, Nanda NC, Saini VD. Fetal Doppler echocardiography: methods and characterization of normal and abnormal hemodynamics. *Am J Cardiol*. 1984;53:572–578.)

Doppler Depiction of Ventricular Outflow

Pulmonic Outflow

PW Doppler

The right ventricular outflow into the main pulmonary artery (MPA) is best imaged in the aortic short axis (Fig. 2.5), which allows visualization of the flow from the RA across the tricuspid orifice into the RV and then into the beginning of the MPA. The orientation of the MPA in this plane often facilitates alignment of the Doppler beam along the pulmonary blood flow axis; this minimizes any errors in estimating the maximum velocity (Fig. 2.5). Doppler frequency shift waveforms from the MPA are characterized by rapidly accelerating and decelerating slopes with sharp peaks during the right ventricular systole. Because electrocardiography cannot be performed reliably in the fetus, the phases of the cardiac cycle can be determined by the concurrent M-mode tracing of the pulmonary valve movement. The RV stroke output can be determined from the MPA

Doppler frequency shift data if the angle of insonation and the MPA cross-sectional area are also known. The first step is to determine the temporal mean velocity of the MPA blood flow. Assuming a flat velocity profile, pulmonary arterial blood-flow velocity can be calculated from Doppler frequency shift signals by using the Doppler equation:

$$v = f_d \times c/2fc \times cos\phi$$

where v represents the velocity of flow, f_d the Doppler frequency shift, fc the transducer frequency, ϕ the angle of insonation, and c the velocity of sound in tissue. Once the instantaneous flow velocity is determined, the stroke volume is obtained from the temporal mean of the peak velocity during one cardiac cycle; and integrating this value, the cross-sectional area of the pulmonary artery is determined. The latter is calculated from the diameter and constitutes one of the major sources of error as the radius is squared to obtain the area. The RV output is then obtained by multiplying the stroke volume by the fetal heart rate. The determination of RV stroke volume is depicted in Figure 2.6.

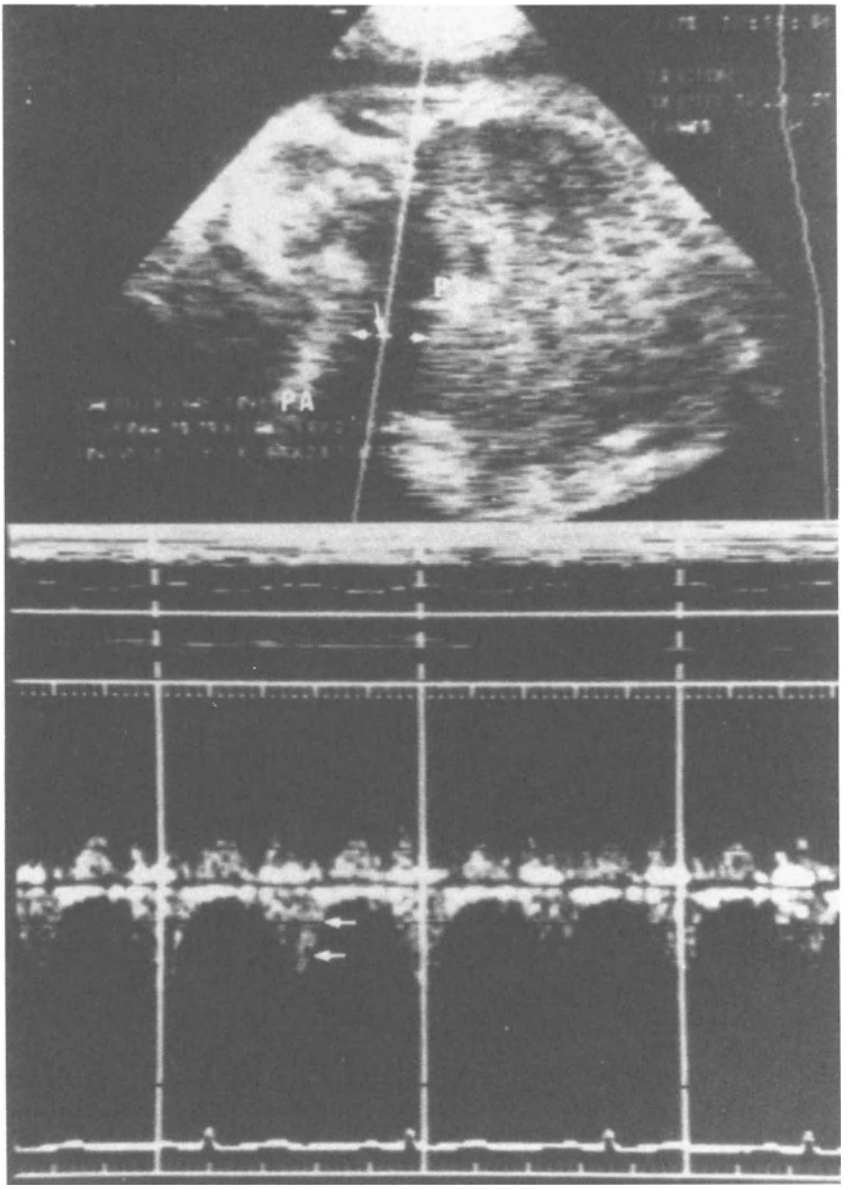
Color Doppler

Imaging of flow by DCFM in the MPA produces a graphic depiction of the pulmonic flow entering into the descending thoracic aorta via the ductus arteriosus (Fig. 2.7A,B). (See Color Plate III). Furthermore, with transducer manipulation and angling, it is also possible to observe the distribution of MPA flow into the right and left pulmonary arteries. With the color Doppler imaging, the flow in the ductus often appears to be of higher intensity; this is because of the greater velocity of ductal flow. In our experience, color Doppler assists in quickly identifying the appropriate echocardiographic plane and in confidently aligning the Doppler beam along the direction of pulmonary flow.

Aortic Outflow

PW Doppler

The PW Doppler duplex system permits measurement of Doppler frequency shift signals from the ascending aorta, aortic arch, and descending thoracic aorta. As described in the previous section dealing with the pulmonic outflow measurement, initially, these vascular locations are imaged using appropriate echocardiographic planes (Fig. 2.8). The cursor line representing the path of the Doppler beam is then placed parallel to the expected direction of aortic flow. As depicted in Figure 2.9, aortic Doppler waveforms show steep systolic and diastolic slopes with sharp peaks; these features are more pronounced in the ascending aortic flow than in the pulmonary flow. Furthermore, when the Doppler beam is parallel to the flow axis with a zero angle of insonation, the flow in the ascending aorta demonstrates a flat velocity profile. Once the aortic Doppler frequency shifts are determined, the LV stroke volume and cardiac output are calculated following the procedure previously described for the RV outflow.


PA

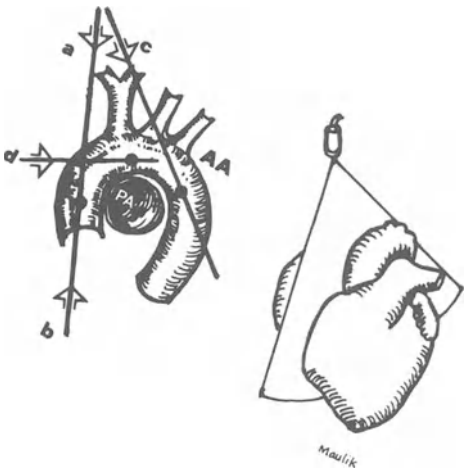


FIGURE 2.8. Schematics showing Doppler interrogation of aortic outflow. (AA, aortic arch; PA, pulmonary artery; a, b, c, d, various placements of the Doppler beam.) Right panel demonstrates the two-dimensional echocardiographic plane for Doppler placements a and c. (*Source*: Reprinted with permission from Maulik D, Nanda NC, Perry, GJ. Application of Doppler echocardiography in the human fetus. In: Maulik D, McNellis D, eds. *Doppler Ultrasound Measurement of Maternal–Fetal Hemodynamics*. Ithaca, NY: Perinatology Press; 1987.)

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FIGURE 2.6. Doppler characterization of pulmonary artery (PA) flow and measurement of right ventricular stroke volume in a normal fetus. (A) the Doppler sample volume, indicated by a short transverse bar (oblique arrow) was placed along an M-line cursor in the midlumen of the PA imaged by two-dimensional echocardiography. Maximal inner PA diameter (d) horizontal arrows) at the level of the Doppler sample volume measured 0.9 cm. The cross-sectional area at this level was calculated as 0.636 cm^2 ($3.14d^2/4$). (PV, pulmonary valve.) (B) the Doppler frequency shifts (D) obtained from the PA. Deflection above the baseline (B) represents flow toward the transducer, and deflection below the baseline denotes flow away from the transducer. As would be expected, the predominant flow is directed away from the transducer toward the distal PA and is characterized by sharp peaks with rapidly accelerating and decelerating slopes. The maximal area under the flow curve for one cardiac cycle was measured in kHz/s (vertical distance between the two horizontal arrows = 0.5 kHz) and converted into maximal velocity curve area (s-cm/s) (A) using the instrument calibration factor $K = 25.667$ cm/s-kHz. Multiplying A by the PA cross-sectional area gave the stroke volume of 3.76 mL. Cardiac output was then calculated by multiplying the stroke volume by the fetal heart rate. The vertical lines represent 2-s time markers. (M, M-mode tracing; E, maternal electrocardiogram.) (*Source*: Reprinted with permission from Maulik D, Nanda NC, Moodley S, Saini VD. Fetal Doppler echocardiography: methods and characterization of norma and abnormal hemodynamics. *Am J Cardiol*. 1984;53:572.

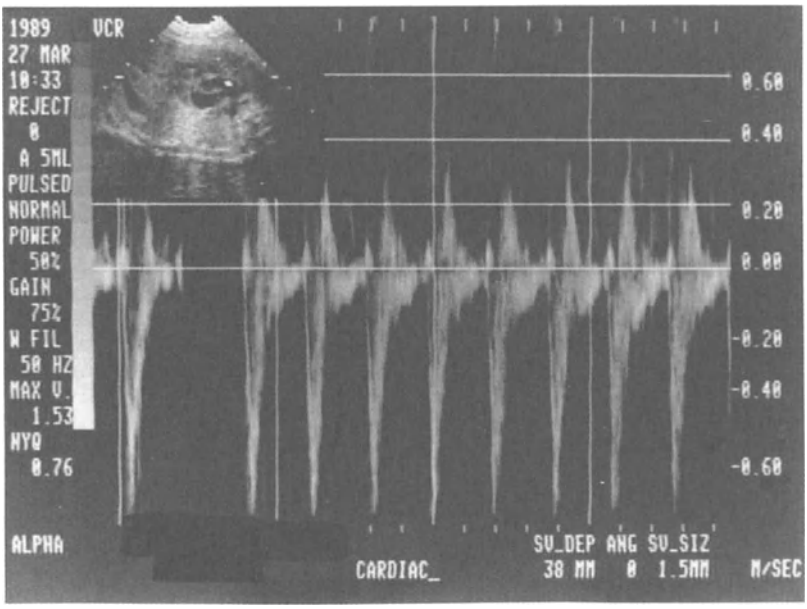

FIGURE 2.9. Doppler frequency shift waveforms from the ascending aorta. Note the steep slopes and the sharp peak of the waveform.

Color Doppler

Consistent with the preceding experience, DCFM visualization of flow patterns superimposed on 2-D echocardiographic images of the cardiac anatomy significantly facilitates rapid identification of the aortic outflow. Furthermore, it also enhances pulmonary outflows, especially in the same patient, and allows accurate placement of the Doppler beam along the direction of flow. Using this technique, it is possible to reduce the angle of beam incidence almost to zero in both the pulmonary and aortic outflow tracts in the same patient in most cases (90%). Obviously, such an alignment of the Doppler beam significantly contributes toward accuracy of volumetric measurement. Significant errors, however, can be made in volumetric measurement when estimating vessel cross-sectional area and the angle of incidence of the Doppler beam; these will lead to a greater error in the volumetric flow results. This limits the utility of absolute flow-rate data. Assessment of relative flow changes is less prone to such limitations. Our investigations indicate that in the human fetus the RV output is greater than the LV output. Recently, this observation has been further confirmed by DeSmedt and co-workers,[19] who also noted that this RV dominance decreased as the pregnancy approached term. An essential feature of fetal circulation is the parallel functioning of both the ventricles so that the cardiac output in a fetus is the combined ventricular output. In sheep fetuses, the RV contributes two thirds and the left, only one third of the combined output.[15]

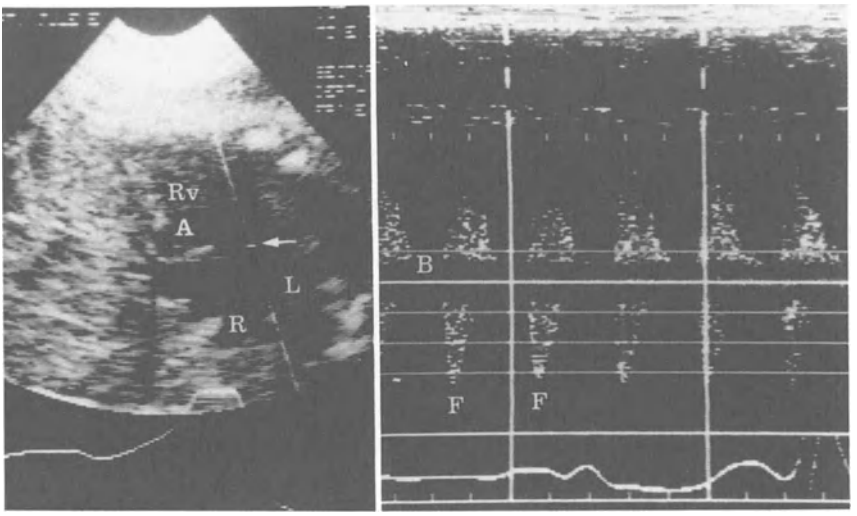

FIGURE 2.10. Fetal Doppler echocardiographic examination in tetralogy of Fallot and aneurysmal dilatation of the main pulmonary artery. The large echo-free space present on the left of the aorta on real-time two-dimensional examination (A) was demonstrated by pulsed Doppler to be vascular in nature, because pulsatile flow (B) similar to that obtained in the pulmonary artery could be demonstrated within it (B). This Doppler finding helped us make a confident diagnosis of aneurysmal dilatation of the main pulmonary artery. The arrow denotes the location of the Doppler sample volume. (A, aorta; B, Doppler baseline; F, Doppler waveforms; L, left branch of the pulmonary artery; R, right branch of the pulmonary artery; RV, right ventricle.) (*Source*: Reprinted with permission from Maulik D, Nanda NC, Saini VD, Thiede HA. Application of Doppler echocardiography in the assessment of fetal cardiac disease. *Am J Obstet Gynecol.* 1985;151:951–956.)

Doppler Echocardiographic Assessment of Abnormal Hemodynamics

The utility of Doppler echocardiography as a diagnostic tool is well established in cardiologic practice, where it constitutes a major component of noninvasive cardiac diagnoses. In fetal applications, the potential of the technique in supplementing M-mode and 2-D echocardiographic diagnosis of fetal cardiac disorders has been demonstrated. For example, the Doppler demonstration of a pulsatile flow in a large echolucent space in the vicinity of the MPA suggested the diagnosis of congenital aneurysm of the MPA, which was confirmed postnatally[5] (Fig. 2.10). Similarly, Doppler study can substantially assist 2-D echocardiography in defining other congenital cardiac malformations such as tetralogy of Fallot, transposition of great vessels, and ventricular hypoplasia. Surprisingly, anomalous hemodynamic patterns also have been noted, even in the absence of any sonographically recognizable structural abnormalities. This is exemplified in

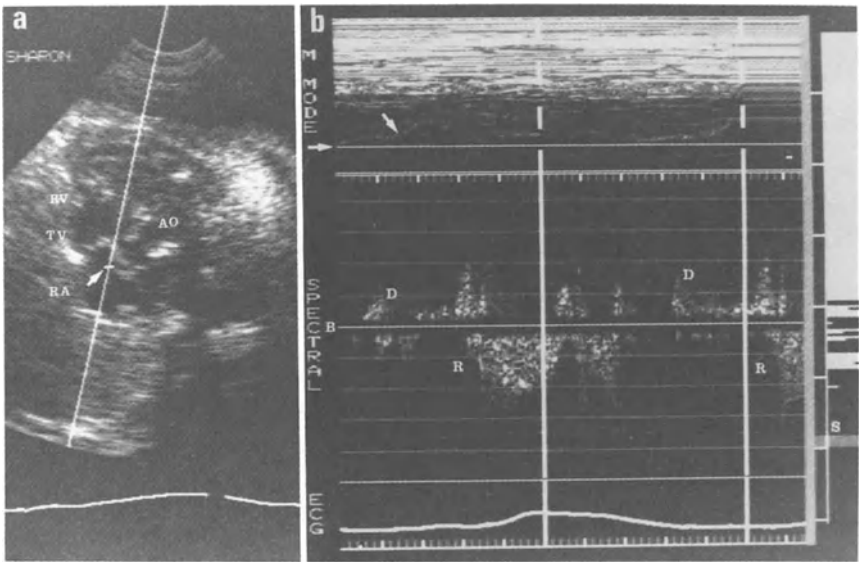

FIGURE 2.11. Doppler identification of tricuspid regurgitation in a fetus with complete heart block and heart failure. (A) The Doppler sample volume (oblique arrow) was placed in the right atrium (RA) imaged in the aortic (AO) short-axis plane. (B) The Doppler tracing showed prominent reversed flow (R) during systole indicative of tricuspid incompetence. Normal flow patterns were seen during diastole (D). The M-mode echocardiogram (oblique arrow) was used to time the diastole and systolic phases of the fetal cardiac cycle. The horizontal arrow denotes the position of the Doppler sample volume on the M-mode. (B, Doppler baseline; TV, tricuspid valve.) (*Source*: Reprinted with permission from Maulik D, Nanda NC, Saini VD, Thiede HA. Application of Doppler echocardiography in the assessment of fetal cardiac disease. *Am J Obstet Gynecol.* 1985;151:951–956.)

Figure 2.11, a Doppler echocardiographic demonstration of tricuspid regurgitation in the presence of an anatomically normal tricuspid valve in a fetus with congenital heart block. We have also encountered examples of mild tricuspid regurgitation in the fetus without any demonstrable cardiac pathology. The significance of this phenomenon remains to be elucidated. In contrast, any significant tricuspid or mitral regurgitation is invariably associated with cardiac anomalies. In our initial report,[4] we noted that during an ectopic beat, RV stroke volume may be reduced by 60%. Subsequent investigations have substantially expanded the Doppler application in studying the hemodynamic effects of fetal cardiac arrythmia. Lingman and Marsal[20] observed that the systolic rising slope and peak value of the maximum aortic velocity were significantly increased in the first beat following the compensatory pause in fetuses with supraventricular extrasystole; this observation confirmed the Frank-Sterling phenomenon in the fetus and was later corroborated by Reed et al.[21]

Conclusion

Introduction of Doppler echocardiography has substantially expanded noninvasive investigation of central circulation of the human fetus. The procedure generates unique hemodynamic information on fetal cardiac activity, which supplements the diagnostic utility of the existing echocardiographic imaging techniques. In addition, the use of DCFM allows vivid depiction of fetal cardiac flow patterns in real time. Although both techniques have certain limitations, their clinical utility in diagnosing fetal cardiac pathology has already been demonstrated. As witnessed in pediatric and adult cardiologic practice, Doppler echocardiography has become a useful diagnostic modality in obstetrics, not only as a supplement to M-mode and 2-D echocardiography but also as a unique tool for obtaining central hemodynamic information in fetal health and disease. The technique requires considerable technical expertise. Thus, an adequately focused training is imperative in this field. As clinicians accumulate experience, a significant expansion of the application of fetal Doppler echocardiography is anticipated.

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3
Invasive Fetal Assessment by Fetal Blood Sampling

JOSHUA A. COPEL AND PETER A. GRANNUM

The development of the discipline of maternal–fetal medicine has been hampered by the lack of direct access to the fetus. With the development of high-resolution, real-time ultrasound, we have acquired a way to perform a "physical exam" of our fetal patients, but the idea of a modern internist or pediatrician making diagnoses or administering treatments without laboratory tests of patients is obviously untenable.

Recently, access to the fetal circulation has been obtained through fetal blood sampling. In the past, the only sources of fetal blood were either placentocentesis, which resulted in samples contaminated with maternal blood, or fetoscopy, which was hampered by a high rate of pregnancy loss. As discussed in this chapter, easy access to the fetal circulation has significantly altered the practice of perinatal medicine.

Fetoscopy

The earliest attempts to obtain fetal blood samples were through an operating fetoscope. This was a variation on a needlescope, having an approximate outer diameter of 1.7 mm, a great improvement over the original instruments used, which were substantially larger. The procedure required maternal sedation and local anesthesia; a stab wound was made in the maternal abdomen down through the fascia with a scalpel. Then a trocar and sheath were introduced, and the fetoscope replaced the trocar. The site for insertion in the maternal abdomen could be selected using ultrasound to avoid the placenta, but even with that method, fetoscopy carried a risk of pregnancy loss of 5% to 7%, depending on the operator. Blood samples were obtained by visualizing the cord and guiding a needle, 26- or 27-gauge advanced through a side port, into fetal vessels.[1]

Fetal Blood Sampling

Technical Considerations

Fetal blood sampling was initially developed in a few institutions[2-6] and more recently has been adopted by many perinatal centers.[7,8] It may be referred to by different terms, including *percutaneous umbilical blood sampling (PUBS)*, *cordocentesis*, or *funipuncture*.

Depending on personal operator preference, samples can be obtained using linear array or sector ultrasound guidance. A higher frequency transducer allows better resolution of the target and needle. Some operators use a needle guide, while others employ a "free-hand" technique. Most centers employ sterile techniques at least as stringent as those for amniocentesis (sterile gloves, antiseptic skin preparation, and sterile enclosure of the transducer); however, Nicolaides reported good results without wearing gloves during the procedure.[6] General adoption of universal precautions in the United States would require the use of gloves for any procedure involving exposure of medical personnel to blood.

Generally, we have found that the insertion of the cord into the placenta provides an immobile tether, making this the best site for cord puncture. Additionally, when the placenta is anterior, the cord can be reached without entering the amniotic fluid. Free loops of cord, the abdominal insertion of the cord, or even the intrahepatic umbilical vein[9] or cardiac puncture also have been used for sampling.[10]

For difficult procedures with posterior cords or for longer procedures such as fetal transfusions, fetal paralysis with a short-acting agent has been successfully used.[11-14] We have found that this is more helpful than maternal sedation for long procedures and that short sampling procedures can generally be accomplished without fetal or maternal medication. The optimal agent and route of administration are undetermined. Both intramuscular and intravenous routes have been proposed.[12,13] Curare was first used by de Crespingy,[11] but a smaller volume of drug can be used if pancuronium is substituted. Bernstein et al.[14] have proposed that atracurium is preferred, because it is not metabolized in the liver. This is particularly an issue in isoimmunized fetuses, as a result of possible compromise of hepatic function; if emergent delivery is required, prolonged paralysis might occur. Should that occur in a paralyzed fetus, clear communication with the neonatal team would, of course, be necessary to ensure adequate respiratory support until the agent wore off.

After the sample is obtained, testing to ensure its fetal origin must be performed. Generally, fetal red cells are larger than maternal, and a comparison of the mean corpuscular volume from an automated cell counter will give a general indication of origin, although not the purity of the sample. A Kleihauer-Betke stain will give a quantitative assessment, although near term, the fetal cells start to contain significant amounts of adult hemoglobin, which may lead to apparent "mixing" on the Kleihauer-Betke. Recently, the use of serum containing high titers to the i antigen, found only on adult cells, has been proposed to identify fetal samples. This test is easily and rapidly performed at the bedside.[15]

In contrast with the previously described complications resulting from fetoscopy, the loss rate encountered with PUBS has been reported to be as low as 0.5% per procedure.[4] Interpretation of statistics reported in the literature requires consideration of the indications for the procedure in any series. If a large number of anomalous fetuses or severely growth-retarded fetuses are included, the indications for the procedure itself may be the cause of reported losses.

Finally, it is important to note that fetal blood sampling is an invasive procedure and that in the Rhesus (Rh)-negative woman it may result in Rh sensitization. If fetal blood is obtained from an Rh-negative woman for any reason other than known sensitization, it is probably worthwhile to remove a sufficient sample to determine the fetal blood type. If the fetus is also Rh negative, the patient will not need prophylaxis with Rh-immunoglobulin, while if the fetus is Rh positive, prophylaxis will be necessary. In any failed procedure, it is best to assume that the fetus is positive and give the mother Rh-immunoglobulin.

Indications

In the second trimester, fetal blood sampling can be used to aid in the establishment of a variety of diagnoses. Table 3.1 illustrates a number of heritable conditions reported in the literature and in our own experience for which fetal blood sampling could be useful in establishing prenatal diagnosis.

Fetal Karyotypes

Fetal blood can be used to obtain a karyotype in a relatively brief period of time (72 hours) for situations for which anomalies are diagnosed close to the legal limit for pregnancy termination. Rapid fetal karyotype also is desired when an anomaly is found either close to term or when polyhydramnios and threatened preterm labor (uterine irritability) are observed. In selected situations, transabdominal chorionic villus sampling (CVS) may be technically easier or otherwise preferred. If critical times for obstetric decision making are not imminent, amniocentesis generally will provide the same information, albeit more slowly.

Careful consideration must be given to the indication for obtaining the karyotype to interpret the results properly. The karyotype obtained from blood will reflect only that present in the lymphocytes. If a mosaic pattern is obtained from amniocentesis, the fetal blood will reflect only the karyotype of cell lines present in lymphocytes, and a true mosaic pattern in other tissues might not be detected.

Fetal Hematology

The most obvious application of fetal blood sampling in prenatal diagnosis is in the detection of abnormalities of the cellular and chemical elements of blood itself. Knowledge of fetal physiology is required to determine the approaches and timing of fetal sampling, because some metabolic abnormalities may not be identifiable by this approach if relevant marker substances are freely transferred across the placenta (e.g., immunoglobulin G [IgG], which in the fetus is derived

TABLE 3.1. Congenital conditions diagnosable via fetal blood sampling.

Karyotype
Fetal anomaly
Fragile X syndrome
Amniotic fluid mosaicism
Immune deficiencies
Severe combined immune deficiency
Adenosine deaminase deficiency
Other forms
Chronic granulomatous disease
Coagulopathies
Factor deficiencies
Von Willebrand syndrome
Platelet disorders
Isoimmune (idiopathic) thrombocytopenic purpura
Alloimmune thrombocytopenic purpura
Wiscott-Aldrich syndrome
Hemoglobinopathies
Sickle cell anemia
Thalassemia
Alpha
Beta
Viral infections
Toxoplasmosis
Rubella
Varicella
Cytomegalovirus
Parvovirus (fifth disease)
Enzyme deficiencies

in large part from the mother) or are not normally present in the fetus before certain gestational ages (e.g., IgM, not seen reliably before about 20 weeks).

Fetal Hemoglobinopathies

Fetal hemoglobinopathies caused by consistent point mutations (e.g., sickle cell) can be diagnosed through several approaches. In informative families, use of deoxyribonucleic acid (DNA) polymorphisms can be applied to either CVS or amniocentesis specimens to establish diagnoses.[16,17] Both offer the ability to make diagnoses before fetal blood can be reliably obtained.

The diagnosis of the β-thalassemia syndromes is more complex, because the disease is more heterogenous in origin. If the family is "informative," CVS or amniocentesis can be used to establish the diagnosis. If the family is not informative, fetal red blood cells may be required for hemoglobin electrophoresis.[18,19]

In Southeast Asian patients, homozygous α-thalassemia may cause nonimmune hydrops fetalis. When this is suspected, fetal blood sampling can be used

to measure the fetal hemoglobin and hematocrit, and hemoglobin electrophoresis can confirm the diagnosis.[20]

Fetal Coagulopathies

Bleeding disorders that can affect the fetus include defects in the synthesis of coagulation factors and both qualitative and quantitative platelet disorders. Coagulation factor synthetic defects can generally be diagnosed through the analysis of DNA polymorphisms. Similar to hemoglobinopathies, in the absence of an informative pattern (which may be the case if the affected family member has died), direct fetal blood assay for the factor may be required.[21] It is therefore important, if caring for a child who may die, to consider sending blood or tissue samples to a genetic lab for storage, should the couple consider pregnancy later. In addition to assays for the coagulation factors responsible for classic hemophilia (Factor VIII) and Christmas disease (Factor IX), the von Willebrand Factor can also be measured in fetal plasma of patients at risk.[10,22]

Fetal platelet disorders may be inherited or may be due to transfer of maternal antibodies across the placenta. In the Wiscott-Aldrich syndrome, an X-linked disorder, fetal platelets are diminished in number and smaller than normal. Fetal blood sampling has been used to establish this diagnosis.[23] Other fetal platelet disorders that have been diagnosed prenatally include the May-Hegglin anomaly, the thrombocytopenia-absent radius syndrome, and Glanzmann's thrombasthenia.[21] The latter has been reported to be responsible for fetal exsanguination after blood cord sampling near term.[21] Fortunately, the other disorders have not been associated with excessive bleeding from the cord after puncture.

Maternal isoimmune thrombocytopenic purpura (ITP) is a more common disorder. While maternal production of IgG antibodies to her own platelets is generally held to be the cause of the disorder, clinical detection of the antibodies is relatively insensitive. The presentation is that of maternal thrombocytopenia, with no defects in the red or white cell lines. The platelets that are present in the mother tend to be large, as a result of being relatively young, and they function normally. Normal gravidae have been suggested to have a range of normal platelet counts including values otherwise considered low. In one large screening study, the mean maternal platelet count was 225,000, with two standard deviations from the mean reaching as low as 107,000.[24] This low normal range and the insensitivity of antibody detection present a diagnostic challenge.

Because the responsible antibody is an IgG, and thus can cross the placenta, the potential exists for fetal thrombocytopenia and consequent intracranial hemorrhage. In the past, the level of maternal platelets, the presence of detectable antibody, and a history of splenectomy have been proposed as ways of selecting fetuses at particular risk of thrombocytopenia. Fetal scalp sampling in labor has also been proposed as a more direct means of identifying the thrombocytopenic fetus.[25] In our experience, although normal results from fetal scalp samples are reliable and reassuring, obtaining a sample free of artifact (platelet clumping)

may be difficult and may leave the clinician uncertain whether the low value reported is real or not.

Several investigators have successfully demonstrated the value of fetal blood sampling before labor for the identification of the thrombocytopenic fetus.[26,27] The frequency of actual low fetal platelet counts has been surprisingly low. Although Moise[26] found counts below normal (150,000) in 23%, clinically important thrombocytopenia (below 50,000) was only seen in 1 of 23 sampled fetuses. Moise et al.[26] also found a difference between two twins (151,000 and 104,000), suggesting that sampling only one fetus in such a setting is insufficient. Scioscia[27] similarly reported clinically important thrombocytopenia in only one of 20 fetuses studies. Since the appearance of that report, we have studied an additional 20 mothers with no further significant fetal thrombocytopenia (Grannum, unpublished observations).

Based on the experience of Karpatkin et al.,[28] it has been suggested that maternal steroid therapy may be useful in boosting fetal platelet counts, but such therapy is best directed to fetuses with known low platelet counts. Scalp sampling after rupture of the membranes in labor is obviously not suitable, should an attempt at in utero therapy be considered. If the frequency of fetal thrombocytopenia is as low as has been reported, clinical evaluation of the effect of steroids on fetuses with antenatally diagnosed thrombocytopenia will require a large number of mothers to demonstrate a statistically significant effect.

Another variety of fetal thrombocytopenia is that due to maternal antibodies. Alloimmune thrombocytopenia is most commonly caused by maternal antibodies to a platelet antigen termed *PLA-1*, which is necessarily absent from the maternal platelets. In a process similar to red cell alloimmunization (vide infra), the IgG crosses the placenta and attacks fetal platelets. The usual presentation is that of a term neonate from an uncomplicated pregnancy who develops intracranial hemorrhage. Severe thrombocytopenia is then found, with a normal maternal platelet count and a positive maternal screen for anti-PLA-1. Because most adults are positive for the antigen, subsequent pregnancies are at risk for similar problems.

Fetal blood has been obtained in patients at risk, and a variety of therapeutic alternatives proposed, including intensive maternal treatment with immunoglobulins and steroids to suppress antibody production[29] and fetal transfusion with maternal platelets just before delivery.[30]

Fetal Immunologic Disorders

Disorders of white cells that may be diagnosed prenatally include chronic granulomatous disease, immunodeficiency states, neutropenias, and severe combined immune deficiency (SCIDS). Appropriate study of fetal white cells can help establish these diagnoses in pregnancies at risk. Additionally, about 20% of cases of SCIDS are characterized by a deficiency of adenosine deaminase, which may be determined from CVS or amniocytes as well. The biochemical bases of the other forms of SCIDS are not known.[10]

Fetal complement levels can be used to diagnose deficient production of C3 in the fetus.[10] Direct assay for IgG cannot be used to diagnose X-linked hypo-γ-globulinemia, because it crosses the placenta freely. The concurrent absence of B lymphocytes can be used to make the diagnosis, however.

Viral Infections

Congenital viral infections remain a difficult problem in perinatal medicine. Reactivation of chronic cytomegalovirus (CMV) infections may cause fetal morbidity. Other viral infections, such as toxoplasmosis, do not cause fetal effects when they predate the pregnancy, but simply distinguishing acute from chronic infection may be difficult.

Extensive experience has been gained in France with the prenatal diagnosis of toxoplasmosis, because the incidence of congenital toxoplasmosis is high, and seroconversion is easily identified through compulsory screening programs. Maternal treatment with spiramycin, a drug not currently available in the United States outside specific protocols, appears to be safe for the fetus, but the firm diagnosis of fetal infection remains elusive. Daffos[31,32] has shown that no single test can be used to establish or exclude the diagnosis of fetal toxoplasmosis; rather, combinations of tests including ultrasound, fetal serology, hematology, and liver function tests must be used.

Suspected fetal varicella[33] and rubella[34,35] infections also have been evaluated through fetal blood sampling. Both of these infections are of interest because of the fetal variable attack rates in infected mothers and severe effects in those fetuses who contract them. Elevated fetal IgM levels were useful in the reported cases to make the diagnosis.

Another virus that can adversely affect the fetus is CMV. The adverse effects may be seen with either primary infection or reactivation. CMV-specific IgM has been reported to be useful in making the diagnosis.[36]

Intrauterine infection by parvovirus B19, the causative agent of fifth disease and erythema infectiosum,[37] has been associated with nonimmune hydrops fetalis. In affected fetuses, the etiology of the hydrops appears to be an aplastic anemia. Approximately half the adults in the United States are immune based on prior infection. The fetal risk of significant morbidity has been estimated to be less than 2.5% after exposure to a household member and less than 1.5% after prolonged occupational exposure, such as might be experienced by a teacher in a school with widespread erythema infectiosum among its students.[38]

The first step in the management of an exposed pregnant woman is documentation of seroconversion, either by initially negative titers becoming positive or the presence of IgM without IgG on the first sample obtained. If this is found in an exposed gravida, fetal effects may be seen in approximately 40%.[39] Fetal blood sampling in such patients to detect anemia with the possibility of transfusion support through the aplastic crisis may be helpful, although other long-term adverse

fetal effects (e.g., hydrocephaly or microcephaly as may be caused by other viruses) may become evident with such an approach.

Fetal Well-Being

Despite the extensive experience gained over many years with antepartum fetal monitoring, the high false-positive rate of abnormal tests remains a problem. The problems remain similar for the nonstress test, the contraction-stress test, and the behavioral profile. Determining whether a worrisome tracing is a true- or false-positive is easy if the patient is near term and when the cervix is dilated. In that setting, the membranes can be ruptured, a scalp electrode applied, and scalp blood pH determinations obtained as needed. In the preterm fetus, when delivery would be contraindicated in the absence of fetal acidosis, or in the term fetus with a closed cervix, in whom scalp pH sampling would be technically impossible to perform, fetal cord puncture has been employed to determine fetal well-being.[5,7,8]

The practical usefulness of this technique is limited by the likelihood of the worrisome fetal testing result resolving. If no change is seen over time, repeated pH testing is likely to be required at frequent intervals. Performing fetal blood samples at 20– to 30-minute intervals is not likely to be well tolerated by the mother and is likely to increase the procedure-associated risks with each puncture. Nevertheless, in some growth-retarded fetuses, this approach has been used in certain centers, where the information gained is used to initiate a program of maternal bedrest with supplemental oxygen administration in an attempt to improve the fetal environment.[40-43]

Isoimmunization

Fetal anemia resulting from maternal blood group sensitization has been an excellent example of successful prophylaxis, as well as in utero treatment. The availability of Rh immunoglobulin has reduced the incidence of maternal sensitization to the Rh(D) locus. Other antigens of the Rh system (e.g., C, c, E, and e) as well as other "irregular" blood group systems (e.g., Kell) continue to cause fetal and neonatal morbidity and mortality. On occasion, the administration of Rh immunoglobulin may fail to prevent sensitization, or one of the irregular antigens causes sensitization. Then, invasive fetal assessment, and occasionally therapy, are required.

Current approaches to the diagnosis and management of isoimmunization have recently been reviewed.[44] Various combinations of the maternal antibody titers, amniotic fluid assays for bilirubin products (Δ OD 450), ultrasound, and fetal blood sampling have been proposed to identify the anemic fetus.[45,46] Hydropic fetuses tend to have hematocrits below about 15%, but the accurate identification of the prehydropic anemic fetus may be difficult, particularly before 24 weeks, when amniotic fluid analyses are less valid.[45] Furthermore, waiting for the development of hydrops may involve waiting too long and may reduce the fetus's ability to withstand the stress of the transfusion or may lead to subtle, long-term handicaps.

While the relative inaccuracy of amniocentesis in the period before 24 weeks' gestation may complicate management of the sensitized pregnancy, the proper frequency with which fetal blood sampling should be performed in search of fetal anemia remains uncertain. The higher complication rate (compared to amniocentesis) and the potential for enhanced maternal sensitization suggest that routine fetal blood sampling may be overly aggressive.

Although the maternal antibody titer may be raised, it does not necessarily indicate that the developing fetus has the sensitizing antigen and is therefore anemic. We have offered prenatal diagnosis in this situation by fetal blood typing, when the father of the baby might be heterozygous for the sensitizing antigen. (If the father is homozygous for the antigen, the fetus necessarily expresses it.) The fetal hematocrit can be obtained at the same time.[46]

Once the fetus is identified as being anemic in the presence of hydrops, there is little doubt that transfusion can be lifesaving. The original techniques for fetal transfusion, using intraperitoneal placement of blood, carried a high fetal mortality rate.[47] More recent series have suggested that fewer complications may be encountered with modern ultrasound guidance in performing intraperitoneal transfusion.[48]

Fetal intravascular transfusion was first performed on an externalized fetus by Freda.[49] Rodeck et al.,[50] more recently, described using a fetoscope to place a needle in the umbilical cord for fetal transfusion. Many groups have now reported their experience with ultrasound-guided intravascular intrauterine transfusion.[51-57] Others have used the intrahepatic portion of the umbilical vein,[11] or intracardiac approaches.[58] A combination of intravascular and intraperitoneal transfusion has also been advocated, as a way of acutely raising the fetal hematocrit, while providing a reservoir for slower absorption over the interval to the next procedure.[59] Further study of this interesting approach is clearly needed, comparing the frequency that transfusions are required in particular, to determine the relative safety of the combined route.

Theoretic concern exists that adult hemoglobin might not provide oxygen to the fetus efficiently enough at the lower oxygen tension present in the fetus; an increase in oxygen transfer, however, has been observed, which appears to compensate for the differences between fetal and adult hemoglobins.[60] Certainly, considering the natural history of untreated isoimmunization, with rapid fetal deterioration and death, the benefits outweigh any small risks based on this concern. Another recent concern has been the safety of the blood provided to the mother, which we screen for hepatitis B and human immunodeficiency virus. At our institution, blood for fetal transfusion is also screened for CMV and is irradiated to prevent any remaining white cells from causing a graft-versus-host reaction.

Conclusion

We have reviewed numerous current applications of fetal blood sampling in the clinical care of the fetus. Direct access to the fetal vasculature may open the way to numerous other possibilities. Measurement of intravascular pressures may

provide better understanding of the mechanisms active in the development of fetal hydrops. Passage of vascular catheters may allow longer term access. In this way, direct fetal treatment of arrhythmias or infections without repetitive vessel puncture may be possible.

We regard fetal blood sampling as a standard part of maternal–fetal medicine. Nevertheless, real complications occur, including fetal losses. A recent report, from an experienced group, of maternal sepsis[61] after fetal blood sampling is an important reminder of this. Performance of these samples should be undertaken only after thoroughly discussing the anticipated risks and benefits with the parents. Additionally, fetal blood sampling should be attempted only by individuals with extensive experience in other ultrasound-guided invasive procedures, because the optimal time to learn the necessary eye–hand co-ordination is not while placing a needle into a fetal vessel. We have found that one source of experience may be patients undergoing second-trimester termination by instillation of prostaglandin. Others have proposed mechanical teaching models.[62]

In the past, treating the fetus as patient largely referred to obstetric determination of optimal timing and route of delivery. With the development of fetal blood sampling and its acceptance as an almost routine tool in perinatology, we have progressed further toward that goal.

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4
Preterm Labor: Prediction, Prevention, and Treatment

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Despite extensive efforts by the medical community, preterm delivery remains a major cause of perinatal morbidity and mortality in the United States. The present 8% rate of preterm delivery has been constant for much of this century. Despite the introduction of new pharmacologic agents to arrest preterm labor, protocols to detect patients susceptible to preterm labor, and devices to monitor uterine activity, no decrease in the rate of preterm delivery has occurred.

Preterm infants are defined as being less than 37 completed weeks (259 days) of gestation at birth, including those delivered prematurely for maternal indications or from preterm premature rupture of membranes of preterm labor. A birthweight less than 2500 g was, but is no longer, used to define prematurity because it does not allow differentiation of infants born prematurely from term infants experiencing intrauterine growth retardation.

The understanding of parturition is limited, which hampers attempts to decrease the incidence of preterm labor. Therefore, focus on identification of women at increased risk for preterm labor with an emphasis on prevention has resulted. It is hoped that early diagnosis of preterm labor will allow more effective treatment. Until a more complete understanding of the etiology of preterm labor is achieved, this approach continues to offer the most hope.

Prediction of Preterm Delivery

Risk Factors Associated With Preterm Labor and Delivery

Previous Obstetric History

Fundamental to attempts to effectively decrease the incidence of preterm delivery is the identification of patients potentially benefitting from early intervention. A woman's previous reproductive performance provides insight into expectations for her subsequent pregnancies. The recurrence risk for preterm delivery has been found to be three times that of a patient with no history of preterm delivery and may be as high as 70%.[1-4] The risk of preterm delivery increases in proportion with the number of previous early deliveries, while the

risk is reduced considerably when a woman has delivered a previous pregnancy at term.[2] Prior pregnancy losses at less than 20 weeks seems to have the same impact as preterm deliveries in excess of 20 weeks in terms of assessing risk for subsequent preterm delivery. However, patients who have undergone first-trimester terminations or spontaneous abortions are not at a greater risk than the population at large.[4] Unfortunately, the majority of patients experiencing preterm labor and delivery do not have a history of previous losses, and therefore the attributable risk is low,[3] limiting the usefulness of this information.

Maternal Factors

Maternal uterine anomalies are associated with premature labor and delivery. A recent review by Heinonen et al.[5] of 182 cases of uterine anomalies and reproductive outcome found a 23% rate of premature labor. Fetal survival was best (86%) in patients with complete septate uteri, while the lowest perinatal mortality rates were found with bicornuate uterus (50% fetal survival) and unicornuate uterus (40% fetal survival). The presence of multiple large leiomyomata is also associated with preterm delivery.[6] Uterine bleeding before the third trimester, regardless of etiology, also has a high predictive value for preterm delivery, because preterm-delivery rates as high as 66% have been associated with it.[1]

Preterm labor and delivery is associated with low socioeconomic status.[1,7,8] An analysis of United States birth certificate data demonstrates an increase in low birth weight deliveries among black women. A more prominent effect was noted in lower educational levels within racial groups.[9] Subsequent studies have revealed that low birth weight is secondary to preterm delivery and does not merely reflect intrauterine growth retardation in this patient population.[10] Black infants have higher rates of perinatal mortality and low birth weight than Mexican-Americans or Anglo-Saxons.[11] Preterm-delivery rates correlate with maternal age as teenagers, regardless of parity, are at a higher risk of preterm delivery.[8,12] Primigravidas $>$ 30 years old are also at increased risk.[8]

Maternal smoking during pregnancy is associated with premature delivery.[1,13] It causes a reduction in birth weight independent of maternal and fetal factors. Meyer and Tonascia[13] found that the neonatal mortality rates of infants of smoking mothers was almost twice the rate of nonsmokers and was attributable to the increased risk of premature delivery.

Low maternal weight at the beginning of pregnancy is associated with preterm delivery. Maternal preconception weight $<$ 50 kg is associated with a threefold increase in the rate of preterm delivery when compared to women weighing $>$ 57 kg.[1] A controlled trial of nutritional supplementation in black, urban woman revealed that the only favorable effect of supplementation was the prevention of low birth weight infants of heavy smokers.[14] An increase in very premature births and neonatal deaths, however, was associated with intrauterine growth retardation in the presence of high-protein supplementation.

The effect of employment on duration of gestation is controversial. Generally, the perinatal outcome is improved in employed females,[1] and no difference in

preterm-delivery rates of sedentary versus nonsedentary employment seems to exist.[15] Nonemployed women in lower socioeconomic groups are at particularly high risk of preterm delivery, but this fact is explained by obstetric or medical factors.[15] The lower birth weights noted in infants of obstetric residents is a result of intrauterine growth retardation, not premature delivery.[16]

Newton and Hunt[17] found stress, related to life events, is associated with low birth weight and prematurity. Stressful events are more likely to be precipitating factors of preterm delivery when they occur in the third trimester. Maternal perception of anxiety, however, does not appear to influence prematurity rates.

The effect of coitus on preterm-delivery rates remains to be determined. The frequency of sexual intercourse has not been shown to influence length of gestation in patients lacking a history of preterm deliveries.[18] However, high-risk women with a history of being treated for preterm labor were prospectively monitored for uterine activity and found to have an increase in uterine contractility in the immediate postcoital period. The increased level of uterine activity spontaneously subsided within 2 to 3 hours without treatment.[19]

Infection

Maternal infection seems to be associated with preterm delivery. Preterm birth is associated with an increased incidence of endometritis, whether or not premature rupture of membranes (PROM) occurred.[20] Aerobic and anaerobic cultures of amniotic fluid in the presence of intact membranes revealed that amniotic fluid may be sterile when patients were not in labor, although 13 to 31 amniotic fluid samples were culture-positive.[21] The organisms most frequently isolated were *Peptococcus, Bacteroides* sp, and *Fusobacterium*. Subsequent work has not confirmed the high frequency of positive amniotic fluid cultures in the presence of preterm labor and has found subclinical infection to be an uncommon cause of refractory preterm labor.[22]

The enzyme phospholipase A2 liberates arachidonic acid esters from membrane phospholipids, leading to the synthesis of prostaglandins by the placental membranes. Release of phospholipase A2 from the amnion and chorion, therefore may be involved in the initiation of labor. Phospholipase activity has been isolated from *Bacteroides fragilis, Peptostreptococcus, Fusobacterium*, and *Streptococcus viridens*.[23] In an attempt to establish a causal relationship between vaginal flora and preterm labor, Minkoff et al.[24] cultured pregnant patients early in the second trimester and found *Trichomonas vaginalis* to be associated with premature rupture of membranes. *Ureaplasma urealyticum* carriers were more likely to develop premature labor but not preterm delivery. Colonization of the vagina with *Bacteroides* sp led to more frequent delivery of infants weighing less than 2500 g and an increased frequency of PROM. Although vaginal flora identification in the second trimester may help identify women at increased risk of premature delivery, the relative risk for all these organisms is less than 2:1.[24] Prophylactic administration of oral antibiotic therapy effectively prolongs gestation.[25,26] Both erythromycin and ampicillin delay delivery, independent of culture results, when given as an adjunct to tocolytic therapy.

Risk Assessment Scores

Attempts to integrate all of the risk factors into a risk score to identify high-risk patients[1,7,27] have shown that scoring systems are more accurate in predicting preterm delivery in multiparous women as opposed to primigravidas because of past pregnancy outcome history. The effectiveness of the various systems ranges from identification of 9% of primigravidas and 25% of multiparas who develop preterm labor[28] to detection of ⅔ of all preterm deliveries.[27] Creasy et al.[27] predicted that 10% of patients screened using their scoring system were at high risk. Although these patients accounted for ⅔ of all preterm deliveries, only ⅓ of this high-risk group actually developed preterm labor with delivery. An improvement in accuracy was found if patients were screened at the initial prenatal visit and again at 26 to 28 weeks' gestation.

Biochemical Markers

Unfortunately, animal models for initiation of human parturition have not been identified. Nevertheless, it has been hypothesized that a change in hormonal milieu from progesterone to estrogen dominance accompanies the onset of labor, regardless of gestational age. Decreased progesterone levels are found in patients with preterm labor that is idiopathic or related to placental abruption.[29] However, a very low sensitivity of serial measurement of plasma estradiol-17B and progesterone concentrations was found because preterm delivery could not be predicted using these measurements.[30]

A basic protein has been discovered in the plasma of all pregnant women, and it has been localized in placental trophoblastic tissue. A sharp rise in concentration occurs approximately 3 weeks before the onset of spontaneous labor regardless of gestational age.[31] Preliminary work suggests interleukin 1 may be a signal for initiation of preterm labor.[32]

Other biochemical markers for preterm delivery have not proved to be useful. Patients with lupus anticoagulant (LAC) frequently undergo induced preterm delivery for fetal and maternal indications[33,34] but do not have spontaneous preterm labor and delivery. Patients with elevations of maternal serum α-fetoprotein (MSAFP) greater than 2.3 multiples of the median are more likely to deliver infants weighing less than 2500 g.[35] Elevated MSAFP is associated with prematurity and increased perinatal mortality, but the low birth weight is probably secondary to intrauterine growth retardation.[36]

Prevention

Prevention of preterm delivery may be possible by early identification of women at increased risk with alteration of controllable risk factors.[7,12,37-40] In addition, surveillance of uterine activity may identify preterm labor earlier. In the past, less than 20% of patients delivering preterm were candidates for tocolysis at the time of hospitalization. Preterm patients were excluded from tocolytic therapy

because of imminent delivery or ruptured membranes.[41] It is hoped that preterm-prevention programs will identify preterm-labor patients earlier, thereby increasing the number of patients that are tocolytic candidates. Weekly prenatal visits and patient education appear to decrease the incidence of preterm delivery.[37] The prevention-program patients were more often candidates for tocolysis, thereby reaching term more frequently. Early recognition and intervention, however, have not been universally found to prevent preterm delivery. Main et al.[38] applied similar risk-assessment methodology to poor, innercity women and found no improvement in preterm-delivery rates in women enrolled in the prevention program over a 16-month period.

A French national perinatal policy found preterm-prevention programs (not limited to high-risk groups and involving patient education) were most effective in preventing premature delivery.[39] Women of lower education levels and from lower socioeconomic groups were slower to respond to prevention programs, often requiring 4 years before demonstrating significant results. Subsequent studies demonstrated similar positive effects of prevention programs,[12,40] especially for multiple-gestation pregnancy.[12]

The cornerstone of the preterm-prevention programs includes patient education of signs and symptoms of preterm labor, prenatal risk assessment with attention to controllable risk factors, close surveillance of the high-risk patient, and prompt patient evaluation whenever signs of labor occur.

Cervical Change

The relationship of cervical effacement and dilatation to delivery has been studied extensively.[18,42-46] A minority (15%) of primigravidas and the majority (72%) of multigravidas have cervical dilation of 1 cm at 24 weeks' gestation, [43] which is not associated with preterm delivery. Further cervical dilatation is pathologic, especially if the cervix is dilated $>$ 2 cm before 30 weeks of gestation.[44] Cervical change may be diagnosed by serial vaginal exams several weeks before preterm labor and delivery occurs and may be the only clinical finding that predicts preterm delivery.[46] Because other clinical signs and symptoms of preterm labor poorly predict preterm delivery,[45,48] serial cervical examination has become a mainstay of diagnosis. No evidence exists that weekly vaginal exams increase the frequency of preterm labor or other complications.[42,46]

Ambulatory Uterine Monitoring

In an effort to enhance the diagnosis of preterm labor, ambulatory activity monitoring is receiving much attention. Maternal self-palpation of uterine contractions is characteristic of preterm-prevention programs[37] and if, effective may prove to be an economical method of predicting preterm labor.[49] Unfortunately, the effectiveness of this method has been questioned. Newman et al.[50] reported a poor correlation of self-detection of uterine contractions with tocodynamometer recording of uterine activity. Patients identified only a minority (15%) of contractions during the study period.

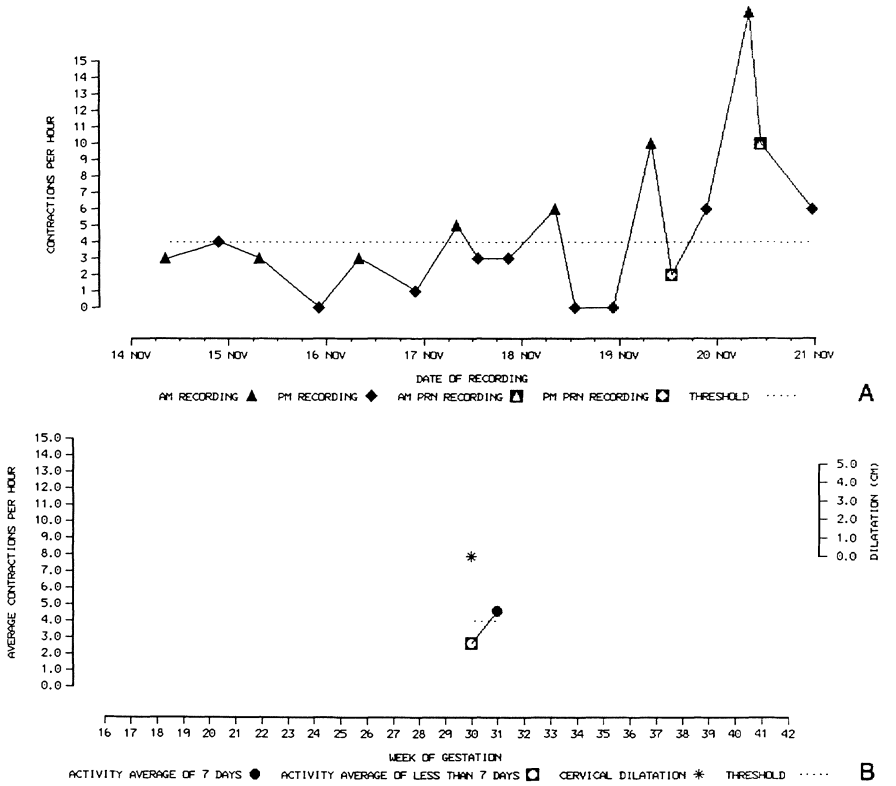

FIGURE 4.1. Case example of Healthdyne Home Uterine Monitoring. A 23-year-old G2 P0010 woman at high risk for preterm delivery was admitted for preterm labor at 23 weeks' gestation. Tocolytic therapy was initiated during hospitalization and continued as an outpatient. Daily home uterine-activity monitoring was performed. The patient delivered at 37 weeks' gestation. Uterine activity was increased (greater than threshold) during the week before delivery. (A) Current week, uterine activity; (B) A Weekly summary.

Ambulatory home uterine contraction monitoring has been shown to be effective in prolonging gestation in high-risk patients.[51-53] This form of uterine monitoring reveals increased uterine activity in patients who experience preterm labor or delivery.[54,55] This activity is often present several weeks before the onset of labor. Increased uterine contraction frequency is observed 24 hours before the development of clinically apparent cervical changes.[56] The value of uterine activity as a marker for subsequent preterm labor has also been described by Main et al.[57] in a group of innercity patients with no history of preterm labor. Recent work suggests that uterine contraction frequency is a significantly more sensitive indicator of early preterm labor than prospectively collected maternal signs and symptoms (Fig. 4.1).[58,59] The value of uterine activity, monitoring, however, was recently questioned by Iams et al., who examined the role

of intensive nursing contact in patients supplied with home uterine monitoring systems. In a prospective study, the home monitor did not lower the rates of preterm labor or delivery or increase the gestational age at delivery.[60] Therefore, this issue needs to be further addressed before the usefulness of home monitoring systems can be fully determined.

Treatment

Treatment of preterm labor between 26 and 33 weeks' gestation is cost- effective because the increased costs of prenatal care are offset by a decreased use of neonatal care.[61] Although tocolysis of patients not in labor increases costs and morbidity, it can be avoided by documenting cervical effacement and dilatation before initiating therapy. The policy of requiring documentation of cervical change despite uterine activity may lead to missed opportunities for successful tocolysis. Recently, it has been observed that differentiation of "true" from "false" labor may be possible by the documentation of fetal breathing movements.[62-64] The absence of fetal breathing movements may suggest the presence of true labor, thereby justifying tocoloysis in the absence of cervical change.

Unfortunately, all of the available tocolytic agents to inhibit preterm labor have untoward effects. There is much controversy regarding which agent is most appropriate for therapy in different clinical situations. It is also important to remember that despite the widespread use of tocolytics, no decrease in the incidence of premature births in the United States has occurred in recent years.[65]

β-Mimetics

β-mimetic agents act by stimulating β_2-adrenergic receptors. The effect on uterine muscle results from smooth muscle relaxation. The drug binds with cell surface receptors, thereby activating adenyl cyclase, which accelerates the conversion of adenosine triphosphate to cyclic adenosine monophosphate. The resulting myosin light chain kinase activity interferes with cellular actin–myosin interaction via the reduction of intracellular free calcium ions.[66]

β-Mimetics are excreted by the kidney but cross the placenta and enter the fetal circulation. These agents can be taken orally or can be administered intravenously or intramuscularly. Prolonged treatment, irrespective of route of administration, results in a desensitization of β_2-receptors of the human myometrium during pregnancy,[67] because lower binding site concentrations in both fundal and lower uterine segments of myometrium are found. Down-regulation of receptors may explain the limited duration of the relaxant effect of β-mimetics observed during prolonged treatment.

Before and after approval of ritodrine by the Food and Drug Administration (FDA) in 1980, multiple studies examined the tocoloytic effect on length of gestation. Ritodrine decreases the frequency and intensity of uterine contractions.[68-70] Clinical trials in comparison with ethanol showed improvement in prolongation

of gestational age at delivery with fewer side effects.[71] Spellacy et al.,[72] could not demonstrate a beneficial effect of ritodrine in prolonging pregnancy when compared to placebo therapy. Additional investigation revealed that ritodrine inhibits the initial stages of preterm labor but that duration of pregnancy was not prolonged significantly.[73] A multicenter, randomized, prospective, double-blind study of ritodrine, ethanol, and placebo revealed that a significant number of days were gained in utero in the ritrodrine patients.[74] A greater number of infants delivered at more than 36 weeks' gestation and weighed more than 2500 g while the incidence of neonatal death and respiratory distress syndrome were reduced. The effectiveness of β-mimetic therapy was found to be greatest when pregnancies were less than 33 weeks' gestation.

Initial work comparing terbutaline, another β-mimetic agent, to placebo showed terbutaline to be effective in prolonging pregnancy. In this study, patients were randomly selected to receive terbutaline or placebo. Patients were initially treated with at least 8 hours of intravenous medication, which was followed by 3 days of intermittent subcutaneous administration before maintenance oral therapy. The majority (80%) of terbutaline patients and a minority (20%) of placebo patients delivered at term.[75] Subsequent work has confirmed the effectiveness of intravenous terbutaline at prolonging gestation.[76]

Intravenous β-mimetics have become the primary agent for tocolysis of the preterm labor patient with oral therapy used after successful intravenous tocolysis. Oral ritodrine therapy lowers the incidence of recurrent preterm labor episodes that require recurrent intravenous therapy.[77] Oral terbutaline has been shown to prolong gestation and decrease the incidence of idiopathic respiratory distress syndrome.[78]

Comparisons of routes of administration of β-mimetics have shown intermittent subcutaneous terbutaline followed by oral medication to be as efficacious as intravenous ritodrine and intravenous terbutaline.[79] Subcutaneous therapy requires a lower dosage of drug when compared to intravenous therapy. Recently, continuous subcutaneous administration of terbutaline via pump has been introduced and has yielded promising results.[80] It seems effective in prolonging pregnancy and further lowered the total daily drug dosage (< 3 mg/24 hours). Patients seem to tolerate the continuous pump well without significant complications.

The side effects of β-mimetics are primarily the result of stimulation of β_2-receptors outside the uterus and are usually mild, not serious.[75,76] Hypotensive complications from peripheral vasodilatation are more common with older, less specific β_2-mimetics. Ritodrine widens pulse pressure[68-70] by raising systolic blood pressure (approximately 12%) and lowering diastolic blood pressure (approximately 10%).[70] Mean arterial pressure, however, remains unchanged.

As a result of the vasodilatation effects, β-mimetics must be used with extreme caution in bleeding patients; these drugs counteract the body's normal compensatory responses to volume depletion (vasoconstriction). In addition, maternal tachycardia from blood loss may be masked by the direct effect of the drug. β-mimetics also must be used with caution in patients with a history of cardiac disease because of the increase in heart rate and cardiac output[70,81] from β-mimetic therapy.

Cardiac arrhythmia is a complication of β-mimetic therapy even in patients without a prior history of cardiac disease or myocardial ischemia. Premature ventricular contractions, premature nodal contractions, and atrial fibrillation have been reported,[82] which usually respond to oxygen therapy and discontinuance of tocolysis.

Chest pain in patients receiving β-mimetic tocolysis must be evaluated promptly and thoroughly. The decrease in aortic diastolic blood pressure with maternal tachycardia shortens the diastole period. This reduces subendothelial oxygen supply despite the increase demand. The risk of subendothelial ischemia associated with β-mimetic tocolysis suggests that a baseline electrocardiogram (EKG) be performed on candidates for ritodrine tocolysis. In the presence of chest pain, cardiac symptoms, or maternal tachycardia in excess of 130 beats per minute (bpm), the drug should be stopped and an EKG performed.[82] The cardiovascular side effects, including hypotension, tachycardia, chest pain, and shortness of breath, usually occur with an increasing infusion rate.[83] Severe cardiovascular complications, EKG changes consistent with myocardial ischemia, and pulmonary edema have been reported in up to 5% of patients treated with intravenous terbutaline.[84]

Pulmonary edema is the most common serious complication of β-mimetic therapy but appears to be noncardiogenic in origin. Preterm labor patients have lower plasma colloid osmotic pressures than nonlaboring patients of the same gestational age. Plasma colloid osmotic pressure is further lowered by the administration of intravenous ritodrine.[85] Furthermore, ritodrine raises the concentration of antidiuretic hormone and aldosterone, thereby blocking the excretion of salt and water.[86] The propensity toward the development of pulmonary edema may be further aggravated by the fluid overload that is frequently administered to patients presenting in preterm labor.[82] An isotonic glucose solution should be given in lieu of normal saline to decrease the incidence of pulmonary edema.[86] Fluid restriction to < 2 l in a 24-hour period is also helpful in avoiding pulmonary edema.[73,82] Glucocorticoids may also predispose patients to pulmonary edema[68,82,84,86]

Multiple metabolic changes have been associated with β-mimetic use. The catecholamine effects induce glycogenolysis, thereby increasing glucose and insulin concentrations.[87] These increased glucose and insulin levels return to normal values at 48 to 72 hours after initiation of treatment despite continued administration of the drug.[88] The diabetogenic effect of β-mimetics is not clinically significant in patients with normal glucose tolerance.[89] In contrast, patients with glucose intolerance need to be monitored for the development of hyperglycemia and ketoacidosis. Although intravenous ritodrine acutely affects glucose metabolism, chronic oral ritrodrine has little effect on glucose homeostasis in the nondiabetic patient.[90] Unlike ritodrine, however, long-term oral terbutaline is associated with glucose intolerance. Patients on oral terbutaline have a 33.1% incidence of abnormal 3-hour glucose tolerance testing versus a rate of 2.8% in the control group.[91] Additional metabolic changes associated with β-mimetic therapy include apparent hypokalemia. The greatest change in serum potassium

levels is noted 3 hours after initiation of tocolytic therapy.[87] This results from movement of potassium intracellularly as a result of increased glucose and insulin levels instead of a decrease in total body potassium. Serum potassium levels return to normal within 24 hours and rarely require treatment.[82]

Magnesium

Obstetricians are experienced with the administration of magnesium sulfate as a result of its routine use in the treatment of preeclampsia. Recently, the drug is being used as a tocolytic agent. Magnesium acts by antagonizing the action of calcium in uterine smooth muscles at the myoneural junction.[92,93] The drug is excreted renally. The maximum serum level achieved depends on the rate of infusion. For example, at an infusion rate of 1 g/h, the serum magnesium plateau is reached in 24 hours, while a 2 g/h infusion rate results in a plateau within 6 to 8 hours.[92] Because of the prolonged time interval to plateau state, an initial bolus dose is usually given. Serum levels of 5 to 7 mg/dL usually are sufficient to inhibit contractions.[93]

Magnesium sulfate inhibition of labor has been successful in delaying delivery for 48 hours in 70.6% to 92.3% of patients.[93-95] It is an effective tocolytic agent if therapy is initiated before active phase of labor.[94,96] Especially if the cervix is dilated $\leq$ 2 cm.[93] Spisso et al.[94] found a significant decrease in respiratory distress syndrome in infants of patients successfully tocolyzed for 48 hours.

Comparative studies of intravenous magnesium sulfate and β-mimetic agents, ritrodrine or terbutaline, show similar efficacy of the drugs.[95-98] The tocolytic success rates of the drugs for delaying delivery for 48 hours were similar (96.3% of ritodrine patients and 92.3% of magnesium patients).[95] Combined therapy failed to improve these rates when compared to single-agent therapy and was associated with an increase of the untoward effects. Examining the effect on prolonged delay of gestation ($>$ 7 days) also showed comparable efficacy of magnesium and ritodrine (75% and 72%).[98]

The use of oral β-mimetic maintenance therapy after completion of intravenous magnesium therapy is found to further improve success rates in preterm labor patients with intact membranes.[94] Oral magnesium gluconate is also being used for maintenance therapy following successful magnesium tocolysis.[99] The serum magnesium levels achieved in patients being maintained on oral therapy were higher than pretreatment values but were not in the range required for initial tocolysis.

Untoward side effects of intravenous magnesium are not as common or severe as side effects seen with the β-mimetics.[94-97] The symptoms of nausea, dry mouth, emesis, and dizziness are rarely severe enough to require drug discontinuance.[98] Flushing resulting from peripheral vasodilatation is usually transient during the initial bolus diffusion. Lethargy occurs as serum levels approach the toxic range (10 mg/dL) and usually respond to a decrease in the infusion rate.[98] The overall rate of maternal side effects has been reported to be 7% with less than 2% of patients requiring the drug to be discontinued.[93] The most serious side effect of magnesium

tocolysis is respiratory depression. Pulmonary edema has been reported in less than 1% of patients treated.[93]

One concern regarding magnesium tocolysis is the effects on the fetus. A continuous infusion of magnesium more than 24 hours before delivery may be associated with low 1-minute apgar score.[100] Neonatal depression of the respiratory center and muscle weakness usually resolves spontaneously by 24 to 36 hours of age. Neonatal neurologic exams, however, following magnesium tocolysis are similar to control groups, and the neurologic performance of the infants did not correlate with cord magnesium levels or total dose of magnesium administered.[101]

Indomethacin

Indomethacin is a prostaglandin-synthesis inhibitor that interferes with prostaglandin's role in the initiation of labor. The drug is absorbed rectally and orally. In a prospective, randomized, double-blind study, indomethacin was significantly more effective than placebo in inhibiting preterm labor during a 24-hour course of treatment.[102] Delivery was postponed at least 72 h in 79% and postponed for more than 1 week in 67.2%.[103] Maternal side effects are minimal but include mild gastrointestinal discomfort with oral therapy. Initial work showed minimal fetal adverse effects.[102-104] No evidence of premature closure of the ductus arteriosus, persistent fetal circulation, or neonatal platelet dysfunction was observed in 183 patients treated with indomethacin for short courses of therapy (< 48 hours).[102-103] Therefore, it was recommended that the drug be limited to patients less than 35 weeks' gestation with discontinuation of the drug if delivery is inevitable or imminent.[104] Unfortunately, subsequent work has reported a higher incidence of fetal effects. Serial fetal echocardiogram was performed on 14 patients undergoing tocolytic therapy with indomethacin for < 72 hours.[105] The gestational ages ranged from 26 to 31 weeks. Ductal constriction was noted in 50% of the patients, with three patients having tricuspid regurgitation. These findings were unrelated to gestational age of the fetus or the serum indomethacin levels in the mother. All patients had resolution of the constriction within 24 hours of discontinuation of the drug without long-term sequelae. Indomethacin also decreases amniotic fluid volume by reducing fetal urinary output and is used to treat polyhydramnios.[106] Amniotic fluid volume was followed serially in 26 patients on chronic indomethacin therapy,[107] and decreased amniotic fluid volume was noted in 35% of patients. The fluid volumes normalized after indomethacin was discontinued. The development of oligohydramnios appeared idiosyncratic and was unrelated to dosage given or gestational age at onset of therapy.

These potentially serious complications of indomethacin therapy may severely limit its use. Further investigation is required before it is accepted as a tocolytic agent. Any patients placed on indomethacin will require extremely close follow-up for possible decreased amniotic fluid volume and closure of the ductus arteriosus.

Calcium Channel Blockers

Nifedipine has promise as a potential tocolytic agent. Its effect as a calcium channel blocker is at the level of the uterine smooth muscle. In a comparison study of nifedipine and ritodrine, nifedipine seemed to delay delivery longer than ritodrine,[108] because 75% of the nifedipine and 45% of the ritodrine patients postponed delivery 48 hours. The side effects include flushing of the face, neck, and chest in 90% of patients.[108] Insignificant decreases in both systolic and diastolic blood pressure have been noted. Nifedipine increases fetal heart rate without affecting maternal heart rate.

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5
Percutaneous Umbilical Blood Sampling and Intravascular Fetal Therapy

SCOTT N. MACGREGOR

Access to the fetal circulation enhances our ability to study fetal physiology and to diagnose a variety of fetal disorders.[1-11] In addition to fetal blood sampling, access to the fetal circulation offers an improved means of treating disorders such as fetal isoimmunization, fetal coagulation disorders, and fetal cardiac arrhythmias.[12-18] Fetal blood sampling was initially performed in 1973 by use of either placentocentesis or fetoscopy-directed umbilical blood sampling.[19,20] Pure fetal blood was difficult to obtain by placentocentesis because samples were most often contaminated by maternal blood or amniotic fluid. Furthermore, the risk of fetal loss was significant.[21] Fetoscopy allows aspiration of pure fetal blood from the umbilical vein; however, this invasive procedure requires hospitalization of the patient and is difficult to perform with advancing gestation. In addition, the procedure-related pregnancy loss rate has been reported to be between 2% and 5% in the largest series.[22]

In 1983, a new sampling procedure was reported that combined the simplicity of placentocentesis with the efficiency of fetoscopy. Daffos et al.[1] obtained pure fetal blood by introduction of a fine needle into an umbilical vessel near its placental origin under continuous ultrasound guidance. This procedure, known as either *percutaneous umbilical blood sampling (PUBS)* or *cordocentesis*, offers several advantages over earlier techniques of fetal blood sampling. PUBS is an outpatient procedure requiring neither maternal sedation nor local anesthesia and can be performed from 17 weeks' gestation until the end of pregnancy. Furthermore, this procedure may be used for both withdrawal and injection, may be repeated many times during the pregnancy, and is safer than previous techniques. The primary application of PUBS was initially prenatal diagnosis in pregnancies with suspected congenital infection, fetal coagulation disorders, or fetal chromosomal abnormalities[1,2]; however, the indications for use of this technique have continued to expand.[6,9,10,17,18,23-27] In this chapter, I will describe the technique of PUBS, review its applications for fetal diagnosis and treatment, and discuss the known complications of this new procedure.

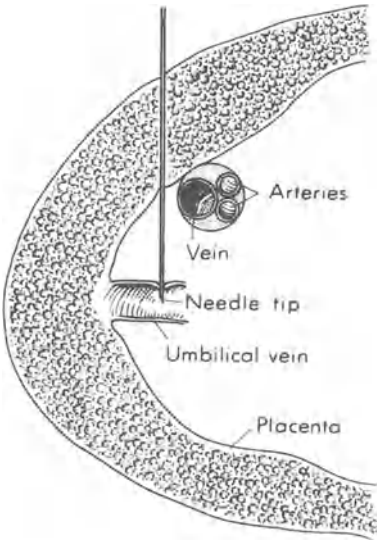

FIGURE 5.1. Technique of percutaneous umbilical blood sampling.

Methodology

Percutaneous umbilical blood sampling is performed under direct ultrasound guidance. The technique has been described using both sector and linear-array ultrasound[1,3]; the sector transducer (usually 5 MHz) offers somewhat greater flexibility as a result of the smaller size of the transducer. New curvilinear transducers may offer advantages similar to the sector transducer while providing a linear-array image more commonly used in obstetric ultrasound. The placental insertion of the umbilical cord is located after performing routine fetal evaluation using high-resolution, real-time ultrasound imaging. The umbilical cord insertion on the placenta is the preferred site for cord puncture, whether the placenta is located anterior, posterior, lateral, or fundal within the uterus (Figure 5.1). A free loop of umbilical cord is the secondary site for needle placement if fetal interposition does not allow access to the placental insertion. In addition, puncture of the umbilical vein at both the umbilical cord insertion on the fetal abdomen and the intrahepatic portion within the fetus have been described.[28] Twenty- to twenty-five-gauge spinal needles, ranging in length from 9 to 18 cm, have been used for umbilical vessel puncture. In the largest series reported (France), a 20-gauge spinal needle was used exclusively,[9] whereas in the United States, most centers prefer a 22-gauge needle.[10,15,29-32]

After initial ultrasound evaluation, the maternal abdomen is prepped and drapped using sterile techniques. Free-hand or needle-guide techniques may be used to perform PUBS under ultrasound guidance. The free-hand technique is performed by either single or dual operators. The ultrasound transducer is main-

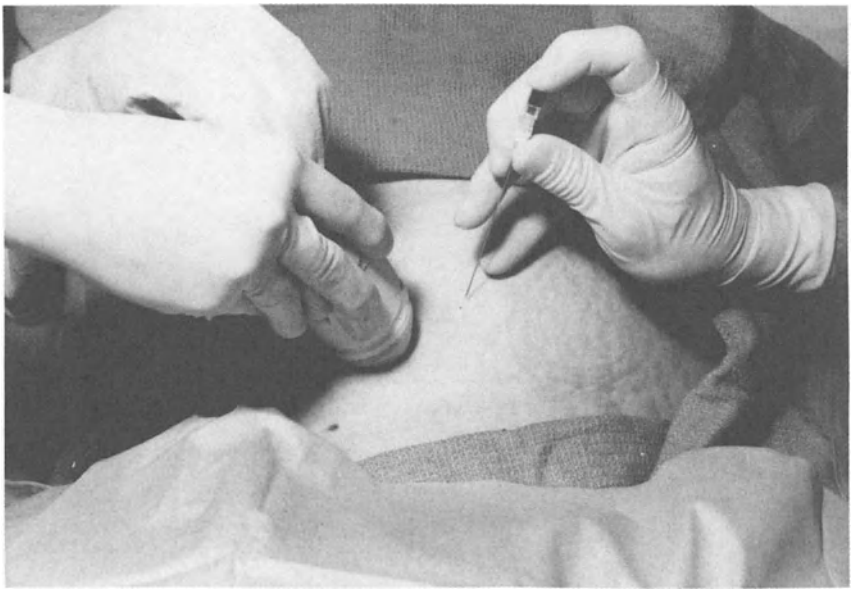

FIGURE 5.2. Percutaneous umbilical blood sampling: dual operator using sector ultrasound.

tained in an immobile position while visualizing the intended puncture site, and the needle is introduced in the plane of the ultrasound near the transducer. The needle tip emits echoes, and its progress toward the umbilical vessel may be easily followed by ultrasound visualization. Alternatively, a needle guide may be affixed to the sector transducer to ensure needle introduction in the plane of the ultrasound. The angle of needle insertion may be adjusted with many of the needle guides; however, fine adjustments of needle angle and direction are difficult after insertion into the maternal abdomen. Although the choice of technique depends on operator preference, the free-hand technique offers greater flexibility in making adjustments after needle insertion into the maternal abdomen and, therefore, may allow fewer needle insertions. The different techniques for PUBS are shown in Figures 5.2 and 5.3.

Maternal sedation is not necessary; however, short-acting benzodiazepines, such as diazepam and midazolam HCl, may be administered to reduce excessive maternal anxiety. Likewise, local anesthesia is not necessary but may be used. Prophylactic antibiotics are not routinely administered for fetal blood sampling. Several authors have recommended the use of prophylactic antibiotics for prolonged therapeutic procedures, such as intravascular fetal transfusion.[29,30] Similarly, prophylactic tocolytic agents, either subcutaneous or intravenous terbutaline (0.12 to 0.25 mg) or intravenous ritodrine HCl (3 mg), may be administered for prolonged procedures to avoid needle dislodgment from uterine contractions.

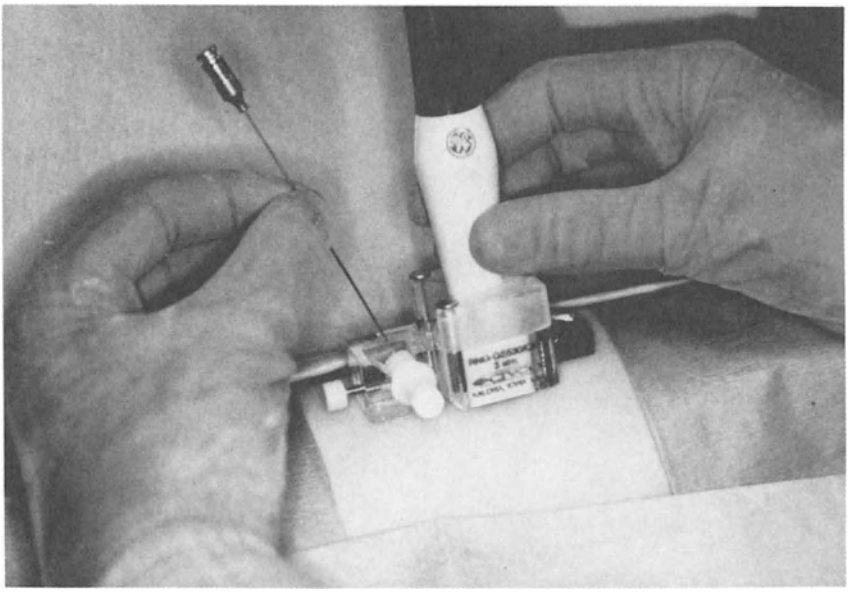

FIGURE 5.3. Percutaneous umbilical blood sampling: needle guide using sector ultrasound.

The volume of fetal blood sampled is usually 1 to 3 mL. This volume of blood is adequate for most evaluations. Larger volumes of blood may be sampled with more advanced gestational age. Fetal blood samples must be evaluated to assess the source and purity of the blood sample. The mean corpuscular volume (MCV) on routine complete blood count (CBC) provides a quick indication of whether the sample is of fetal or maternal origin. The MCV should be $> 100\ \mu m^3$ (macrocytic) if the source of the blood is fetal. Kleihauer-Betke testing should be performed on all samples. Pure fetal blood samples will have 100% fetal red blood cells (RBC). An additional test to evaluate the source of the sample and rule out maternal contamination is the evaluation of blood group antigens I and i. Antigen I is present on 99.9% of adult red blood cells, whereas this antigen is undeveloped, and antigen i is present on fetal red blood cells.[33] Anti-I and anti-i antibodies may be obtained from patients with chronic cold agglutinin hemolytic disease. The antibody donors must be from blood group AB to assure the absence of anti-A and anti-B antibodies, which could agglutinate nongroup O fetal RBCs. The anti-I and anti-i cold agglutinins are active at room temperature and may be used to detect maternal blood contamination by either a rapid slide or spin test.[34] The test is particularly helpful for immediate assessment of fetal origin and purity of the sampled blood. Amniotic fluid may also contaminate the fetal blood sample. Peripheral blood smear, using a Giemsa stain, may be used to detect fetal epithelial cells present with amniotic fluid contamination. In addition, amniotic fluid actives some coagulation factors and can cause platelet aggregation. Assessment of coagulation factors II, V, VIII, and IX, as well as platelet count, may be

performed. Normal values of these parameters suggest that the blood specimen is without amniotic fluid contamination.[6] Establishing the origin and purity of the blood sample may be critical to ensure the accuracy of fetal diagnosis. Each type of contamination has different consequences, depending on the disorder under investigation.[6] For example, evaluation of fetal infection in the presence of maternal infection may yield false-positive results if the sample is contaminated with maternal blood. Evaluation of fetal coagulation disorders (coagulation factor or platelet deficiencies) may be severely affected by amniotic fluid contamination. Additional laboratory evaluations are obtained based on the suspected fetal disorder being investigated.

Applications for Fetal Diagnosis

Congenital Infection

The indication for fetal blood sampling was evaluation for congenital infection > 70% of cases in the largest series published (1553 fetal blood samplings).[9] Toxoplasmosis was the indication in two thirds of the total cases. Differences in the incidence of congenital toxoplasmosis infection, as well as in the policy toward routine prenatal toxoplasmosis screening, are responsible for the greater number of samplings for congenital infection in France compared to studies in the United States.[3,10] To diagnose fetal toxoplasmosis infection, fetal blood sampling and amniocentesis are performed at 22 to 24 weeks' gestation.[5] Total immunoglobulin M (IgM) and specific IgM are obtained from the fetal blood sample. In addition, both fetal blood and amniotic fluid are cultured for toxoplasmosis. Congenital viral infections that may be diagnosed by PUBS include rubella, varicella, and cytomegalovirus and herpes simplex virus.[6,9] Similarly, total IgM and viral-specific IgM are obtained when evaluating the fetus for congenital viral infection. Nonspecific fetal blood parameters observed in congenital toxoplasmosis infection, as well as congenital viral infections, include elevated liver transaminases, lactic dehydrogenase (LDH), and γ-glutamyl transpeptidase; decreased platelets; and increased normoblasts on peripheral blood smear.[5,9]

Rapid Karyotype

Results of fetal chromosomal analysis are available within 48 to 72 hours by leukocyte culture of blood obtained by PUBS.[2,9,34] Rapid karyotyping may offer considerable advantages over genetic amniocentesis in selected patients. Pregnant women with advanced maternal age presenting for prenatal care in the late second trimester (20 to 24 weeks' gestation) are candidates for rapid karyotyping by PUBS in an effort to obtain results at a gestational age when pregnancy termination options may be considered. Similarly, in certain pregnancies at increased risk for abnormal fetal karyotype, the ability to obtain results of fetal chromosomal analysis in a timely manner may be critical. Pregnancies complicated by symmetric

intrauterine growth retardation are at increased risk for fetal chromosomal abnormalities. Fetal instability may dictate delivery before the 2-week period required for amniotic fluid karyotyping. Rapid karyotyping by PUBS may facilitate a more rational plan of management. Fetal congenital malformations are also associated with increased fetal chromosomal abnormalities. Rapid fetal karyotyping may be considered in those anomalies detected in the third trimester of pregnancy. The advantages of providing accurate results rapidly include informed consultation of the patients regarding prognosis, alleviating parental anxiety associated with long delay, formation of a rational plan of management for this pregnancy, and providing accurate genetic counseling for future pregnancies.

Coagulation Disorders

Prenatal diagnosis of many hereditary and acquired immune bleeding disorders is possible by direct evaluation of fetal blood obtained from PUBS.[12,16,18,32,35-39] Fetal blood sampling may be considered, as well as for less severe disorders for which the diagnosis allows formation of a plan of management minimizing intrapartum and neonatal complications. In addition, the efficacy of maternal therapy for fetal conditions can be directly assessed during the pregnancy.[16,18,32,37] Surveillance of the fetus by fetal blood sampling gives precise information on which to base clinical decisions to provide optimal maternal and fetal outcomes. Many hereditary bleeding disorders, including hemophilias A and B, Factor deficiencies, von Willebrand's disease, and Glanzmann's thrombasthenia, have been diagnosed prenatally by PUBS.[18] Acquired immune bleeding disorders that have been diagnosed by PUBS include autoimmune thrombocytopenia purpura and alloimmune thrombocytopenia purpura.[12,16,18,36,38,39] The risk of fetal bleeding and exsanguination from the puncture point on the cord are important considerations. Abnormal cord bleeding, however, was not observed in a series of more than 2000 cases of fetal blood sampling, in many of which coagulation factor deficiency or severe thrombocytopenia were observed.[9] Excessive bleeding has been reported in two infants with Glanzmann's thrombasthenia, one with severe von Willebrand's disease and one with hemophilia.[40] Fetal bleeding disorders increase the risk of intracranial hemorrhage during the intrapartum and neonatal periods. Prenatal diagnosis of these disorders may allow in utero transfusion of platelet or factor concentrates and dictate the optimum mode of delivery.

Fetal Growth Retardation

The etiology of fetal growth retardation is multifactorial. Common causes of fetal growth retardation include fetal chromosomal abnormalities and uteroplacental dysfunction. The primary indication for fetal blood sampling in pregnancies complicated by fetal growth retardation is exclusion of chromosomal abnormalities. Additional parameters, however, should be evaluated at the time

of sampling. Blood gas analysis, serum lactate level, plasma thymidine kinase activity (incorporation of thymidine by fetal leukocytes), and erythroblast count should be performed. Findings observed in fetal growth retardation resulting from uteroplacental dysfunction include low blood pH value, increased serum lactate level, decreased plasma thymidine kinase activity, and erythroblastosis (increased normoblasts).[7,24,25,41] Normal values for these parameters may suggest fetal well-being, whereas abnormal values suggestive of chronic intrauterine hypoxia may suggest the need for timely intervention.

Blood Group Isoimmunization

Percutaneous umbilical blood sampling has been used most extensively in the United States for fetal assessment and treatment in pregnancies complicated by blood group isoimmunization.[3,13-15,27-31,42-51] PUBS allows assessment of fetal blood type and precise evaluation of fetal anemia. These parameters cannot be assessed by amniocentesis. In addition, several reports have suggested that amniotic fluid spectophotometric measurements (δ-OD 450) are unreliable in assessing the severity of rhesus's sensitization in fetuses during the mid-trimester.[52-54] Therefore, indications for PUBS in pregnancies complicated by blood group isoimmunization include amniotic fluid δ-OD 450 in Liley zone 2 during the midtrimester or pregnancies in which fetal transfusion is anticipated. In pregnancies in which there is paternal antigen heterozygosity, PUBS may be considered as an alternate method of assessment during the mid-trimester. When the fetal antigen status is the same as the mother, further invasive procedures (either repeated amniocentesis or PUBS) could be avoided. Such an approach, however, may enhance fetal maternal passage of red blood cells, thereby increasing the severity of sensitization. Fetal therapy in severe isoimmunization will be discussed in the following section.

Miscellaneous

Percutaneous umbilical blood sampling has been used in the diagnosis of various other fetal disorders. Hemoglobinopathies, including sickle cell disease and thalassemia, and genetic disorders, including Duchenne's muscular dystrophy, α^1-antitrypsin deficiency, agammaglobinopathy, and Wiscott-Aldrich syndrome, have been diagnosed by PUBS.[2,6,9] Fetal blood sampling has also been used in the evaluation of nonimmune fetal hydrops.[2,6,9] Investigation of nonimmune fetal hydrops includes obtaining the following laboratory tests: fetal karyotype (chromosomal abnormalities), CBC (fetomaternal hemorrhage), viral studies (congenital infection), and hemoglobin electrophoresis (thalassemias). Finally, fetal blood sampling has been performed intrapartum in the evaluation of fetal well-being when cervical dilatation precluded fetal scalp pH assessment.[6,9,24,25] The list of indications for the use of this technique for fetal diagnosis has, and will continue, to expand (see Table 5.1).

TABLE 5.1. Indications for fetal blood sampling.

Diagnosis
Blood group isoimmunization
Congenital infection
Toxoplasmosis
Rubella
Varicella
Cytomegalovirus
Herpes simplex virus
Rapid karyotype
Coagulation disorders
Hereditary
Hemophilias
Factor deficiencies
von Willebrand's disease
Acquired immune
Autoimmune thrombocytopenia purpura
Alloimmune thrombocytopenic purpura
Intrauterine growth retardation
Fetal distress
Nonimmune hydrops fetalis
Genetic disorders
Therapy
Intravascular transfusion
Blood group isoimmunization
Coagulation disorders
Factor deficiencies
Autoimmune thrombocytopenic purpura
Alloimmune thrombocytopenic purpura
Cardiac arrhythmias
Neuromuscular blockade for fetal surgery
Selective feticide

Application for Fetal Therapy

Intravascular Transfusion

Access to the fetal circulation also allows intravascular fetal therapy. The use of PUBS for fetal therapy has been primarily for intravascular fetal transfusion.[3,13-15,27-31,42-51] Indications for fetal transfusion include blood group isoimmunization (rhesus [Rh] or anti-D, anti-Kell, anti-c, anti-E, etc.), fetal thrombocytopenia, and fetal coagulation factor deficiencies.[3,12-16,18,27-31,42-51] The methods used to perform intravascular fetal transfusions are similar to those for fetal blood sampling with few modifications. After initial fetal blood sampling, pancuronium bromide (0.05 to 0.1 mg/kg) is administered to the fetus intravenously. Administration of this nondepolarizing neuromuscular-blocking agent has been shown to be safe and effectively reduces fetal movement without the need for excessive maternal sedation.[42,46,50] Fetal paralysis reduces the risk of needle dis-

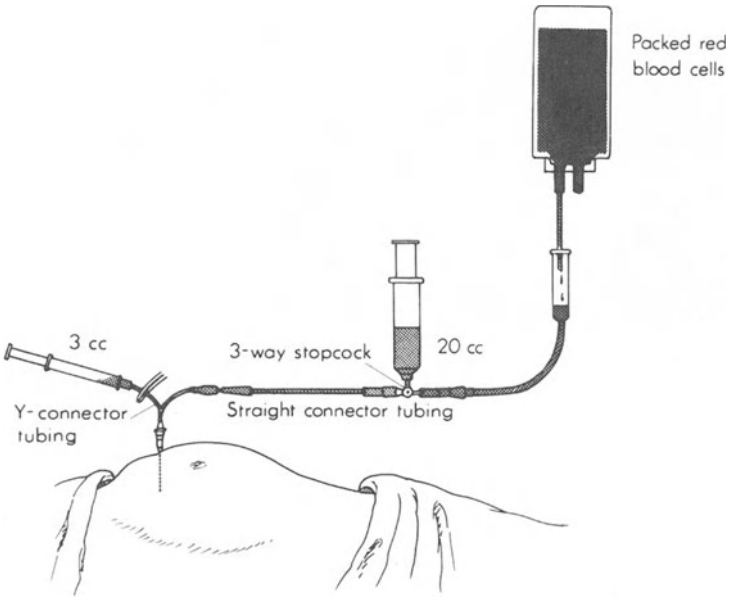

FIGURE 5.4. Setup for intravascular fetal blood transfusion.

lodgment and, therefore, the need for repeated needle insertions. Atracurium besylate (0.4 mg/kg) is another short-acting, nondepolarizing neuromuscular-blocking drug that may be administered to the fetus after initial blood sampling.[29] The setup for fetal blood transfusion is illustrated in Figure 5.4. A Y-connector tubing is attached to the needle, which allows both fetal transfusion and aspiration of a fetal blood sample for assessing the hematocrit without disconnecting the tubing from the needle hub. At repeated sample aspiration, the first milliliter of blood should always be discarded to avoid false elevation of fetal hematocrit by residual packed cells contained within the lumens of the needle and distal tubing. The three-way stop cock allows the donor blood to be drawn into the 20-mL syringe and then transfused at a controlled rate without disconnecting the system.

Transfusions are performed using cytomegalovirus-antibody–negative, irradiated, washed, packed RBCs cross-matched against maternal blood. Estimated transfusion volume is based on the initial fetal hematocrit, the donor hematocrit, and estimated fetoplacental blood volume. The following equation is used to estimate transfusion volume[48]:

$$Vd = \frac{Vi\ (Hctf - Hcti)}{(Hctd - Hctf)}$$

where *Vd* is the volume of donor blood, *Vi* is the initial fetoplacental blood volume (mL), *Hctd* is the hematocrit of the donor blood, *Hcti* is the initial fetal hematocrit, and *Hctf* is the desired final fetal hematocrit. The initial fetoplacental blood volume is calculated by multiplying the estimated fetal weight (kg) by

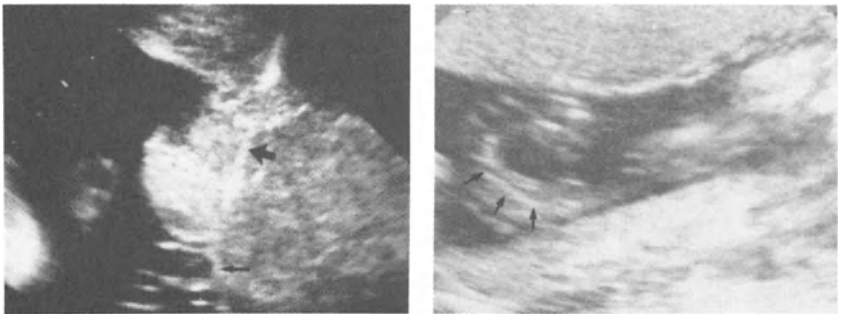

FIGURE 5.5. Ultrasound showing (A) the needle tip within the umbilical vein and (B) turbulence within the umbilical vein during transfusion.

ultrasound times the initial fetoplacental blood volume (mL) per kg fetal weight relative to gestational age in weeks (847.20 − 47.50 [gestational age] + 0.731 [gestational age]).[2] In addition, this formula can be used to estimate the hematocrit when fetal blood cannot be obtained after transfusion.

Donor-packed RBCs are transfused at a rate of 5 to 15 mL/min.[29,30,44] The adequacy of fetal transfusion is determined by the posttransfusion hematocrit, with the desired hematocrit after transfusion being 45% to 50%. Turbulence should be observed within the umbilical vessel throughout the blood transfusion to ensure proper needle tip placement (Fig. 5.5).

Exchange transfusions have been performed[13]; however, most centers have used straight transfusions.[29,31,48] Although significant overexpansion of the neonate's intravascular space may result in cardiac decompensation, the fetal circulation is in continuity with the placental vasculature, which is a low-resistance, large-volume vascular bed. Donor RBCs may be transfused to fetuses at rates up to 15 mL/min and in quantities that double the calculated circulating fetoplacental blood volume without fetal compromise.[44,48] Unlike the neonate, for whom exchange transfusions lower both bilirubin and maternal antibody levels, the fetus has bilirubin cleared and antibody rapidly replaced by transfer across the placenta. Exchange transfusion removes the fetal blood cells, thereby reducing further hemolysis; however, at the second transfusion, only small amounts of fetal RBCs usually remain.[47] Therefore, exchange transfusion probably should be considered only at the first transfusion. In summary, exchange transfusion offers little advantage over straight transfusion and may significantly increase the time required for the procedure, thereby increasing the risks of complications.

Timing of repeat transfusion is based on the predicted decline in fetal hematocrit over time. Prediction of fetal hematocrit decline following intravascular transfusion may be calculated based on the following equation[47]:

$$Hct\ pred = Hct\ f \times (EFW1/EFW2) \times (120 - \text{days})/120$$

where *Hct pred* is the predicted hematocrit at the subsequent transfusion or birth, *Hct f* is the final hematocrit at the index transfusion, *EFW1* is the estimated fetal

TABLE 5.2. Protocol for intravascular fetal transfusion.

1. Place patient on the fetal heart-rate monitor and uterine tocodynometer in the labor and delivery unit for 20 to 30 min (baseline tracing).
2. Notify anesthesia of the planned procedure if gestational age assessment is ≥24 weeks.
3. Perform ultrasound evaluation of the placenta for cord insertion and fetus for evidence of hydrops fetalis, position, and estimated fetal weight.
4. Obtain cross-matched blood for transfusion from the blood bank and notify appropriate laboratories of anticipated stat tests.
5. After obtaining the initial fetal blood sample, administer pancuronium bromide, 0.1 mg/kg estimated fetal weight.
6. Estimate transfusion volume based on the initial fetal hematocrit, and begin fetal transfusion.
7. Repeat fetal blood sampling after infusing the estimated transfusion volume to ensure adequate transfusion.
8. Monitor the fetal heart rate and uterine activity after the procedure until discharged (at least 60 min).

weight by ultrasound at the index transfusion, *EFW2* is the estimated fetal weight by ultrasound at the subsequent transfusion, and days is the number of days between the index and subsequent transfusion or birth. This equation assumes that donor RBC survival in the fetal circulation is 120 days. A previous case report suggests that the life span of transfused adult cells in the fetus may be shorter, approximately 100 days.[55] An additional assumption is that fetoplacental blood volume increases in direct proportion to fetal weight gain, which may not be exact.[44,48] Despite the limitations of these assumptions, this formula has been used to accurately predict fetal hematocrit decline.[47] Alternatively, Nicolaides et al.[44] have suggested that the fetal hematocrit usually decreases by 1%/d. Transfusion interval after the first transfusion is usually 10 to 14 days, depending on the severity of the fetal anemia. Transfusions can usually be delayed 21 to 28 days after the second and subsequent transfusions. Our protocol for intravascular fetal transfusion is summarized in Table 5.2.

The overall survival of severely isoimmunized fetuses treated with intravascular intrauterine transfusion has been reported to be between 76% and 87%.[29-31] Of particular note, intravascular fetal transfusion has been shown to reverse hydrops fetalis and greatly improve survival in these fetuses.[15,29-31] Survival in severely isoimmunized fetuses with hydrops fetalis was reported to be 80% in a series of 20 fetuses with evidence of hydrops fetalis at the first intrauterine transfusion.[30] Previous reports describing pregnancy outcome in isoimmunized pregnancies treated with intraperitoneal transfusions suggested an overall survival of 70% to 80% in nonhydropic fetuses[56]; survival in hydropic fetuses was approximately 20%.[57] Direct intravascular transfusion eliminates the erratic and incomplete absorption of RBCs inherent with the traditional intraperitoneal approach. In addition, fetal anemia is accurately assessed and the adequacy of fetal transfusion evaluated with the intravascular technique. Most importantly, survival of these severely isoimmunized fetus is improved with intravascular versus intraperitoneal fetal transfusion, especially in those fetuses with hydrops fetalis.

Cardiac Arrhythmias

Fetal supraventricular tachycardia may cause fetal congestive heart failure and nonimmune hydrops fetalis. Fetal cardioversion is often recommended, even in the absence of fetal heart failure.[58] Conversion of the fetal supraventricular tachycardia is usually attempted by maternal administration of digoxin, verapamil, or procainamide.[58] Direct fetal therapy by percutaneous umbilical cord puncture may be considered when a fetus with supraventricular tachycardia is unsuccessfully treated by maternal drug administration.[17] Of note, in a previous report describing direct fetal digitalization for supraventricular tachycardia after maternal digoxin administration failed to produce a sustained cardioversion, the fetal digoxin concentration was much lower than maternal digoxin concentration, suggesting poor transplacental passage of digoxin.[17] In the future, direct treatment of fetal supraventricular tachycardia may be considered as first-line therapy.

Neuromuscular Blockade for Fetal Surgery

Percutaneous fetal surgery, such as urinary bladder shunt placement or pulmonary cyst aspiration, are facilitated by fetal neuromuscular blockade. Neuromuscular blockade may be achieved by intravenous or intramuscular administration of pancuronium bromide or atracurium besylate.[29,42,46,50,59] Intramuscular administration may be technically easier; however, PUBS combined with intravascular administration of neuromuscular blocking agents may offer the advantage of obtaining blood for fetal karyotype in those pregnancies complicated by congenital malformations. Fetal paralysis may also facilitate fetal diagnostic evaluation by magnetic resonance imaging to confirm ultrasound diagnosis of fetal anomalies.

Miscellaneous

Access to the fetal circulation may allow diagnosis and treatment of inherited disorders, such as hemoglobinopathies (α- and β-thalassemias and sickle cell anemia), and agammaglobulinemia with stem cell or precursor cell transfusions.[2,3] Selective feticide may be performed by intravenous administration of potassium chloride, air, or hypertonic saline in pregnancies complicated by multifetal gestation, severe fetal–fetal transfusions in the second trimester, or multiple gestation with an anomalous fetus.[2,26] Administration of these agents may incur risk to the remaining fetus(es), resulting in unplanned pregnancy loss.

Complications

Complications associated with PUBS result from puncture of the amniotic cavity and from puncture of the umbilical vessel. Complications associated with membrane puncture are similar to those observed with amniocentesis, including

TABLE 5.3. Complications associated with percutaneous umbilical blood sampling.‡

	Number	Percentage
Attempted	116	100
Successful	109	94
Morbidity		
Bradycardia	9	8
Vasospasm (presumed)	6	5
Hematoma	3	3
Bleeding (>60 s)	1	1
Infection	1	1
Emergency cesarean section*	4	3
Total	11	9
Mortality		
Fetal	2	2
Neonatal	1	1
Total	3	3

*Emergency cesarean sections were all performed for fetal bradycardia.
‡[MacGregor and Socol] (unpublished data, 1989)

premature rupture of membranes, uterine contractions, and placental bleeding. These problems usually resolve and are of little consequence. Infection is an additional complication that can occur with either amniocentesis or PUBS. Intraamniotic infection has been observed after PUBS and appears to be related to prolonged, difficult procedures.[29-31,49] Complications associated with umbilical vessel puncture include cord bleeding, hematoma formation, and arterial spasm. Bleeding from the site of puncture is usually observed but rarely exceeds 60 s.[9] Wharton's jelly may aid umbilical vessel hemostasis. In addition, amniotic fluid stimulates the coagulation cascade and platelet aggregation and may contribute to hemostasis.[6] Arterial spasm has been observed on several occasions and usually results in fetal bradycardia [MacGregor] (unpublished data, 1989). Arterial spasm may cause fetal hypertension and baroreceptor stimulation, thereby resulting in fetal bradycardia. Relief of arterial spasm will usually result in resolution of fetal bradycardia. Fetal bradycardia may also be observed after fetal transfusion, especially when the fetal hematocrit after transfusion is > 50%. This bradycardia resulting from increased fetal intravascular volume is usually mild (100 to 120 beats per minute) and is of little consequence. Fetomaternal hemorrhage may also occur as a result of PUBS. In one patient with Rh sensitization, the anti-D titer increased from 1:16 to 1:4096 during a 3-week period following PUBS. [MacGregor] (unpublished data, 1989). The increased antibody titer was likely the result of fetomaternal hemorrhage at the time of initial fetal blood sampling. Fetal intravascular transfusion or intravascular administration of chemotherapeutic agents have the theoretic risk of causing embolism and associated sequelae. Few reports have examined the procedure-related morbidity associated with fetal blood sampling and fetal transfusion.[49] Table 5.3

TABLE 5.4. Mortality associated with intravascular fetal transfusion.

Study	Deaths*/Procedures (%)	Survivors/No. Pregnancies (%)
Berkowitz et al.[29]	4/45 (9%)	13/17 (76%)
Grannum et al.[30]	5/72 (7%)	21/26 (81%)
Barss et al.[31]	2/45 (4%)	11/13 (85%)
MacGregor et al.‡	3/70 (4%)	20/23 (87%)

*Deaths include fetal and neonatal deaths.
‡[MacGregor and Socol] (unpublished data, 1989)

summarizes our experience at Northwestern University (Evanston Hospital and Prentice Women's Hospital). Fetal bradycardia occurred twice after fetal blood sampling, once resulting from cord hematoma requiring emergency cesarean delivery of a viable neonate and the other from presumed vasospasm with spontaneous resolution in a severely growth-retarded fetus. The remaining complications all occurred in fetuses undergoing intravascular fetal transfusion. The overall procedure-related morbidity was 9%.

The procedure-related mortality associated with PUBS appears to be comparable to midtrimester amniocentesis.[2,9] Daffos et al.[2] reported four cases of intrauterine fetal demise in their first 606 diagnostic fetal blood samplings. Two of these fetal losses were remote from the procedure (>3 weeks) and may be unrelated. The overall perinatal mortality in this series was 0.7%. More recent data from this group suggested that the mortality rate has remained <1%.[2] The procedure-related mortality rate associated with midtrimester amniocentesis is 0.5%.[60] The mortality rate associated with intravascular fetal transfusion is greater than that associated with fetal blood sampling alone. Table 5.4 summarizes the results of four large series in which fetuses were treated with percutaneous intravascular fetal transfusions.[29-31] As mentioned previously, the overall survival was between 76% and 87% in fetuses with severe isoimmunization; the procedure-related mortality was between 4% and 9%. In most instances, demise occurred in those fetuses who were most severely anemic at the time of the procedure.

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6
Current and Future Perspectives of Fetal Genetic Diagnosis

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The past 25 years have been a time of remarkable advances in medical genetics, particularly in prenatal diagnosis and prevention of genetic disorders. In 1976, the National Institutes of Health (NIH) completed a multicenter study on the safety and accuracy of amniocentesis.[1] Before amniocentesis, prospective parents at risk for a conception with a chromosomal anomaly or an inborn error of metabolism had no alternative but to take their chances or to refrain from procreating. With the introduction of amniocentesis, couples at significant risk for a conception with Trisomy 21 (Down syndrome) or Tay-Sachs disease, for example, could undergo prenatal diagnosis in the second trimester to determine the genetic status of the fetus. Fetal diagnosis was expanded with the development of ultrasonography, permitting in utero identification of a broad spectrum of structural defects associated with genetic and developmental disorders. Currently, amniocentesis in the second trimester of pregnancy is considered a conventional medical technique to be offered as a standard of care for diagnosing chromosomal aberrations because of advanced maternal age, a previously affected conception, or a familial chromosomal rearrangement, and for diagnosing inborn errors of metabolism because the parents are carriers of a mutated gene.

First-trimester fetal diagnosis was performed by Kazy et al.[2] and by Old et al.[3] in 1982. It was first introduced in China[4] in the 1970s but then abandoned because of its use to selectively abort female fetuses. First-trimester fetal diagnosis became possible with the availability of ultrasound to closely monitor the transcervical passage of a catheter into the chorion frondosum and the aspiration of villous tissue for genetic analysis. The development of any new prenatal diagnostic technique generates two main issues: the safety of the procedure and the accuracy of the genetic analysis. For transcervical chorionic villous sampling (CVS), its safety in comparison to amniocentesis was recently the subject of evaluation.[4,5] Because of the concern of infection as a consequence of CVS performed transcervically, Smidt-Jensen and Hahnemann[6] have proposed a transabdominal approach for all CVS. There are also serious concerns about whether the chorion accurately represents the genotype of the developing fetus, particularly in its chromosomal constitution.[7] Although more than 5 years have passed since CVS was first performed in the United States, less than 100 medical centers

perform transcervical and transabdominal CVS. CVS must still be considered a developing technology at the present time. One objective of this chapter is to provide a critical assessment of the current status of CVS, emphasizing the issues of obstetric safety and accuracy of genetic analysis.

While first trimester CVS is yet to be established as a conventional approach to the fetal diagnosis of genetic diseases, two new approaches are currently the source of intensive investigations. One area of research involves determining if it is possible to isolate and genetically analyze fetal cells from the maternal peripheral blood circulation. A second area of investigation is termed *preimplantation genetic diagnosis*, i.e., using the techniques of in vitro fertilization (IVF) to determine the genotype of embryos before implantation. These two approaches will be described in separate sections.

Chorionic Villous Sampling

First trimester genetic diagnosis by CVS offers the possibility of a new generation of prenatal testing. CVS can be performed between 9 and 12 weeks' gestation, and the results of chromosomal, enzymatic, and deoxribonucleic acid (DNA) analyses can be available within hours by the direct processing of villous tissue. Confirmation of the genetic analyses is possible with short-term cell cultures within 7 to 10 days. In contrast, amniocentesis is performed at 15 to 17 weeks' gestation, and results are usually not available for 2 to 4 weeks. For women who are at significant risk for a conception with a genetic disease, CVS also offers distinct psychological benefits, because the availability of results early in pregnancy should greatly reduce the amount and duration of parental anxiety. CVS has considerable medical advantages when a genetic abnormality is detected: An elective first-trimester termination is associated with reduced maternal morbidity and mortality, when compared to late midtrimester terminations following amniocentesis. And finally, CVS offers patient privacy, which is not possible with amniocentesis.

Concern has been expressed about the safety of CVS.[6-9] Overall, fetal loss rates following CVS are obviously higher than amniocentesis, because it is performed at a time when the background rate of spontaneous abortion is much higher than in the period following amniocentesis. The possibility that CVS increases birth defects, prematurity, intrauterine growth retardation, and stillbirths has been raised, along with such maternal risks as perforation of the uterus, hemorrhaging, infection, and the sequelae of placenta previa and accreta.[10]

Concern has also been expressed about the accuracy of genetic analyses based on chorionic villi.[7,10,11] The possibility that the chorion does not reliably represent the fetal genotype has been raised because discrepancies between the chromosomal makeup of the chorion and that of the fetus have been reported.[12] The issue of discrepancies may seriously negate the medical and psychological benefits attributed to CVS and thereby inhibit or prevent its becoming a routine prenatal test. An assessment therefore is required of the diagnostic capability and

TABLE 6.1. Fetal losses related to sampler and ultrasonographer.

	Sampler 1			Sampler 2			Sampler 3		
	US operator			US operator			US operator		
	1	2	3	1	2	3	1	2	3
Total CVS	2044	420	–	167	37	55	111	41	–
Losses	54	10	–	2	1	5	1	1	–
Percentage	2.6	2.4	–	1.2	2.7	9.1	1.0	2.4	–

CVS, chorionic villous sampling; US, ultrasonography.

accuracy of CVS when applied to a large population at risk for a spectrum of genetic disorders.

Obstetric Considerations

The competence and the experience of the sampling team are the major factors affecting obstetric outcome following CVS. Of particular importance are the characteristics of spatial orientation, manual dexterity, and judgment. Most significant is that the physician performing the sampling procedure must be thoroughly experienced and skilled in ultrasonography. Whether performed transcervically or transabdominally, CVS requires the constant and continuous translation of a two-dimensional image on the ultrasound screen into a three-dimensional representation. This level of skill cannot be acquired easily or learned; rather this ability to interpret a series of two-dimensional images into three dimensions represents a function of the central nervous system, perhaps an inherited form of "eye–mind–hand" coordination. One immediate problem with CVS is that the transcervical and transabdominal procedures are deceptively simple. Indeed, what could be simpler than to insert a plastic catheter or a spinal needle under ultrasound guidance into a pregnant uterus and aspirate a sample of the chorion into a syringe? This naive view implies that, as with amniocentesis, most obstetricians and ultrasonographers will be readily able to perform CVS. This view has also lead to unrealistically low assessments by patients and their physicians of the obstetric risks associated with first-trimester fetal diagnosis. Although it may be possible with a minimum of skill and training to successfully perform CVS, these are procedures

TABLE 6.2. Fetal losses related to weeks of gestation.

Weeks of gestation	8	9	10	11	12	13
CVS total	120	1274	941	249	26	1
Losses	5	32	26	10	1	0
Percentage	4.2	2.5	2.8	4.0	3.9	0

CVS, chorionic villous sampling.

TABLE 6.3. Fetal losses and sample weight.

	Weight	Standard deviation
CVS total	19.2 mg	+/−12.5 mg
Losses	16.4 mg	+/−9.6 mg

CVS, chorionic villous sampling.

that demand much more skill and ability than the routine ultrasound examinations of the second and third trimesters of pregnancy.

The success of any prenatal diagnostic program is measured in the number of pregnancy losses following the sampling procedure, whether CVS or amniocentesis. The variables associated with a fetal loss may be divided into three types, human, biologic (gestational age at time of sampling and weight of sample), and environmental (placental position). Examples of the human factors include the skills of the physician and the ultrasonographer performing the procedure. An analysis of these factors in the case of transcervical CVS indicated that the choice of ultrasonographer had a direct relationship to pregnancy outcome (Table 6.1). There was a high loss rate with ultrasonographer No. 3, and this person was not permitted to continue in the program.

As shown in Table 6.2, fetal losses following transcervical CVS ranged from 2.5% when performed at 9 weeks' gestation to 4.2% at 8 weeks' gestation. While there was no statistical difference between weeks of gestation and fetal loss rate, the trend suggests that the safest time to perform transcervical CVS is 9 and 10 weeks. Similar data have yet to be developed for transabdominal CVS.

No relationship was observed between fetal loss rate following transcervical CVS and (1) weight of villous tissue (Table 6.3); (2) placental position (Table 6.4); or (3) number of samplings required to obtain a satisfactory sample (Table 6.5). In contrast, however, the safety study reported by the National Institute of Child Health and Human Development[4] indicated that retroverted and fundal placentas were associated with a higher fetal loss rate, while an earlier report by a study group of the United Nations World Health Organization showed a direct relationship between number of samplings performed and fetal loss rate.[12]

TABLE 6.4. CVS losses related to placental position.

Position	CVS total	(%)	Losses	(%)
Anterior	1050	(40.4)	28	(37.3)
Posterior	1326	(50.9)	38	(50.7)
Lateral	122	(4.6)	5	(6.7)
Retroverted				
Anterior	15	(0.5)	1	(1.3)
Posterior	18	(0.6)	0	(0)
Fundal	5	(0.3)	1	(1.3)

CVS, chorionic villous sampling.

TABLE 6.5. Fetal losses and number of catheter passages.

Number of passages	1	2	3
CVS total	2357 (91%)	212 (8%)	26 (1%)
Losses	67 (91%)	6 (8%)	1 (1%)

CVS, chorionic villous sampling.

Accurate assessment of the fetal loss rate that is directly due to the CVS procedure is difficult to obtain. Multicenter studies conducted in the United States[4] and Canada[5] suggest that the risk of transcervical CVS is 0.6% to 0.8% greater than that of amniocentesis. Thus, if the procedural risk of amniocentesis is 0.2%, the fetal loss rate that is due to transcervical CVS would be 0.8% to 1.0%. These estimates of fetal loss rates may be inflated, because many centers participating had limited experience in performing CVS—as few as 25 procedures at several centers before the start of both studies. Data from more experienced centers suggest that the fetal loss rate attributable to CVS may be similar to that of amniocentesis.[4,14]

The risk of spontaneous abortion by 20 to 28 weeks as a function of maternal age with a normal ultrasound evaluation at 7 to 12 weeks' gestation is compared between a chromosomally normal population undergoing transcervical CVS and two control groups (Table 6.6). The total fetal loss rate was actually lower in the women undergoing CVS (2.5%) in comparison to the two "no-procedure" groups (3.0% to 3.1%). This is not unexpected, because the lower rate is a direct effect of the CVS procedure itself, namely, the identification of chromosomally abnormal conceptions, some of which would spontaneously abort if part of the "no-procedure" groups. The spontaneous abortion rate occurring between 9 and 20 weeks' gestation that is due to chromosomal aberrations is estimated to be 0.46% (Table 6.7). The total corrected fetal loss rate following CVS would then be 3.0%, which does not differ significantly from the two control groups (Table 6.6).

TABLE 6.6. Risk of spontaneous abortion by 20 to 28 weeks as a function of maternal age with normal ultrasound at 7 to 12 weeks.

	Maternal age			
	30–34 years	35–39 years	>40 years	Total
No procedure				
Study 1	6/283 (2.5%)	6/133 (4.5%)	0/16 (0%)	12/387 (3.1%)
Study 2	11/438 (2.5%)	4/51 (2.6%)	3/19 (14%)	18/604 (3.0%)
CVS procedure	0/166 (0%)	37/1270 (2.9%)	5/215 (2.3%)	42/1651 (2.5%)

Study 1. *Source:* Wilson, R.O., Kendrick, V, Wittman BK, McGillivray. Risk of Spontaneous Abortion in Ultrasonically Normal Pregnancies. Lancet 1984;2:920.

Study 2. *Source:* Gilmore, DH and McKay MB. Spontaneous Fetal Loss Rate in Early Pregnancy. Lancet 1985;1,107.

CVS, chorionic villous sampling.

TABLE 6.7. Estimate of spontaneous abortion occurring between 9 and 20 weeks gestation that is due to chromosomal aberration.

Chromosome aberration detection method	Maternal age
CVS	32/1651 = 1.94%
Amniocentesis	12/815 = 1.48%
Estimate of spontaneous abortion due to chromosomal aberration	0.46%

CVS, chorionic villous sampling.

Other Obstetric Complications

Other obstetric complications following CVS have been addressed and include the following four concerns:

How often is it necessary to have a second prenatal diagnostic procedure because of failure to obtain an adequate sample of villi, maternal contamination, or inconclusive results? Of the 2235 patients in the NIH-sponsored study,[4] 49 patients (2.2%) required a second CVS or an amniocentesis because of procedural or laboratory failures. An additional 17 patients (0.7%) underwent amniocentesis after CVS because the diagnosis, mainly of mosaicism or pseudomosaicism, was ambiguous. With more experienced groups, procedural or laboratory failure is less than 0.5%, particularly with the addition of transabdominal CVS providing a second approach; about 1% of CVS patients may require a backup amniocentesis to clarify ambiguous CVS cytogenetic results.[14]

How often do patients use CVS for fetal sex selection, rather than for its intended purpose of genetic diagnosis? In the United States, it is estimated that less than 1% of women undergoing CVS terminated a pregnancy for reasons of sex selection.[4]

How often does infection result from transcervical CVS? Based on the multicenter study conducted by the NIH and involving 4260 patients, 12 cases were associated with fetal loss due to infection, or 0.3%; no cases of serious maternal infection were reported.[4]

In terms of newborns, there appear to be no differences between infants who underwent CVS or amniocentesis with regard to length of gestation, birth weight, Apgar scores, complications of labor and delivery, or length of hospital stay.[4]

Genetic Considerations

This section will review those genetic considerations important to obstetricians in counseling their patients concerning first-trimester fetal diagnosis by CVS.

The incidence of chromosomally abnormal conceptions in women is higher at the time of CVS than that of amniocentesis. That is because between 12 and 16

TABLE 6.8. Maternal age and risk of chromosome aberration at the time of CVS.

Maternal age (years)	Number of pregnancies	Number abnormal	Percentage abnormal
34	411	4	1.0
35	1000	11	1.1
36	1048	15	1.4
37	936	21	2.2
38	876	15	1.7
39	744	19	2.6
40	521	16	3.1
41	323	16	4.9
42	197	9	4.6
43	113	9	8.0
44	53	7	13.2
45	28	2	7.1
46	9	1	11.1
47	6	2	33.3

weeks' gestation, approximately 20% to 30% of chromosomally abnormal fetuses will spontaneously abort. The incidence of chromosomal aberrations at the time of CVS increases with maternal age, from 1.0% at 34 years of age to 2.6% at 39 years of age and from 3.1% at 40 years of age to 33% at 47 years of age (Table 6.8).

For women who experienced a previous conception with one of the common autosomal trisomies (13, 18, and 21), the recurrence risk (i.e., the risk of a second affected conception) was 2.3% (Table 6.9). This means that such women have a risk similar to that of women 39 years of age (Table 6.8).

Additional studies indicate that women with a "family history of a chromosomal aberration" are at less risk than women aged 34 years, 0.8%; that enzymatic analyses based on villous tissue are extremely accurate in the diagnosis of inborn errors of metabolism; and, to date, no false-negative CVS karyotypes have been reported (i.e., no reports of a normal chromosomal analysis at the time of CVS followed by the birth of a baby with a chromosomal aberration).[14] Two major diagnostic problems occur with genetic analyses based on chorionic villous tissues because (1) discrepancies occasionally occur between chorion and other extraembryonic tissues (e.g., amniocytes) as well as embryonic tissues; (2) discrepancies exist among chorion tissues (e.g., between direct chromosome preparations based on cytotrophoblast tissue and long-term tissue culture based on the mesenchyme cells); and (3) maternal contamination is a source of potential diagnostic errors, particularly when the original sample was small (<5 mg) and cultured over a long period of time.

The diagnostic accuracy of cytogenetic results based on first-trimester CVS will shortly be reported from a seven-center study, supported by the National Institute of Child Health and Human Development.[15] For 6033 patients who had a successful CVS procedure, the rate of obtaining a cytogenetic diagnosis was

TABLE 6.9. Recurrence risk at time of CVS for women with a previous chromosomally abnormal conception.

Previous abnormality	Total pop.	Occurrence at CVS		
		Trisomy 13	Trisomy 18	Trisomy 21
Trisomy 13	17	–	–	–
Trisomy 18	36	1	–	1
Trisomy 21	213	1	2	1
Total	266	2	2	2

extremely high, 99.6%. There were no incorrect sex predictions and no diagnostic errors involving the common trisomies, 13, 18, and 21; sex chromosome aneuploidies; or structural chromosome aberrations. Chromosome mosaicism was observed in only 0.83% of all CVS cases but was confirmed in amniocentesis or fetal tissues in 0.19% (1 in 500 cases). These cases did represent potential diagnostic problems and required that the interpretation to the patients be provided by an experienced team of medical geneticists and counselors knowledgeable about the clinical significance, if any, of the unusual chromosomal findings. Maternal cell contamination occurred in 1.9% of long-term cultures, although this apparently did not present any diagnostic dilemmas. The study concluded that, overall, a very high degree of laboratory success and diagnostic accuracy was observed when chromosomal analysis was based on either direct preparations of cytotrophoblast tissue or long-term tissue culture. Concern was expressed about the potential effect of maternal contamination on biochemical and DNA studies, especially studies involving DNA analyses applied to small numbers of cells, which could yield false-negative diagnostic results. This study, similar to others,[16,17] concluded that chromosomal analysis based on long-term tissue culture of villous tissue may be more accurate than direct chromosome preparations in those cases involving discrepancies.

Concluding Considerations

The present status of transcervical CVS is that this technique is a consistently reliable method for obtaining fetal tissue for genetic analysis, that it is a safe procedure with an acceptable loss rate and no long-term sequelae, and that it is an appropriate early alternative to amniocentesis. The major issues remaining with transcervical CVS are (1) a critical evaluation of the technologic variables to minimize fetal loss and maximize sampling efficiency and (2) strategies for making transcervical CVS available to a larger percentage of patients. Transabdominal CVS is currently being evaluated by a multicenter study supported by the National Institute of Child Health and Human Development. The general consensus at the present time is that CVS has an obstetric risk/benefit ratio similar to that of the transcervical approach.

Preimplantation Genetic Diagnosis

The standard approaches to the fetal diagnosis of genetic diseases are CVS, amniocentesis, and more recently, percutaneous blood sampling (PUBS). Each of these procedures is associated with obstetric risks to the mother and to the fetus. If a genetic abnormality is detected, the only alternative to continuing the pregnancy is an elective termination. For parents at significant risk for a genetically abnormal conception, the possibility as well as the experience of repeated pregnancy terminations produce severe emotional trauma. This would be avoidable if a genetic diagnosis were to be made before implantation.

In the past 20 years, techniques have been developed for the manipulation and culture of mammalian gametes and embryos outside the female reproductive tract (for review, see Jones et al.[18]). IVF is now an established treatment for certain forms of female infertility and, more recently, of male infertility. The techniques of IVF and embryo transfer offer the possibility of conducting genetic analyses on developing embryos before implantation. This possibility appears to be a natural extension of the rapidly developing field of IVF.[19,20]

A model for the preimplantation diagnosis of human genetic disease is illustrated in Fig. 6.1[21]: High-risk patients undergo ovarian stimulation to recruit as many follicles as possible, which then are aspirated transvaginally under ultrasound guidance. Following insemination and fertilization, each embryo is cultured in vitro to the four-cell stage, individually biopsied using techniques of micromanipulation, and genetically analyzed. If the biopsy is conducted at the four-cell stage and the genetic analysis is completed within 24 hours, the normal embryos are transferred to the patient in the same cycle. If the biopsy is performed at a later stage and/or the genetic analysis will not be completed within 24 hours, the embryos are cryopreserved for transfer in a later cycle. Because preimplantation genetic diagnosis involves the transfer of only normal embryos, initiating a pregnancy associated with a specific genetic disease and thereby requiring an elective termination is avoided. The diagnosis of genetic disease during the preimplantation stages of embryonic development obviates the emotional and physical trauma associated with a high-risk pregnancy and allows the parents to commit themselves to the pregnancy without fear of an affected newborn.

As with any new approach to prenatal diagnosis, the issue of the safety of the biopsy procedure and that of the accuracy of the genetic analysis must be carefully evaluated.

Preimplantation genetic diagnosis in humans could be carried out on spermatozoa, oocytes, or embryos.[20] Two approaches involving preembryos are possible: (1) the biopsy of the preembryo at the four-cell or undifferentiated stage; and (2) the biopsy of the preembryo at the blastula or differentiated stage. Experiments to be described were first conducted on mouse embryos and then on human embryos rejected for transfer because of the presence of three or more pronuclei in the fertilized oocyte. Approximately 5% of all in vitro inseminated oocytes develop three or more pronuclei, presumably because of polyspermy. The protocol

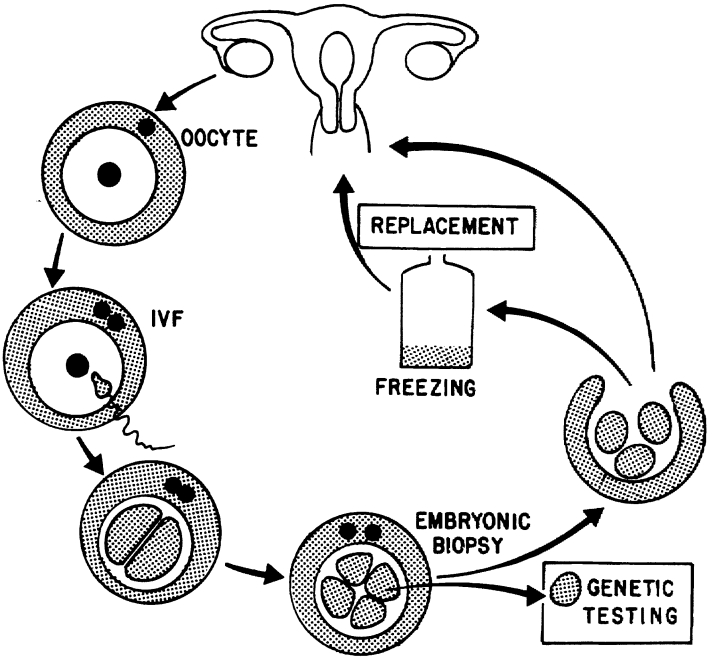

FIGURE 6.1. An overview of preimplantation genetic diagnosis. Preembryos biopsied at the four-cell stage and, depending on time required for genetic analysis, either cryopreserved or transferred to uterus. (*Source*: Reprinted with permission from Verlinsky Y, Pergament E, Binor Z, Rawlins R. Genetic analysis of human embryos prior to implantation: future applications of in-vitro fertilization in the treatment and prevention of human genetic disease. In: Feichtinger W, Kemeter P, eds. *Future Aspects in Human In- Vitro Fertilization*. Berlin: Springer-Verlag; 1987:263.) (IVF, in vitro fertilization.)

for experiment of human triploid embryos rejected for transfer was evaluated and approved by the Institutional Review Board and the Ethics Committees.

The first set of experiments consisted of 50 triploid human embryos at the four-cell stage. The instruments for biopsy consist of a holding pipette and a glass tube for aspiration of one to two cells of the four-cell embryo. The cells of the embryo were placed either in an empty zona pellucida or cultured as a monolayer using conventional tissue culture techniques. Of 50 preembryos biopsied at the four-cell stage, 41 were successfully tissue cultured and thereby available for chromosomal, enzymatic, or DNA analyses. Of 50 preembryos placed in empty zona pellucida, the short-term development of these triploid embryos did not appear to be impaired, as 41 reached either the morula or blastula stages. Overall, 64% of the triploid embryos were technically available for both genetic analysis and transfer. This probably represents the lower rate of success, because triploid embryos have a natural history of embryonic maldevelopment and growth arrest.

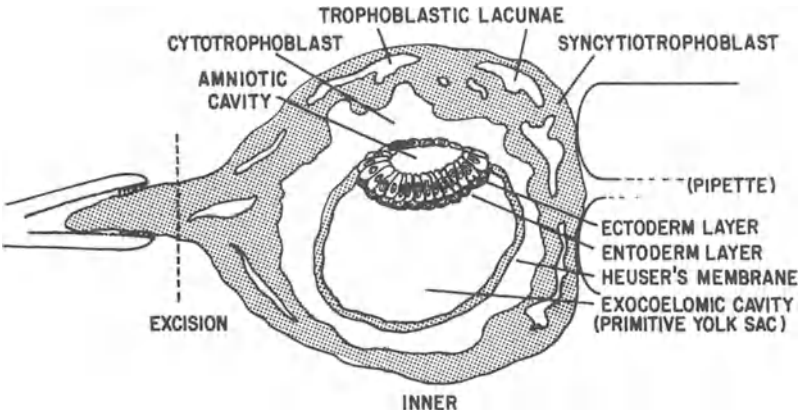

FIGURE 6.2. Preimplantation genetic diagnosis by biopsy at the blastula stage of embryonic development (technique of Edwards).[20] An incision in the zona pelucida (not shown) results in herniation of trophectoderm tissue, permitting its excision for genetic analysis.

A second approach to the preimplantation diagnosis of genetic disease involves the biopsy of the preembryo at the blastula stage (Fig. 6.2).[20] This approach could be termed *early chorionic villous sampling* because trophectoderm tissue, which develops into the placenta, is excised. Using micromanipulation, the blastula is positioned by a holding pipette and glass scalpel before incision of the zona pellucida; the glass scalpel is then inserted into the zona pellucida; trophectoderm tissue herniates through the incised zona pellucida over a 2-hour period; and finally, the trophectoderm tissue is excised. This form of biopsy has been conducted on triploid embryos rejected for transfer. Preliminary experiments with animal models indicate that normal in vitro development occurs after trophectoderm biopsy.[22,23]

The results of biopsies of trophectoderm tissues from 18 human triploid embryos are summarized as follows. After excision of the trophectoderm, some shrinkage of the entire embryonic and extraembryonic mass from the walls of the zona pellucida occurs but only for a short time, and then recovery without any other morphologic changes is observed. Twelve biopsies were established in tissue culture and were thereby available for studies related to chromosomal aberrations and inborn errors of metabolism. DNA studies for sickle cell anemia were successfully conducted on excised tissue from 14 preembryos.

In summary, a series of genetic analyses have been performed on human triploid embryos, which suggest that it will be possible to aspirate oocytes from women at high genetic risk, to biopsy the preembryos and determine their individual genotypes, and then to transfer to these women only those embryos expected to produce a normal clinical outcome. This approach will be applicable for women at risk because of a familial chromosomal rearrangement or an inborn

error of metabolism and for those women at risk for a genetic disease amenable to analysis by DNA probes and recombinant DNA technology.

Prenatal Diagnosis Using Fetal Cells Obtained From Maternal Blood

In the last two decades, fetal diagnosis of severe congenital disease with selective termination of affected pregnancies has gained widespread acceptance. Until recently, fetal diagnosis had been limited to the second trimester of pregnancy because fetal samples suitable for diagnosis could only be reliably and safely obtained after 16 weeks of gestation. The main obstetric methods involved, ultrasound and amniocentesis, carry relatively little risk in expert hands, although fetal blood sampling is less safe. The laboratory diagnosis is also reliable, providing quality control is rigorous.

Fetal diagnosis of sporadic congenital diseases such as chromosomal disorders and neural tube defects is now widely practiced. However, fetal diagnosis of inherited diseases for which the risk in each pregnancy is much higher is restricted by the difficulty of prospective identification of at-risk couples. Consequently, fetal diagnosis has hitherto been most beneficial to groups of mothers at relatively low risk and has led mainly to reassurance. Therefore, while only a relatively small proportion of pregnancies have been terminated, the service is very helpful both for the families involved and for society in terms of costs and benefits.

One of the most exciting and fruitful recent advances in medical genetics is the rapid development of DNA technology. It is now possible to diagnose the presence of genes responsible for sickle cell anemia, thalassemia, phenylketonuria, cystic fibrosis, and muscular dystrophy, using direct DNA methods. DNA methods can be applied to extremely small quantities of tissue of any origin, even single cells! This contributed in part to the search for alternative and earlier sources of fetal cells for diagnosis of hereditary diseases. Accordingly, obstetric methods were developed for sampling the chorionic villous tissues of the early placenta, which has the same genotype as the embryo/fetus. CVS has the potential for the prevention of both high-risk and low-risk conditions, but its widespread applicability can be assessed only when the obstetric risk to the mother and fetus has been fully defined.

Both amniocentesis and CVS require considerable procedural expertise as well as specialized personnel and equipment; consequently, both are costly procedures. As a result, both techniques have been applied to a limited number of at-risk couples. These methods are therefore not suitable in their present form for widespread screening of pregnancies. The desirability of such screening is obvious, as most genetically defective offspring occur in couples considered to be at low risk. An ideal method for screening pregnancies for genetic abnormalities would be one that is noninvasive, rapid, relatively inexpensive, potentially automatable, and easy to perform soon after conception. As with any screening

method, its specificity might not be as critical as its sensitivity. It would be an early step in an algorithm of evaluation of pregnancy. Abnormalities detected by such a method might lead to more specific confirmatory tests, e.g., CVS, amniocentesis, or PUBS, and the predictive value of a negative result would be maximized at the expense of the predictive value of a positive result.

Current Status

Publications claiming the presence of fetal cells in maternal circulation as early as 10 to 14 days after implantation suggest the exciting possibility of performing prenatal genetic diagnosis starting with the simple removal of a sample of the mother's blood.[24-30] Three types of fetal cells reportedly have been found in the peripheral blood of pregnant women: syncytiotrophoblast and cytotrophoblast cells, fetal red blood cells, and fetal mononuclear cells, probably of lymphocytic origin. The early evidence consisted of demonstrating structures with the morphology of syncytiotrophoblast in the venous drainage of the gravid uterus.[24] With advances in the characterization of the immunobiology of trophoblast, reagents became available that labeled these cells with some degree of specificity. First, polyclonal antisera and then monoclonal antibodies, which recognize antigenic determinants relatively unique to trophoblast plasma membranes, became available.[31] The use of some of these reagents toward isolation and purification of fetal trophoblast from maternal circulation has been the subject of several publications.[30,32] Although these authors claim to have isolated trophoblast cells, based on morphology and immune labeling with the reagents used to isolate the cells, none have reported successful culturing, biochemical analysis, or karyotyping of the isolated cells. Also, none have attempted multiparameter analysis of these cells with antibodies to multiple antigens known to be expressed simultaneously by trophoblast cells. Such immunophenotypic, genetic, and biochemical studies are obviously required before the nature of these purported fetal cells can be unequivocally established.

Similarly, the use of antibodies to human leukocyte antigens (HLA) followed by identification of Y chromatin have been used to isolate and purify cells of fetal origin from maternal blood.[26,27] Although the authors admit that they did not know the true nature of these fetal cells, they suspected that they belonged to the lymphoid lineage. Also, although the authors refer to work in progress of culturing these cells, no follow-up is available since publication.

Because fetal cells are presumably "rare events" in maternal blood, the techniques used in any approach to isolate, purify, and study these cells must have the following characteristics: the isolation procedure must be rapid, highly efficient, and highly specific. One of the most promising methodologies being investigated is the combination of a specific antifetal antibody conjugated with a fluorochrome, followed by flow cytometry and fluorescence-activated cell sorting.[26,30] An attempt at improving the signal/noise ratio and the speed of analysis and sorting are the subject of another group's research.[29]

The available evidence was sufficiently suggestive that the National Institute of Child Health and Human Development recently (1987) provided support to two medical genetic centers to undertake a systematic approach to the study of the use of fetal cells obtained from maternal blood for prenatal diagnosis of genetic defects. At present, the main focus of these investigators is to determine if fetal cells are actually present in the maternal peripheral circulation. There is little doubt that while trophoblast cells reach maternal circulation, they are "deported" to the lungs, where they are removed and prevented from remaining in the peripheral blood in significant numbers. There is considerably less incontrovertible evidence that trophoblast does indeed reach the peripheral blood. Reports suggested that using a monoclonal antibody that reacts with trophoblast, cells were recovered from peripheral blood that appeared morphologically as mononucleated or multinucleated trophoblast.[30,32] The most recent reports,[33,34] however, indicated that this interpretation was incorrect, that in reality, fetal HLA antigen had been trapped by maternal monocytes and thereby assumed the appearance of fetal cells in the maternal peripheral circulation.

Recombinant DNA Technology

The ability to detect specific genetic alterations related to specific diseases usually requires substantial amounts of genomic DNA and the appropriate molecular tools to detect the lesion. Recently, Saiki et al.[35,36] have described a powerful method that allows the selective amplification of unique sequences of DNA for subsequent analysis. This method requires the synthesis of very specific oligonucleotide primers that can be used to amplify specific homologous sequences. The method is termed *polymerase chain reaction* (PCR) and is based on repeated cycles of denaturation of the double-stranded DNA sample at high temperature, annealing of the oligonucleotide primers to the DNA template at low temperature, and extension of the primers using DNA polymerase. The advantage of PCR is the ability to selectively enrich for specific sequences of DNA to allow genotypic analysis from minute quantities of genomic DNA, even from a single cell.

This approach has been applied to pregnant patients with sickle cell anemia, i.e., women with only S hemoglobin. Blood was drawn in the third trimester, and PCR was conducted to amplify only hemoglobin A. Analysis was made for the presence of hemoglobin A, because its source could be only of fetal origin. In four of five patients, amplification of hemoglobin A was detected, indicating that the fetus was heterozygous (AS) for the hemoglobin gene; three of these four patients have delivered heterozygous infants, as expected if the father was the original source of the hemoglobin A gene. Two patients, including the one failing to exhibit hemoglobin A amplification, have not as yet delivered. These results suggest that fetal cells are indeed present in the maternal circulation.

Several criticisms are directed toward this interpretation, however. Two sources of contamination giving false-positive results have yet to be eliminated.

First, it is becoming increasingly evident that laboratory contamination is a serious problem when minute amounts of genomic DNA are amplified. Foreign DNA may be derived by the mere collecting of specimens and handling of test tubes, and meticulous attention to this possibility is required. Second, persons with sickle cell anemia frequently have been transfused, and this raises the possibility that foreign lymphocytes with the hemoglobin A genotype are circulating in their peripheral blood. To rule out the possibility that the hemoglobin A detected in the blood of pregnant sickle cell patients (SS genotype) resulted from laboratory contamination or from previous blood transfusions, the following natural experiment has been proposed: monitoring the peripheral blood of pregnant hemoglobin A women (AA) whose husbands have sickle cell disease. The presence of hemoglobin S in the peripheral blood of such women will prove that at least DNA sequences derived from the fetal genotype are present in the maternal circulation.

These issues remain unresolved at present: Are fetal cells or at least DNA sequences derived from the fetus present in the peripheral circulation of the mother during pregnancy? And, is it possible to develop noninvasive, rapid, and accurate techniques for use in the early prenatal diagnosis of human genetic diseases? The prospects for providing such an approach are exciting, but the goals have yet to be achieved.

Summary

First-trimester fetal diagnosis by CVS is rapidly becoming available for women at high risk for a conception with a genetic disorder. Multicenter studies in the United States[4] and Canada[5] indicate that the safety and the accuracy of transcervical CVS compares favorably to that of amniocentesis. No significant maternal complications were observed, and only a slight but not significant increase in pregnancy loss rates was reported. An extremely high degree of laboratory success and diagnostic accuracy was observed for chromosomal, enzymatic, and DNA analyses of genetic diseases.[15]

The next generation of fetal diagnosis is likely to involve genetic studies performed on embryos before implantation.[20] Using the conventional techniques of in vitro fertilization and embryo transfer, it may be possible to analyze single cells derived from the developing embryo or from extraembryonic tissue.[21,22,23] Following the analysis, only unaffected embryos would be transferred, thereby ensuring that a normal pregnancy would be initiated. Such an approach would be applied to pregnancies at significant risk for a chromosomal aberration or an inborn error of metabolism.

Research is currently in progress on the possibility of isolating or at a minimum analyzing fetal cells (genes? DNA sequences?) from the peripheral blood of pregnant women.[33,34] Although evidence indicates fetal cells cross the placenta, the presence of fetal cells in the maternal circulation during pregnancy has not been firmly established.[33] If it proves possible to analyze the fetal genotype from a sample of the mother's blood, this would have a dramatic impact on the overall effect

of genetic diseases in humans: All women could potentially be screened without the obstetric risks associated with CVS and amniocentesis; and such screening, if applied to pregnant women at large, has the potential of significantly reducing not only the incidence of genetic disease in the newborn but also its concomitant economic, societal, familial, and personal costs.

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7
Current Concepts in Substance Abuse During Pregnancy

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Over the past 10 years, research investigations toward a better understanding of the impact of substance abuse during pregnancy on the developing fetus has increased dramatically. These investigations have progressed from simply determining if a certain drug "crosses the placental barrier" and the adverse effects seen in the neonate to highly sophisticated studies determining the mechanisms of drug action on the fetus. As a result of both ethical and technical constraints, much of this information has been gathered from experimental animal data. This chapter highlights some of these experimental findings and reviews our current knowledge of maternal–fetal pharmacology of substance abuse. A review of the clinical findings relating to substance abuse in human pregnancy was recently presented in this series.[1]

Placental Drug Transfer

There is little doubt that all drugs that have ready access into the central nervous system will also distribute readily across the placenta and exert direct actions on the fetus. It has been demonstrated repeatedly that the placenta does not "protect" the fetus from the commonly abused substances such as methadone and cocaine. These drugs have been detected in both cord blood and neonatal urine after delivery.[2,3] The magnitude of adverse effects on the fetus therefore depends on the extent of drug distribution to the fetus. Maternal–fetal pharmacokinetic studies in the pregnant ewe have revealed differences in the rate and extent of fetal exposure to different substances of abuse.

Numerous studies have demonstrated rapid equilibration of ethanol across the placenta between mother and fetus, with fetal blood levels being virtually identical to maternal blood levels at all times.[4-6] The rate of elimination of ethanol from fetal plasma has been found to be similar to that in maternal plasma and can best be described by Michaelis-Menten kinetics.[6] These suggest that elimination of ethanol by the fetus is limited and is for the most part driven by maternal elimination.

The placental transfer of most opioid drugs was also found to be extremely rapid after intravenous administration to the mother, with peak fetal blood levels occurring in less than 5 to 10 minutes for methadone and morphine.[7-9] Despite the apparent rapid transfer of these drugs across the placenta, however, fetal blood levels remained lower than maternal levels at all times after drug administration. Unlike the rapid equilibration of ethanol between the mother and the fetus, there is no evidence that such an equilibrium is achieved with any of the opiates.

Likewise, the distribution of cocaine to the fetus was found to be very rapid, with fetal levels approaching 15% of maternal levels by 3 to 5 minutes after intravenous administration to the mother.[10] Fetal levels, however, were again significantly lower than maternal levels at all times after drug administration.[10] Thus, in general, lipid-soluble compounds of low molecular weight are readily distributed across the placenta to the fetus, although equilibrium is seldom achieved between the mother and fetus for most drugs.

An exception to this, however, is the placental transfer of tetrahydrocannabinol (THC) following marijuana smoking. THC was barely detectable in fetal plasma by 30 minutes after maternal smoke inhalation, and peak blood levels did not occur until 2 to 4 hours later and were significantly lower than maternal levels.[11] The reason for the apparent slow distribution to the fetus of such an extremely lipid-soluble compound is not known. A possible contributing factor may be the very extensive binding of THC to maternal plasma proteins (99%), so that only a very small free fraction is available for diffusion across the placental membranes.

In all of the preceding studies, the elimination half-lives in the fetus were found to be similar to those in the mother, indicating that elimination of these drugs from the fetus is largely dictated by maternal elimination characteristics. The persistently lower drug concentrations in the fetus, however, even after chronic repeated exposures, indicate that perhaps with the exception of ethanol, these drugs are also cleared from the fetus directly.[12] In the absence of fetal drug clearance, one would expect the maternal and fetal compartments to come into equilibrium, and maternal and fetal drug concentrations would be equal. However, with the exception of renal clearance of meperidine by the fetal lamb,[13] little experimental evidence supports fetal clearance of drugs of abuse. The presence of metabolites in fetal plasma alone does not imply fetal biotransformation ability because lipid-soluble metabolites of maternal origin may be readily distributed to the fetus, as has been demonstrated for normeperidine.[7] On the other hand, morphine glucuronide has been detected in fetal plasma, and because the glucuronide has been shown not to cross the placenta to any measurable extent, it is most likely of fetal origin.[14] These more recent findings suggest that fetal drug clearance plays a significant role in determining the extent of fetal drug exposure. It follows also that the extent of fetal exposure to a maternally administered drug may not be constant throughout gestation, resulting from maturation of drug-elimination processes.[15]

Experimental data from animal studies support findings in humans that many drugs, including meperidine and ethanol, are distributed into amniotic fluid. The appearance of drug in amniotic fluid is usually delayed, but the peak concentra-

tion usually far exceeds the concurrent concentrations in maternal and fetal plasma.[6,7] Metabolites, such as normeperidine and acetylaldehyde, have also been detected in amniotic fluid. Because many of the drugs of abuse and their metabolites are weak bases, accumulation in amniotic fluid can result from the lower pH of amniotic fluid, thus resulting in a reservoir of drug in utero. Elimination of drugs from amniotic fluid may occur via diffusion across membranes into the fetal and/or maternal circulation and by fetal swallowing of amniotic fluid. For lipid-soluble drugs, such as meperidine, diffusion across the membranes into maternal circulation has been shown to be the predominant pathway.[7]

Adverse Effects on the Fetus and Neonate

A major advancement in research on adverse effects of substance abuse on the fetus has been the change in emphasis from morphologic teratology studies to functional studies. Although it has been known for quite some time that exposure to many drugs of abuse early in development may result in morphologic malformations such as the fetal alcohol syndrome, it is now quite apparent that drug exposure later in development may result in functional abnormalities.

Prenatal exposure to a number of drugs of abuse has been linked to shorter gestational lengths and lower birth weights, including ethanol,[16] opiates,[17] and cocaine.[18,19] Maternal smoking of either nicotine cigarettes or marijuana cigarettes has also been reported to result in lower birth weights.[19-21] In addition, marked tremors and startles and altered visual responsiveness were reported in infants born to marijuana users at 2 to 4 days of age.[22] Infants exposed to cocaine had significant depression of interactive behavior and poor state organization.[18] As with infants born to heroin or methadone users, it is difficult in the neonatal period to distinguish between direct effects of the drug on neurologic development versus withdrawal symptoms. Some behavioral and neurologic disturbances, however, appear to persist into early childhood. Many children exposed to opiates prenatally have been found to be hyperactive, with shorter attention spans, decreased fine-motor coordination, and abnormal sleep–wake patterns.[23]

A significant problem associated with these studies is the large number of subjects necessary because of the high incidence of polydrug abuse. Many of these clinical investigations are still in their preliminary stages, and a full assessment will require a larger number of pregnancies and longer follow-up on these children. The different mechanisms by which this diverse group of drugs affect fetal growth and development are not yet understood, although recent findings have suggested that both direct effects on the fetus as well as indirect effects on maternal and placental physiology may be involved. In addition, recent evidence suggests that dose–response relationships in the fetus may be quite different from those in adults. These differences may be due to differences in receptor populations, effector systems, or normal regulatory mechanisms. Because it is not yet possible to study directly drug effects on fetal brain function and metabolism in the human, much of this information was obtained using the pregnant sheep

model, and significant advances have been made toward a better understanding of the pharmacodynamic actions and mechanisms of ethanol, opiates, marijuana, and cocaine on the fetus.

Ethanol

The administration of ethanol to the ewe resulted in a prolonged suppression of fetal breathing movements and alterations in fetal electrocortical activity without significant effects on arterial blood gas values.[24] The effect on fetal breathing movements was dose dependent and associated with a decrease in fetal heart rate and cerebral oxidative metabolism.[25] The exact mechanisms by which ethanol affects fetal cardiorespiratory function has not yet been ascertained, although it appears unlikely that these changes are due to acetaldehyde because no temporal relationship was observed between fetal blood acetaldehyde levels and the changes measured in fetal cardiovascular and brain function.

Cocaine

The adverse effects of maternal cocaine use on the fetus appear to be due to both cocaine's action on uteroplacental perfusion as well as direct action on the fetus. Intravenous administration of cocaine-produced dose-dependent increases in maternal and placental vascular resistance, a reduction in uterine blood flow and fetal hypoxemia, tachycardia, and hypertension.[26] While the fetal hypoxemia is secondary to a reduction in uterine blood flow, the fetal tachycardia and hypertension are largely due to placental transfer of cocaine and a direct action on the fetus. This was confirmed by direct administration of cocaine to the fetus. Cocaine is thought to act on uterine blood vessels by blocking reuptake of norepinephrine, thereby potentiating the vasoconstrictive actions of norepinephrine. Chronic exposure to cocaine may result in a gradual desensitization to the cardiovascular actions of catecholamines as a result of receptor down-regulation. This, however, has not yet been demonstrated.

Opiates

Many of the adverse effects of opiates on the fetus that have been described appear to be due to direct drug actions on the fetus. Maternal opiate administration has been reported to result in significant changes in fetal cardiorespiratory and neurobehavioral function without affecting maternal hemodynamics or uterine perfusion. Low doses resulted in central nervous system (CNS) excitation in the fetus, with desynchronized electroencephalogram (EEG) activity and increased muscle tone and activity.[27-29] This was also associated with continuous breathing movements[27,28,30,31] and increased heart rate and heart-rate

variability.[27] No significant change in uterine blood flow or oxygen delivery to the fetus were noted, although a significant increase in fetal oxygen consumption and fetal cerebral metabolism were observed.[30] Higher doses resulted in CNS depression with synchronized EEG activity, suppression of total motor activity, and apnea.[30,32] Both the low-dose excitatory response as well as the high-dose depressant response could be reproduced by direct administration of the opiates to the fetus, providing further evidence that they were mediated by direct actions on the fetus.[33,34]

Considerable efforts have been put into studying the mechanisms of action of opiates on the fetus. The dramatic excitatory effects of opiates on the fetus have been quite unexpected, and the dose–response relationships have been found to be much more complicated than in the adult. These excitatory effects were observed over a wide range of doses and appear to be mediated by specific opiate receptors in that they could be abolished by naloxone pretreatment.[33,34] The depressant response can also be blocked by naloxone.[35] Although tachycardia and CNS excitation have occasionally been reported in adults, they have not been of the intensity observed in the fetal lamb. The stimulation of breathing movements certainly appears to be unique to the fetus. The effects of morphine on the incidence of fetal breathing movements can be described by a biphasic dose–response curve, with stimulation at lower doses and suppression at higher doses.[33] In contrast, the effects of opiates on fetal heart rate is best described by a bell-shaped dose–response curve because bradycardia was never observed even with very high doses of morphine.[34]

Both the biphasic dose–response curve for fetal breathing movements and the bell-shaped dose–response curve for fetal heart rate suggest that they may be the result of opiate interactions with multiple opiate receptors. Recent studies using receptor-selective opioid peptides have revealed that fetal tachycardia was seen only following intracerebroventricular administration of μ-selective peptides and not with δ-selective peptides.[36] δ-selective peptides have been reported to cause tachycardia in adult animals. The lack of response in the fetus suggests either the lack of δ-receptors at that stage of development or the absence of a functional second-messenger system. These possibilities are now being examined.

Thus, direct effects of the opiates on the fetus can differ both qualitatively and quantitatively from those in the adult. These findings also imply that opposing effects may be observed in the fetus, depending on the dose of drug consumed by the mother. At the present time, it is difficult to speculate whether the low-dose or high-dose response is more detrimental to the fetus. The low-dose excitation state has been shown to be associated with an increase in metabolic rate, which in the absence of increased supply to the fetus may result in a reduction of energy supply available for growth. As in the adult, consequences of repeated exposure to opiates are also affected by the development of tolerance. Rapid onset of tolerance to both low-dose and high-dose morphine effects have been demonstrated in the fetal lamb.[37,38] Concomitant with the development of tolerance, there was also evidence for physical dependence with alterations in fetal sleep–wake patterns following cessation of low-dose morphine infusion.[37]

Tobacco Smoking

The investigation of the effects of tobacco smoking in an animal model has been greatly hampered by the lack of a convenient method to introduce tobacco smoke to an alert animal. Consequently, most studies have employed parenteral administration of nicotine.

Cigarette smoking has been shown to result in a significant reduction in the incidence of fetal breathing movements in human pregnancy.[39,40] A similar finding was confirmed in the fetal lamb when nicotine was administered to the mother.[41] Concomitant with the suppression of fetal breathing movements were an increase in fetal blood pressure, decrease in fetal heart rate, and a decrease in fetal partial pressure of oxygen (Po_2). On the other hand, direct administration of nicotine to the fetus actually induced a brief burst of fetal breathing movements, no change in arterial blood gases, and an increase in blood pressure and heart rate. These findings suggest that the suppression of fetal breathing movements following maternally administered nicotine was most likely due to fetal hypoxemia as a result of uterine vasoconstriction. This proposal is supported by the fact that these effects were blocked by treatment of the ewe with phentolamine to prevent the sympathomimetic response. These findings illustrate how adverse effects in the fetus may be mediated by indirect drug actions on maternal or placental physiology.

In addition to the effects of nicotine on fetal breathing movements, recent evidence suggests that direct administration of nicotine to the fetus results in a dose-dependent alteration of the organization of EEG states in the fetus as well as changes in the frequency characteristics of the EEG. (unpublished data) With continuous exposure to nicotine, tolerance developed rapidly to the effects on fetal EEG, and the organization of EEG states returned to normal despite continuous drug exposure. Abnormal organization of EEG states, however, was once again observed on discontinuation of nicotine infusion, demonstrating the development of physical dependence in the fetus (unpublished data).

Marijuana

Unlike tobacco smoke, the large number of cannabinoids in marijuana, many of which are pharmacologically active and may interact with each other, has made it difficult to justify studying the effects of a single component of marijuana smoke. The recent development of a simple system for introduction of marijuana smoke to large animals has made it possible for numerous investigators to study the effects of marijuana smoking on the fetus.[11] Introduction of marijuana smoke to pregnant ewes resulted in significant reductions in maternal respiratory rate and arterial Po_2.[42,43] Because this marked reduction in Po_2 was not associated with either carbon dioxide retention or systemic acidosis, it has been suggested that marijuana induces a maternal ventilation/perfusion imbalance.[42,43] This maternal hypoxemia resulted in a significant reduction in fetal oxygen tension,

which remained depressed after maternal values had returned to control levels.[43] The prolonged reduction in fetal oxygen tension suggested that marijuana smoke inhalation may impair placental gas transfer by disrupting perfusion balance between the maternal and fetal circulations. In a recent study, Clapp et al.[44] demonstrated that marijuana smoking has a direct relaxant effect on both maternal and fetal placental vascular smooth muscles. This effectively decreases the normal heterogeneity of flow and actually improves macroscopic placental perfusion balance. The significant reduction in fetal oxygen tension can therefore only be explained by a perfusion imbalance at the microscopic level. Another possibility may be that marijuana smoking stimulates fetal activity and results in increased oxygen extraction. This possibility currently is being examined.

Summary

It is hoped that this review has served to illustrate the tremendous progress that has been made in the last 10 years toward a better understanding of the maternal–fetal pharmacology of substance abuse. This advance has primarily resulted from systematic investigations in experimental animal research. The magnitude of adverse effects in the fetus consequent to maternal drug use is clearly determined by the extent of fetal drug exposure. But in addition to maternal–fetal pharmacokinetics, drug effects in the fetus may be further complicated by drug actions on placental function and unconventional dose–response relationships in the fetus resulting from immature receptor–effector systems.

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8
Stabilization and Transportation of the Critically Ill Obstetric Patient

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Pregnancy does not exclude women from potentially dangerous activities and situations including those related to occupation and recreation. Any injury that can occur to a young adult may also occur to a pregnant woman and place her in a critically ill condition. Though difficult to determine accurately, it is estimated that 7% of pregnant women will seek medical assistance as a result of accidental injury.[1] In addition, obstetric complications such as hypertension, diabetes, seizures, and hemorrhage may also lead to life-threatening physiologic states. Medical and nursing personnel, as well as other health care professionals involved with emergency care and transport, may be faced with difficult decisions in the planning and implementation of care for such patients. Stabilization and ultimate transportation of a critically ill pregnant woman may be necessary at any level of institution. Those responsible for delivering obstetric care must be confident in their ability to stabilize a physiologically unstable pregnant woman.

Setting Priorities

When a pregnant patient becomes physiologically unstable or critically ill, she presents a dilemma to the medical and nursing staff because of the difficulty in the identification of care priorities. Use of the acronym STABLE may be of assistance when setting priorities in emergency situations when stabilization is imperative. Each letter of the word represents an action that the nurse and physician must implement to achieve patient stability (Fig. 8.1).

S = Stay Calm

The ability to stay calm in an emotionally trying situation is a task that all professionals strive to achieve. It may also be the single most important thing that one can do to facilitate stabilization of the critically ill patient, for without this the approach to emergency care easily may become chaotic. The ability to stay calm in an emergency is hindered further by the body's reflexive response to a stressful event. As the central nervous system reads input as a threat, the sympathetic

FIGURE 8.1. STABLE.

S	=	STAY CALM
T	=	TRIAGE
A	=	ASSESSMENT
B	=	BABY
L	=	LAUNCH
E	=	EVALUATE/EVACUATE

branch of the autonomic nervous system stimulates the release of potent catecholamines resulting in an increase in the heart rate, respirations, and blood pressure. This sympathetic activity is responsible for an increase in cardiac output, partially achieved by the shunting of blood into the central circulation from nonvital organs. Known as the "fight-or-flight" response, the physiologic change may hinder the clinician's ability to think clearly in an emergency.

To achieve calmness and control, the physician and nurse may use biofeedback techniques such as purposeful select muscle relaxation or the slowing of respirations with the exercise of deep breathing. In the hospital and ambulatory setting it is important that calmness be achieved at the bedside. In the event a care provider is unable to remain calm, a team member should have the authority to remove the individual from the bedside and replace the clinician with a substitute until calmness is achieved. Calmness, similar to panic, is contagious; and a focused, deliberate stabilization effort will more likely achieve the best results for both patient and staff.

T = Triage

The second priority in the stabilization phase is to triage the patient and implement cardiopulmonary resuscitation (CPR) if indicated. The three steps of establishing an airway, initiating respirations, and beginning chest compressions are utilized and are vital to initiate prior to additional stabilization and emergency management procedures. The physiologic changes of pregnancy, which include an increase in tidal volume, reduced residual capacity, and increased oxygen consumption due to the demands of the pregnancy, result in a maternal chronic compensated acidosis. This predisposes the patient to rapid exhaustion of oxygen reserves that produce rapid deterioration in periods of cardiopulmonary insults.

Medical complications of pregnancy such as hypertension, heart disease, asthma, and collagen vascular disease increase the risk of cardiopulmonary arrest in the pregnant patient. Acute complications of pregnancy that may include trauma, drug overdose, shock, pulmonary embolism, myocardial infarction, and anesthesia reactions are also associated with maternal arrest in pregnancy.[2-6]

CPR

Each step in the implementation of CPR is preceded by an assessment technique. To establish unresponsiveness, the physician or nurse should speak loudly to the patient and shake the patient for a response. If there is no response from the woman, the first step is to establish an airway using the head-tilt and chin-lift or jaw-thrust maneuvers. Assessment for breathing is done by feeling and listening for the movement of air and observing for chest expansion. If breathing is absent ventilations should immediately be started by delivering two slow breaths of 1 to 1½ seconds each. If the rescuer is unable to ventilate the patient, repositioning of the patient's head is first attempted followed by the delivery of two more breaths. If the airway is obstructed, chest thrusts—rather than subdiaphragmatic thrusts—should be used in pregnancy when performing the Heimlich maneuver. A finger sweep of the mouth is then performed to remove any foreign object that may have been dislodged.

If intubation is to be performed by an experienced and trained health care team member, care must be given to prevent airway trauma and hemorrhage due to the increased circulation to the respiratory tract that occurs during pregnancy.

The establishment of an airway and ventilation is followed by an evaluation of cardiac activity via the palpation of carotid arterial pulsations. If pulsations are present, ventilation is continued at 12 breaths per minute. If there are no pulsations, external chest compressions are started at a rate of 80 to 100 per minute. During CPR efforts, blood flow is most probably achieved by phasic fluctuations in intrathoracic pressure rather than by compression of the heart between the sternum and spinal column.[7-9] Therefore, the gravid uterus must be displaced during CPR to prevent an increase in intrathoracic pressure, a decrease in preload, and an obstruction of flow through the abdominal aorta. Displacement can best be accomplished by assigning an individual to apply constant lateral pressure directed from the patient's right side to her left, or by using a wedge placed directly beneath her right hip.

Fifteen chest compressions followed by two breaths is accomplished if there is one rescuer, and reassessment of the patient if accomplished after every four cycles. When two rescuers are implementing CPR, five chest compressions are followed by the delivery of one breath. If the patient is intubated and on a ventilator, the chest compressions are delivered at a rate of 80 to 100 per minute, and the ventilation rate is set at 12 to 15 breaths per minute. CPR should not be interrupted for longer than 30 seconds and should be continued until it has been determined that the patient cannot be revived.

A = Assess

Assessment of the unstable pregnant patient is a followup of simple triage measures. Following the start of resuscitation efforts, a rapid head to toe assessment with major emphasis on pulmonary, cardiovascular, and neurologic status should be completed. The cardiovascular assessment should minimally consist of the heart rate; blood pressure; cardiac rhythm; heart sound character; the presence or absence or a rub, gallop, or murmur; color and temperature of the skin; the color and capillary refill time of the nailbeds; the amount of jugular vein distention in a 45° angle; dependent or independent edema; and the quality of pulses. The respiratory assessment should include the respiratory rate; the quality of respirations; the presence of abnormal respiratory patterns; breath sounds; and the production and quality of sputum. Neurologically, parameters to be assessed include the patient's orientation; motor response; verbal response; Glascow coma scale; pupil size, equality, and reaction; strength; and behavioral responses. A critical care assessment flow sheet for rapidity of documentation may be useful to the obstetric team in repetitive assessments. The acquisition of assessment findings will further assist the stabilization team in the identification of the major cause of the physiologic unstable state and assist in further care planning.

B = Baby

After the team has stayed calm, initiated CPR, and completed the maternal assessment, fetal evaluation should begin. The most common cause of fetal death is maternal death; therefore, immediate stabilization measures are most appropriately directed toward the mother.[10] During an emergency when the maternal life may be in jeopardy, two significant questions need to be answered regarding fetal status. They are: (1) what is the best estimate of gestational age, and (2) is the fetus alive? Even when maternal death is imminent, maternal resuscitation is continued until fetal age and status are determined.[11] These questions may be rapidly addressed by the practitioner at the bedside who has access to antepartum records, fundal height measurements, or a bedside ultrasound device. Once this information is obtained, it becomes imperative that it be communicated to the stabilization team. If the patient's condition deteriorates, information indicating the fetus to be 38 weeks with an audible heart rate becomes just as relevant as information indicating the fetus to be 18 weeks' gestation with no audible heart rate. Both sets of data may influence immediate plans of action.

In the absence of acute danger to the mother, additional information concerning fetal status may be obtained. This may include amniocentesis to evaluate fetal lung maturity, and ultrasonography for biophysical profile testing. A continuous electronic fetal heart rate monitor should also be applied if it does not interfere with maternal resuscitation and stabilization activities. Intervention specific to the pregnancy may become necessary but should not conflict with the maternal

plan of care. Such measures, including tocolysis or administration of other medications, should not jeopardize the maternal health in any way.

L = Launch

After the team has stayed calm, initiated CPR, and completed maternal and fetal assessment, it is time to implement the medical and nursing plan of care through the use of emergency protocols. Protocols become beneficial in the stabilization setting by defining specific team roles, setting a standard for performance, and by decreasing the time delay between arrival of necessary emergency team members and implementation of care. Protocols should be specific to individual hospitals and care settings and should take into consideration the availability of support services (see sample protocols).

E = Evaluate/Evacuate

Once stabilization protocols have been initiated, it becomes necessary to evaluate the effectiveness of the current stabilization measures and to determine the need for alteration of the protocols. The clinician at the bedside should decide if the patient's condition has improved, remains unchanged, or has deteriorated. If the physiologic condition of the pregnant patient has improved, the protocols instituted were probably beneficial and appropriate to the situation. If the condition is unchanged or deterioration has occurred, alternative protocols should be identified and implemented. Once evaluation demonstrates continued improvement over time without major setbacks in the patient's condition, the patient may be sufficiently stable and transport may now be considered. Stabilization is the single most important factor in determining the readiness of the patient for transport. Transportation is defined as the purposeful movement of the patient to an alternative location that can better meet the particular needs of the patient.

The Cycling Process

STABLE represents a dynamic process such that when evaluation is complete, stabilization continues relative to the patient's condition. Table 8.1 shows a sample protocol for stabilization/transport. It is imperative that patients who are critically ill receive the optimum level of care for both mother and fetus with the highest probability of good outcome for both.

Transport

The goal of transportation is the safe and timely movement of the patient to a unit or institution that can better meet the particular needs of the patient. It should be a smooth continuation of stabilization procedures and protocols and should not

TABLE 8.1. Sample protocol for stabilization/transport.

Preeclampsia–Eclampsia
Assessment
Vital signs every 15 min (blood pressure, pulse, respirations)
Cardiovascular/respiratory/neurological assessment
Urine protein and specific gravity
Edema
Deep tendon reflexes
Initial intake and output
Blood coagulation studies
Right upper quadrant pain
Visual disturbances
Fetal heart rate/gestational age/EDC
Uterine activity (frequency, duration, strength, resting tone)
Management
Magnesium sulfate therapy
Administer 6 g $MgSO_4$ as a loading dose.
6 g $MgSO_4$ in 100 cc D5LR to infuse in no less than 15 min.
Administer 2 g/hour as maintenance dose.
Antihypertensive agent if indicated to keep diastolic <110 mm Hg.
Administer 5–10 mg hydralazine hydrochloride IV.
Intake and output
Urine protein
Deep tendon reflexes
Blood coagulation studies every 4–6 h
Serum magnesium levels every 4–6 h
Cardiovascular/respiratory/neurologic assessment every 2–4 h
Seizure precautions
Continuous electronic fetal monitoring–fetal assessment every 15–30 min.
Seizure protocol
For an eclamptic seizure:
1. Administer 2 g $MgSO_4$ IV push over 2–4 min.
If the seizure activity continues:
2. Administer 2 g $MgSO_4$ IV push over 2–4 min.
If the seizure activity continues:
3. Administer 250 mg amobarbitol IV push over 1–2 min.
If the seizure continues:
4. Consider paralyzing and intubating the patient.

be done in haste or panic. The transfer of a patient from one hospital to another is considered a transport, but also included in this definition is the moving of a patient from labor and delivery to an intensive care unit; from the emergency room to labor and deliver; from a general floor to a specialized area; and from a labor room to a larger area such as the recovery room. Any movement of a patient is essentially a transport and should be considered only after stabilization is established. There are, however, unique situations in which stabilization may not be accomplished, resulting in transport of an unstable patient. This action is

1. Have the vital signs continued to fluctuate dramatically?
2. Have medications required significant alterations?
3. Does the patient have a current need for transfusion?
4. Does the patient need an antihypertensive agent (diastolic > 110)?
5. Are you confident that ventilation is sufficient?
6. Is the patient changing her level of consciousness?
7. Are you confident that the patient will not deliver in route?

FIGURE 8.2. Readiness for transport.

taken when resources are exhausted and appropriate care for the patient can be achieved only at an alternate location.

When preparing a patient and family for transport, the clinician should evaluate the readiness of the patient by determining the extent of stabilization (Fig. 8.2). Documentation should be implemented during stabilization procedures and continue during the transport process.

Discussion

The ability of the obstetric team to achieve stabilization of the critically ill obstetric patient may be the single most important predictor of ultimate maternal and fetal outcome. Nurses and physicians who practice obstetrics must be able to remain calm in emergency situations, to remain confident in their ability to establish medical and nursing priorities, and to implement timely and appropriate patient care. Use of the acronym STABLE may assist the health care professional with this challenging process and positively influence the maternal and fetal outcome.

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9
Low Birth Weight and Neonatal and Infant Mortality in the United States: Trends and Current Issues

KWANG-SUN LEE, DIANA WOO, and JUNG-HWAN CHOI

Historic Background

Throughout history, socioeconomic development has been a fundamental prerequisite for the evolution of improvement in the health status of a population. The inverse relationship between infant mortality and the level of economic development is remarkable even to this day (Fig. 9.1).[1,2] In the United States, infant mortality did not begin to show a significant reduction until the beginning of this century; the rate remained at 150 to 160/1000 live births between 1840 and 1900.[3] Not until after 1910 did a precipitous drop in infant mortality occur, with a rate of 89/1000 live births reached in 1919.[3] This remarkable decrease in infant mortality during the first half of this century was realized even before the widespread use of antibiotics and mass immunization; it coincided with a simultaneous and progressive improvement in economic and general living conditions (Fig. 9.2).[4,5]

In the latter half of the twentieth century, neonatal intensive care emerged as one of the major components of pediatric health care. The emergence and subsequent development of this subspecialty are a result of multiple, interacting societal forces on the medical profession. These include (1) the recognition of a slowing in the reduction of infant mortality with the persistence of a relatively high neonatal mortality rate; (2) a lower birth rate, with each individual infant assuming greater social importance in the family; (3) greater interest in the newborn, and particularly in the premature infant, as a result of improved survival of older children; (4) an increased societal concern and a willingness to care for the disabled; and (5) the availability of expanding medical and technologic knowledge that can be used for the care of newborn infants.

In the United States, the number of neonatal intensive care units rose rapidly from 16 units before 1965 to approximately 300 by 1980.[6] With the introduction of intensive neonatal care, a second wave of dramatic decline in infant mortality was noted in the United States.[4,7-9] During the past 34 years, infant mortality in the United States declined by nearly two thirds, from 29.2/1000 live births in 1950 to 10.0/1000 in 1987.[4,5] In the same period, the neonatal mortality rate dropped from 20.5/1000 live births in 1950 to 6.5/1000 in 1987.[4,5]

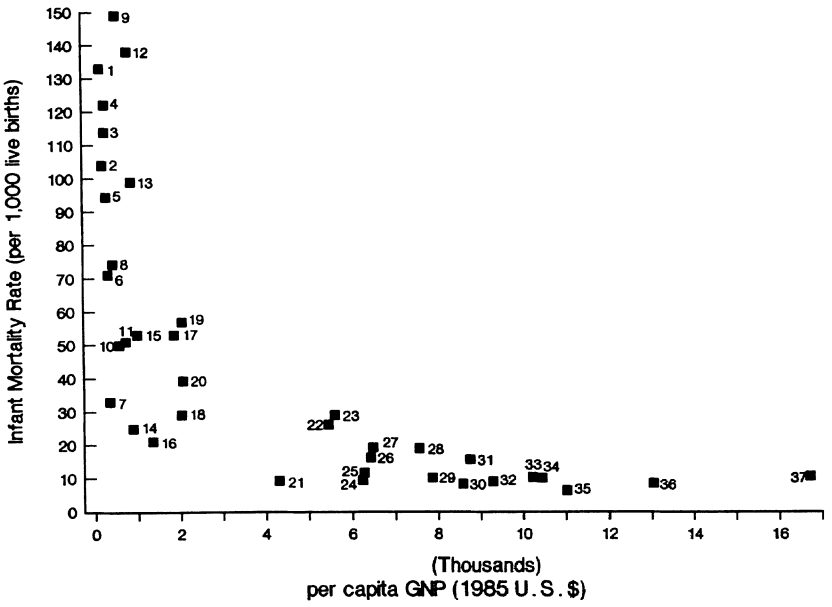

FIGURE 9.1. The relationship between the infant mortality rate and per capita gross national product (GNP) of selected countries (1980–1985).1. Bangladesh; 2. Zaire; 3. India; 4. Zimbabwe; 5. Pakistan; 6. Brazil; 7. China; 8. Egypt; 9. Morocco; 10. Philippines; 11. Thailand; 12. Ivory Coast; 13. Peru; 14. Malaysia; 15. Colombia; 16. Chile; 17. Mexico; 18. Korea; 19. Syria; 20. Argentina; 21. Hong Kong; 22. Romania; 23. Yugoslavia; 24. Singapore; 25. Italy; 26. Bulgaria; 27. Poland; 28. Hungary; 29. United Kingdom; 30. Netherlands; 31. Czechosolvakia; 32. France; 33. West Germany; 34. East Germany; 35. Japan; 36. Canada; 37. United States. (Ref. 1, 2)

Despite this recent remarkable decline in neonatal and infant mortality in the United States, the ranking of these rates among the industrialized countries has been very poor. The infant mortality rate of the United States was ranked 20th for the year 1986, behind those of most developed Western European countries and even behind some of the less affluent Asian countries (Table 9.1).[2] Both neonatal and infant mortality rates, however, differ rather widely among the 50 states of this country as well (Table 9.2).[5]

Neonatal Mortality

As seen in Tables 9.1 and 9.2, among developed countries, including the United States, the major proportion of the variation in the infant mortality rate (IMR) is due to the difference in the first component, the neonatal mortality rate (NMR), with only a small amount attributable to the second component, the postneonatal infant mortality rate (PNMR). In developed countries, neonatal mortality is

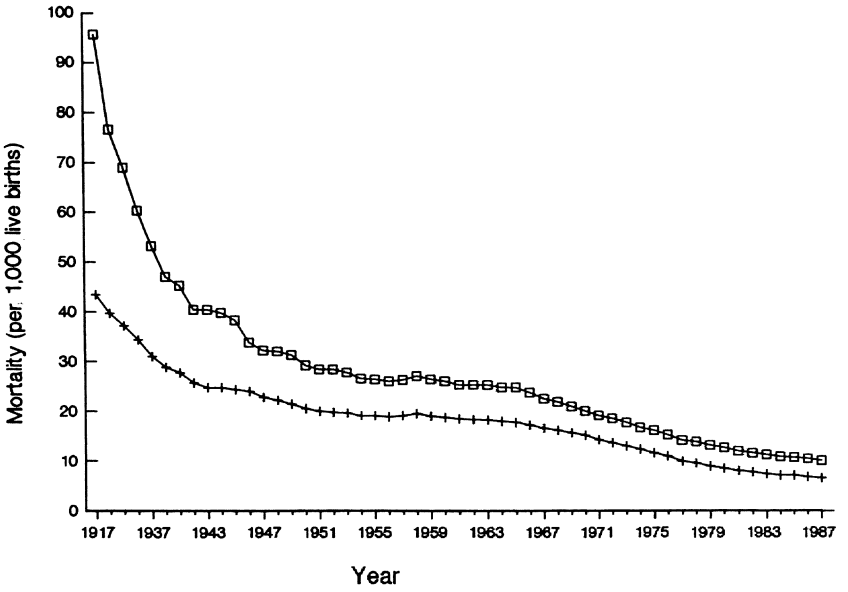

FIGURE 9.2. The infant (□-□) and neonatal (++) mortality rates of the United States, 1917 to 1987. (Ref. 4, 5)

TABLE 9.1. Ranking countries with populations >2,500,000 and infant mortality rates <12 per 1,000 live births for the year 1986.

Country	Rate
Japan	5.2
Finaland	5.8
Sweden	5.9
Switzerland	6.8
Hong Kong	7.7
Netherlands	7.7
Norway	7.8
Canada	7.9
Denmark	8.2
France	8.3
Federal Republic of Germany	8.6
Ireland	8.7
German Democratic Republic	9.2
Singapore	9.4
United Kingdom	9.5
Belgium	9.7
Italy	9.8
Australia	9.8
Austria	10.3
United States	10.4
Spain	10.9
New Zealand	11.2
Israel	11.4

TABLE 9.2. Neonatal and infant mortality rates in 50 states and Washington, DC, 1986.

State	NMR	IMR	State	NMR	IMR	State	NMR	IMR
ND	4.1	8.4	NM	5.4	9.5	Tenn	6.9	11.0
Iowa	5.6	8.5	Tex	6.0	9.5	Fla	7.3	11.0
Mass	5.8	8.5	Mont	5.6	9.6	Va	7.5	11.1
Utah	5.1	8.6	Wash	5.4	9.8	Idaho	6.7	11.3
Colo	5.3	8.6	Ky	6.4	9.8	Ind	7.5	11.3
Me	5.6	8.8	NJ	6.6	9.8	Mich	7.8	11.4
Kan	5.1	8.9	Vt	7.5	10.0	NC	7.7	11.5
Calif	5.6	8.9	Neb	6.6	10.1	Del	8.8	11.5
Nev	4.9	9.1	WVa	6.6	10.2	Md	8.3	11.7
NH	5.9	9.1	Pa	6.8	10.2	La	7.8	11.9
Conn	6.8	9.1	Ariz	5.7	10.3	Ill	8.1	12.1
Minn	5.5	9.2	Okla	6.2	10.4	Miss	7.7	12.4
Wis	5.7	9.2	Ohio	6.9	10.6	Ga	8.5	12.5
Hawaii	6.3	9.3	Mo	6.8	10.7	SC	8.8	13.2
Ore	4.7	9.4	NY	7.3	10.7	SD	7.1	13.3
Ariz	5.5	9.4	Alaska	6.2	10.8	Ala	9.1	13.3
RI	6.5	9.4	Wyo	5.8	10.9	DC	16.1	21.1

NMR, Neonatal mortality rate; IMR, infant mortality rate.

responsible for the major portion of infant mortality, consisting of approximately 60% to 70% of all infant deaths.[4,5,10] Thus, an examination of the causes of neonatal deaths might provide clues for preventive measures needed to decrease infant mortality.

The NMR can be viewed as the sum of birth weight-specific NMRs multiplied by the proportion of live births in each birth weight category.[7] In other words, the NMR has two components: birth weight distribution, and birth weight-specific mortality rates:

$$\text{NMR} = \frac{\Sigma Di}{\Sigma Bi} \times 1000$$

$$\text{NMR} = \left(\frac{B_1}{\Sigma Bi} \times \frac{D_1}{\text{B}_1} + \ldots . + \frac{\text{Bn}}{\Sigma Bi} \times \frac{Dn}{\text{Bn}} \right) \times 1000$$

where ΣDi represents the sum of deaths in all birth weight groups, D_1 through Dn. ΣBi represents the sum of live births in all birth weight groups, B_1 through Bn. B_1/Bi to $Bn/\Sigma Bi$, then, represents the fractional distributions of individual birth weight groups of total live births, ΣBi, and D_1/B_1 to Dn/Bn, individual birth weight group mortality rates.

Neonatal mortality is inversely related to birth weight. In 1980, England had a neonatal mortality rate of 7.6/1000 live births.[10] Although low birth weight infants accounted for only 6.0% of all live births, approximately 60% of all neonatal deaths came from this weight group. Only 0.8% of all live births had birth weights less than 1500 g, but this group was responsible for 64.1% of all low

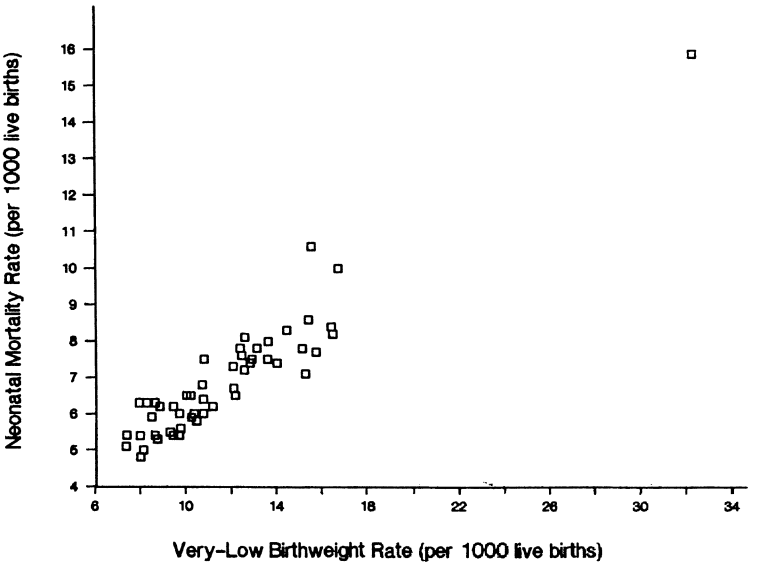

FIGURE 3. The relationship between neonatal mortality rate and very low birth weight rate in 50 states and Washington, DC, 1985 (Ref. 4, 11)

birth weight deaths and 38.7% of all neonatal deaths in the same year.[10] Among the developed communities, approximately 80% of the variance in NMRs can be attributed to differences in very low birth weight rates.[11,12] The greater the proportion of low birth weight infants (<2500 g) in a live birth population, and particularly in the very low birth weight group (< 1500 g), the higher the neonatal mortality rate (Fig. 9.3) and, therefore, the higher the infant mortality rate.

Compared to other developed countries, the relatively high infant mortality rate in the United States can be mainly attributed to its poor birth weight distribution, as evidenced by high very low and low birth weight rates. When neonatal mortality rates are compared among developed countries, birth weight distribution appears to be the major determinant of the NMR, with birth weight-specific mortality rates the minor determinant.

Analyses of US and Canadian vital statistics demonstrate that recent reductions in neonatal mortality in these two countries are due mainly to increasing survival rates in all birth weight groups, particularly very low birth weight infants. This is presumably a result of neonatal intensive care and improved obstetric care.[11,12] Thus, high-quality perinatal medical care seems to be able to improve birth weight-specific neonatal mortality and lower the overall NMR without significantly improving low birth weight rates. When examining a single geographic population over time, the birth weight-specific NMRs thus appear to be the predominant determinant of the overall NMR.

This observation varies from that derived when comparing different geographic populations, where the birth weight distribution is the major determinant

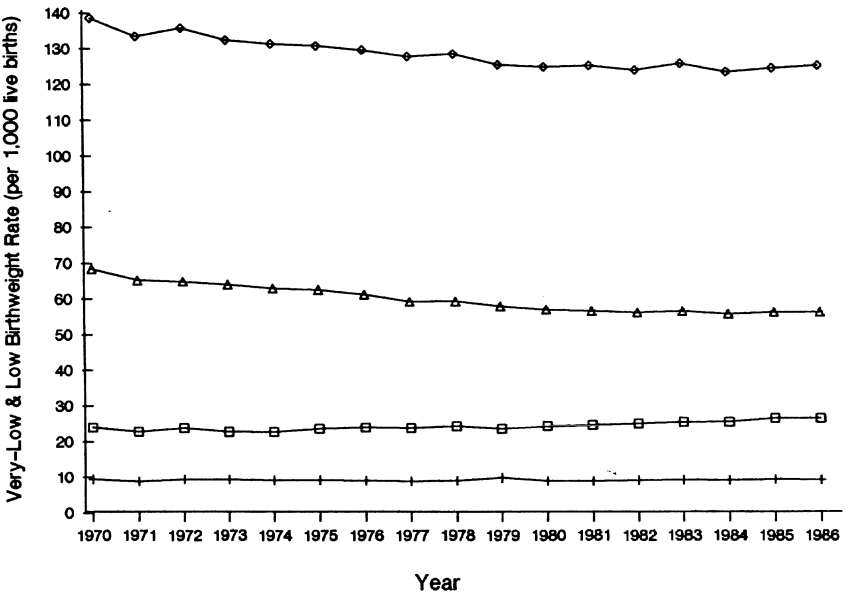

FIGURE 9.4. The very low and low birth weight rates of the United States by race, 1971 to 1986. White (△) and black (◇) low birth weight rates and white (+) and black (□) very low birth weight rates. (Ref. 13)

for the overall crude NMR. This discrepancy simply reflects two observations: (1) that relatively large differences exist in birth weight distribution, particularly in the proportion of low birth weight infants among different geo-ethnic populations, along with (2) the presence of little change in birth weight distribution within each of these individual populations.

Low Birth Weight

Although the recent decline in the NMR, at least in the United States and Canada, has been due primarily to a progressive reduction in birth weight- specific neonatal mortality rates, this approach is obviously indirect and limited. The optimal approach to reduce neonatal mortality, and thus infant mortality, should be directed toward the improvement of birth weight distribution by the prevention of low birth weight outcomes of pregnancy. In recent years, the United States has shown a small but appreciable reduction in low birth weight rates, but the very low birth weight rate, the more important determinant of the NMR, has remained entirely unchanged (Fig. 9.4).[13] A similar trend of little change in low birth weight incidence has been observed in other developed countries.[2]

Factors intimately associated with the NMR, such as maternal age, parity, educational level, marital status, nutritional status, prenatal care, and medical

complications of pregnancy all powerfully affect birth weight distribution.[14-17] There is little evidence that they similarly affect birth weight-specific mortality rates, however. Race is a factor closely related to birth weight and to a lesser degree, to birth weight-specific mortality. Most socioeconomic factors associated with low birth weight outcome and neonatal mortality such as family income, education, and marital status are difficult to subject to either an intervention or a prospective, randomized study. At this time, no evidence clearly shows how any one of these factors is directly related to a low birth weight outcome of pregnancy. Rather, these factors appear to be simply markers for undetermined causes of low birth weight outcomes. Directly identifiable factors such as medical and obstetric complications of pregnancy can explain only a minor proportion of all low birth weight outcomes.

Maternal age is one of the factors that strongly influence birth weight.[18-21] Both old and young mothers are at higher risk of delivering low birth weight infants. Among developed countries, the United States has the highest teenage birthrate, and its proportion of all live births is also the highest.[22] The outcome of infants of older mothers (>35 years) is much the same in all developed countries. The unfavorable outcome of teenage pregnancy, however, appears to be more closely related to other sociodemographic factors associated with pregnant teenagers than to biologic age itself.[20-23] When other sociodemographic factors are controlled for, the outcome of teenage pregnancy is as good or better than that of mothers older than 20 years of age.[21,24]

It is unfortunate that in this country more teenagers from the low socioeconomic stratum have been reproductively active and, indeed, have a higher incidence of low birth weight infants. The high incidence of births from teenagers, however, contributes little to the overall national low birth weight rate, NMRs, and IMRs.[21]

A recent analysis of national vital statistics data indicates that complete prevention of teenage pregnancy during the period 1950 to 1983 would have resulted in a $<10\%$ change in these rates in the United States.[21] When the maternal age distribution of live births in the United States was adjusted to that of Japan, Sweden, or Denmark, low birth weight rates, NMRs, and IMRs again changed very little, indicating that the unfavorable maternal age distribution in the United States does not adequately explain its relatively poor statistics.[25] These observations do suggest, however, that the low birth weight incidence is high throughout the entire reproductive age range in the United States.

The relationship of prenatal care to birth weight and neonatal mortality has been extensively investigated and has produced conflicting results. Earlier studies reported a lack of this association.[26-28] Most of the studies, however, demonstrated its strong correlation with improved birth weight and neonatal mortality.[29-32] Prenatal care may be considered both an intervention and an indicator of maternal behavior, signifying a set of personal beliefs and activities relating to pregnancy and the value of health care.[32] In other words, it is not clear what proportion of this relationship can be attributed to the content and quality of the prenatal care itself or to other factors in women who were self-selected and maintained such care.

A 1981 study, using national vital statistics data, revealed that the initiation of early prenatal care reduced the risk of low birth weight by only 3% among both whites and blacks, when the timing of the first visit was used as a measure of care.[33] When adequacy of care (the time of the first visit and the number of visits in relation to gestational age) was used as an index, the elimination of inadequate care would have reduced the low birth weight risk by approximately 15% among both whites (4.7% to 4.0%) and blacks (11.2% to 9.7%).[33]

In a more recent study on a cohort of 127,558 singletons, born from 1982 to 1983 in Los Angeles county, the difference in the percentage of low birth weight infants born to adults with adequate care compared to a population that included teenagers and adults with inadequate prenatal care was 11.2% versus 11.6% for black mothers and 4.5% versus 4.8% for white mothers.[28] These results suggest that the effect of conventional prenatal care on the incidence of low birth weight is very modest, and even then, the observed effect may not be directly related to the prenatal care itself but may partly reflect the favorable maternal health behavior of women who also sought and maintained prenatal care. To this date, no prospective, randomized trial of prenatal care has been conducted that determines the independent effect of prenatal care per se on pregnancy outcomes.

Conceptually, it is reasonable to believe that protein and/or calorie supplementation during pregnancy will increase fetal weight and hence will reduce the low birth weight incidence. Numerous studies, however, suggest that in developed countries, nutritional supplementation during pregnancy has a minimal effect on birth weight.[34] A randomized, controlled trial of prenatal supplementation carried out among poor black women yielded unexpected results.[34] Women who received balanced protein–calorie supplements had infants with an advantage in birth weight of 41 g over controls, as well as fewer low birth weight infants. The infants of those women on high-protein supplements, on the other hand, had a disadvantage in birth weight of 42 g with increased incidences of premature delivery and neonatal deaths.

Another study conducted in Montreal showed a low birth weight incidence of 5.7% among those supplemented, as compared to 6.8% in the control group, a nonsignificant difference.[35] One disturbing observation in this study was that those women with a previous history of low birth weight infants produced babies with lower birth weights than untreated controls with the same history, although this, too, did not reach significance.

Families living in a poor urban environment of Bogota were also studied.[36] Only those families with at least 50% malnourished children under the age of 5 years were entered into the study. Compared to controls, supplemented mothers produced infants with an average birth weight of 60 g greater and a decreased incidence of low birth weight infants (14.9% vs. 19.5%).

In the winter of 1944 to 1945 during World War II, severe food deprivation occurred in the Western Netherlands. The effect on birth weight was remarkable, with an average reduction of 300 g at the height of the famine.[37] This effect, however, was observed only in those women exposed to starvation in the third trimester of pregnancy; no effect was noted on those exposed in the first two

trimesters. It is interesting to note that the mean length of gestation was not significantly affected in spite of lower birth weights.

These studies suggest that prenatal nutritional supplementation can produce a modest increase in birth weight in infants of women who are undernourished. Such supplementation appears to be more effective when provided in the third trimester when there is relatively greater fetal weight gain. High-protein supplementation seems to be harmful and may actually increase the risk for premature birth and subsequent neonatal death. Thus, it appears that prenatal nutritional supplementation is not necessary for all women, but only for those whose nutritional status is poor. A modest gain in birth weight might then be expected. Overall, nutritional support as part of a prenatal-care regimen cannot be expected to impact on the incidence of low birth weight or on the NMRs and IMRs of the United States.

A few studies have attempted to determine the effect of psychosocial stress on birth weight.[38-40] A recent study measured psychosocial stress in three groups of women with gestational durations of >37, 33 to 36, and <33 weeks.[37] Only 36 (43%) of the 83 mothers whose pregnancies went to term experienced any major stressful life events compared with 20 of the 30 (67%) who went into preterm labor, and 16 of 19 (84%) whose babies were very preterm. The study groups were well matched for age, gravidity, and parity, and the results were independent of social composition. One flaw in this study was that the stressful life events were measured retrospectively in the postpartum period. With this in mind, the project was repeated with measurements of the frequency of stressful life events at three points in time before delivery and immediately afterward.[40] The results of the latter study showed an impressive replication of the earlier one.

The previously cited studies in human have difficulty measuring psychosocial stress as a well-defined independent variable apart from other socioeconomic factors, but the contention that the maternal psychosocial environment directly influences pregnancy outcomes, particularly premature onset of labor, is reasonable and may explain the relationship between sociodemographic factors and birth weight.[37-40] Low socioeconomic groups may have a relatively high prevalence of stressful life events and may lack an adequate response to these events because of poor psychosocial support systems. Could this also explain the differences in pregnancy outcomes among different racial groups? A future study on this subject may yield an important clue as to the pathophysiology of preterm labor and intrauterine growth retardation.

Racial identity has been one of the most significant markers for pregnancy outcomes, low birth weight, and fetal and postnatal mortality in the United States, particularly between white and black populations (Table 9.3).[41-43] The differences in the incidence of low birth weight as well as neonatal mortality remain wide, even after adjusting for the effects of other known socioeconomic and biologic variables such as age, parity, and prenatal-care status.[28,33] Before attributing this difference to a genetic variation, a careful investigation into life patterns and lifestyles of individual racial groups is needed.[43]

TABLE 9.3. Low birth weight rates (percentage of live births <2,500 g) by race in the United States.

Race	Rate
Asian/Pacific Islander*	
Chinese	4.9
Japanese	6.2
Hawaiian	7.0
Filipino	7.4
Other	6.8
All	6.5
White†	5.6
Hispanic†	
Mexican	5.8
Puerto Rican	8.7
Cuban	6.0
Central/S. American	5.7
Other	6.8
All	6.2
Black†	12.4
Native American‡	
Native American, Continental US	6.2
Native Alaskan	5.9
All	6.2

*Data for 1980.
†Data for 1985.
‡Data for 1984.

As shown in Figure 9.5, an underprivileged group in a society may go through the vicious cycle of an unfavorable life pattern for many generations. A piecemeal intervention for one part of such an environment may not produce any appreciable effect. A prenatal-care program or an intensive perinatal health- care program alone, if not addressing other socioeconomic problems such as family, education, and work, cannot be expected to improve pregnancy outcomes of the underprivileged beyond a certain threshold. Even the most modern medical technology, if used in a vacuum, will exert little influence on poor health statistics.

Summary

Throughout history, socioeconomic development has been a fundamental prerequisite for the evolution of improvement in the health status of a population, particularly of infants. In the latter half of the twentieth century, neonatal intensive care emerged as one of the major components of pediatric health care, and a further dramatic decline in infant mortality was noted in the United States. Despite this recent remarkable achievement, the ranking of infant mortality in the United

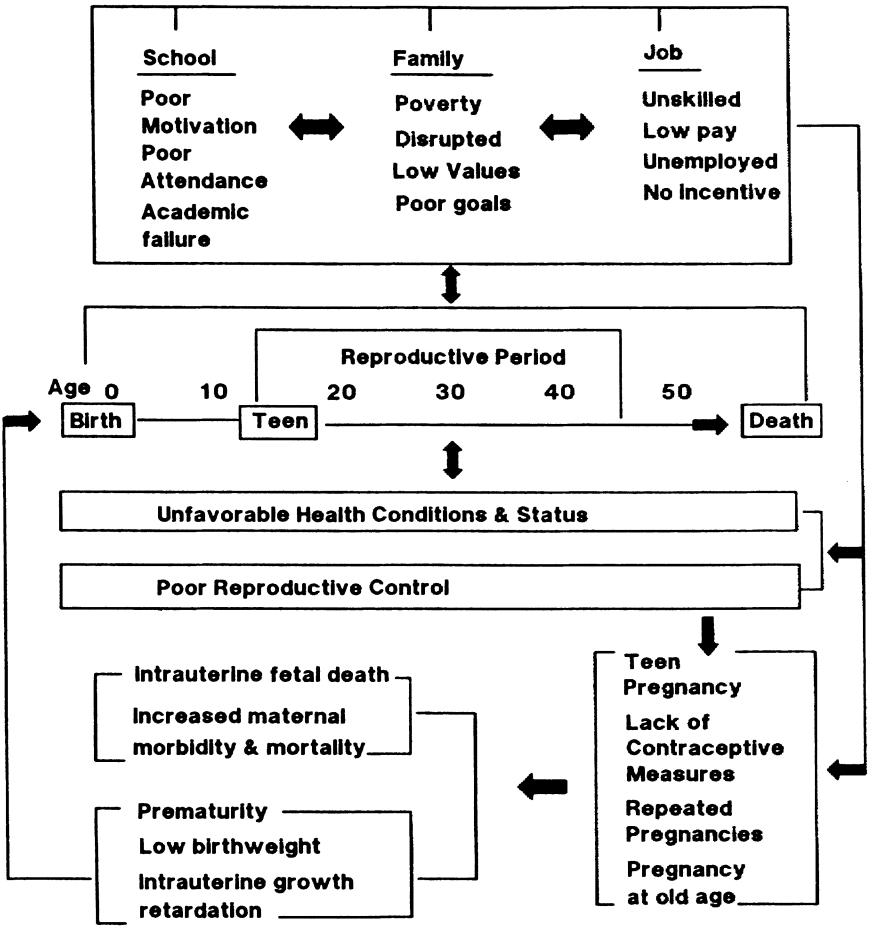

FIGURE 9.5. Schematic view of perinatal health-related socioeconomic and biologic patterns in the life cycle of the underprivileged.

States among industrialized countries has been very poor. Intensive neonatal medical care has improved the IMR by reducing neonatal mortality through lowering birth weight-specific mortality rates. This approach, though effective, is indirect and inefficient. Moreover, since 1980, statistics indicate that a further reduction in the NMR and hence the IMR, may occur very slowly in the United States over the next few decades.

A direct approach, the prevention of the low birth weight outcome of pregnancy, will certainly accelerate a further reduction in the IMR of the United States. Low birth weight is closely associated with multiple interacting factors of maternal health, socioeconomic stress, and biologic status. To date, there has been no clear explanation as to how these factors influence the low birth weight

outcome of pregnancy. An improved socioeconomic status, however, is known to result in a favorable pregnancy outcome, producing a reduction in the incidence of low birth weight and thereby reducing both neonatal and infant mortality.

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10
Newer Methods of Diagnosis and Treatment of Neonatal Sepsis

MARY CATHERINE HARRIS

During the newborn period, infection remains one of the most significant causes of neonatal morbidity and mortality, despite increasing sophistication in infant intensive care and the use of broad-spectrum antimicrobial agents.[1,2] The incidence of neonatal sepsis has not changed significantly during the past 50 years, affecting infants at a rate of 1 to 4/1000 live births; however, the mortality rate for early-onset bacterial infection has declined substantially during this time.[3,4] The mortality rate in the very low birth weight infant has not declined in a similar fashion and remains 10-fold greater than for infants with higher birth weights.[2] Overall, the mortality remains 15% to 45%. Additionally, over one third of survivors with central nervous system involvement ultimately develop neurologic handicaps.[5]

Most bacterial infections occur during the first week of life as a result of exposure to maternal genital microorganisms during the intrapartum period.[6] In recent years, however, the improved survival of low birth weight, critically ill neonates has created a highly susceptible population of premature newborn infants who require hospitalization for extended periods of time. As a consequence, the number of bacterial infections with onset beyond the first week of life has increased dramatically.[7,8] At the current time, 15% of infants in an intensive care unit acquire a nosocomial infection, often with microorganisms resistant to multiple antibiotics.[9]

Before birth, the fetus lives in a sterile environment. For the newborn infant, extrauterine existence depends on a delicate balance between hostile microorganisms in the environment and the infant's intrinsic host defense mechanisms.[10] Although the newborn's immune defense mechanisms began to develop early in gestation, many of these mechanisms do not function as efficiently as in the older child or adult.[11] Significantly, newborn infants are susceptible to infections caused by organisms found in their immediate environment, which are generally considered to be of low pathogenicity. The types of bacteria are remarkably similar to those opportunistic organisms that infect immunosuppressed children.

The neonatal period, therefore, represents a time of unprecedented risk for the development of bacterial infection.[7] Several factors are responsible for the increased susceptibility of the neonate to infectious diseases including perinatal

complications such as premature or prolonged rupture of membranes and maternal fever,[12,13] maternal colonization with potentially pathogenic microorganisms,[2] virulence of the bacterial challenge,[14] prematurity, functional immaturity of neonatal host defense mechanisms,[11,15] and fetal and neonatal nutritional status.[16,17] However, the neonate's susceptibility to opportunistic organisms and the significant morbidity and mortality from infection during the newborn period strongly implicate intrinsic impairment of host defense mechanisms as major factors influencing the risk of bacterial disease.

In general terms, the neonatal immune system may be described as anatomically competent yet antigenically inexperienced and functionally deficient.[11] Recent investigations have identified abnormalities in every wing of the newborn immune response, including deficiencies of T- and B-cell functions, circulating antibody and complement levels, and mononuclear and polymorphonuclear leukocyte defense mechanisms.[18] B lymphocytes, though present in adequate numbers, produce low levels of antibody, most likely because of deficient T- and B-cell or macrophage interactions.[19] Complement levels are 50% lower in term neonates than adults, and both classic and alternative pathway activation sequences are deficient.[20] Although some T-cell functions are intact in newborn infants, lymphokine production and T–B-cell interaction may be impaired. Lastly, although studies of monocyte function in newborn infants have yielded controversial results, investigations of neutrophil supply and function have revealed deficiencies that may significantly compromise neonatal host defenses.[21,22]

Several modes of transmission have been documented for both bacterial and viral pathogens during the neonatal period. Most viral and chronic congenital infections (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex [TORCH] infections) are transmitted hematogenously across the placenta. In contrast, however, most neonatal bacterial infections occur within the first week of life following exposure of the fetus to microorganisms colonizing the maternal genital tract.[6] Exposure of the neonate occurs either by the ascending route in utero through ruptured membranes or by contamination during passage through the birth canal. In the case of group B streptococcal infection, Blanc[23] has designated this sequence of events *the ascending amniotic infection syndrome*. Pathogenic bacteria first colonize the maternal genital tract and then spread upward through the cervix into the amniotic cavity, resulting in chorioamnionitis. Susceptible infants either inhale or swallow bacteria and develop generalized sepsis.

Besides exposure during the birth process, other sources of nosocomial acquisition have been documented. Horizontal transmission from hospital or community sources may occur, although this is an infrequent mode of transmission of infection. Significant nosocomial transmission of group B streptococci to neonates born to culture-negative women has been detected in nurseries in which there is a high rate of exogenous introduction of these organisms by maternally infected infants.

The coagulase-negative staphylococci have emerged recently as significant nosocomial pathogens in the neonatal intensive care unit.[24,25] Although long

considered ubiquitous commensals and nonpathogenic culture contaminants, the coagulase-negative staphylococci may become invasive pathogens in chronically instrumented or immunocompromised patients. The increased susceptibility of the population of very low birth weight premature neonates to this organism, therefore, is most likely secondary to the combined effects of malnutrition, invasive monitoring, and an immature, compromised immune system.

Over the past four decades, several shifts in the predominant organisms causing neonatal sepsis and meningitis have occurred (Table 10.1).[26,27] Before the development of sulfonamides, the gram-positive cocci, particularly the group A streptococcus, were responsible for most cases of neonatal sepsis.[28] With the introduction of antibiotics, the gram-negative bacilli, particularly *Escherichia coli*, became predominant organisms. *Staphylococcus aureus* was a major pathogen during the 1950s.[29] Since the early 1970s, the group B streptococci and gram-negative enteric bacteria have become the most common etiologic agents[1,6]; however, the causative agents vary among different institutions and between countries.[27] In the United States, the group B streptococcus is the most common neonatal pathogen causing acute early-onset bacterial disease, whereas the coagulase-negative staphylococci, particularly *Staphylococcus epidermidis,* represent the most common nosocomial pathogens. In Europe and Africa, in contrast, *S epidermidis* is more frequently associated with acute early-onset bacterial sepsis. The mechanism responsible for the changing pattern of bacterial isolates is unknown, although patterns of antibiotic usage and natural fluctuations in prevalent bacteria probably play some role.[27]

Diagnosis

In the newborn infant, the symptoms and signs of bacterial infection are often nonspecific and may mimic those associated with many other noninfectious illnesses.[2,3] Historical information and risk factors may be helpful, although most clinicians have witnessed infants who quickly progressed to fulminant sepsis and death. The major goal for the clinician, then, must be prompt and accurate identification of all infected infants. One factor that may confuse the diagnosis of infection is the administration of maternal antimicrobial therapy during labor. Although this therapy has been shown to reduce the incidence of group B streptococcal colonization and early-onset disease,[30] in this situation, systemic cultures for bacteria become uninterpretable. Another concern is that certain organisms, particularly the coagulase-negative staphylococci, which were previously considered culture contaminants, may represent pathogenic isolates in premature, immunocompromised hosts.[24] Blood cultures growing coagulase-negative staphylococci may be difficult to interpret as pathogenic or contaminant isolates in this population. Conversely, blood and cerebrospinal fluid cultures, considered the gold standard for the diagnosis of sepsis, may identify only 82% of neonates with actual bacterial disease.[31]

TABLE 10.1. Predominant bacteria in neonatal sepsis and meningitis.

Decade	Predominant bacteria	Other important pathogens
1930s	Group A streptococci	*Escherichia coli* *Staphylococcus aureus*
1940s	*Escherichia coli*	Streptococci
1950s	*Staphylococcus aureus*	*Escherichia coli* *Pseudomonas aeruginosa*
1960s	*Escherichia coli*	*Pseudomonas aeruginosa* *Klebsiella–Enterobacter*
1970s	Group B streptococci	*Escherichia coli* *Listeria monocytogenes*
1980s	?*Staphylococcus epidermidis* ?Streptococci	

Source: Reprinted with permission from Philip AGS. *Neonatal Sepsis and Meningitis*. Boston, Mass: GK Hall & Co; 1985:8.
Total data for the 1980s not tabulated as yet.

As a consequence of these factors, and the risks of delaying treatment of a potentially fulminant disease, many infants ultimately receive antibiotic therapy when only a few are truly infected. Philip[32] has estimated the ratio of sepsis workups to proven cases to be 11:1 in the intensive care nursery. An important secondary goal for the clinician, then, should be to determine which cases represent true infection and require a full course of antimicrobial therapy. In other cases, the clinician can discontinue antibiotics when clinical and cultural information makes the diagnosis of sepsis unlikely. This practice may lessen the development of resistant microorganisms within the nursery and may reduce the costs of antibiotic therapy and hospitalization. Because of these considerations, several laboratory tests have been developed and evaluated for their efficacy in the diagnosis of neonatal infection.

The diagnosis of infection is most frequently made using a combination of historical information obtained from both mother and infant, clinical information from a detailed physical examination of the infant, and laboratory information from a variety of diagnostic tests currently available. Historical factors associated with a higher risk of neonatal infection include clinical amnionitis, maternal fever, or uterine tenderness, premature and prolonged rupture of membranes, and maternal genital colonization with pathogenic bacteria.[2,33] Prematurity is an extremely important risk factor.[34] Several studies have documented a 10-fold greater risk of infection in infants delivered before 34 weeks' gestation.[35]

Clinical signs and symptoms are frequently present in the infected neonate but are often nonspecific in nature and may mimic those observed in many other noninfectious processes. The most prominent of these are respiratory distress, lethargy, fever or hypothermia, and feeding intolerance.[2] Clinical signs that develop later include peripheral vasoconstriction with resultant pallor, systemic hypotension and cardiovascular instability, sclerema, petechiae, purpura, and seizures.[27]

Cultures

The gold standard for the diagnosis of sepsis is the isolation of the organism from systemic cultures including blood or cerebrospinal fluid. The diagnostic workup, therefore, should include blood and cerebrospinal fluid cultures, a complete blood count with differential and platelet count, and a chest film when there is evidence of respiratory distress. If the clinical condition of the infant permits, ideally, two blood cultures should be obtained.[36] This practice will improve the likelihood of identifying the specific pathogen involved. A second blood culture growing the same organism will also make contamination less likely, in circumstances where this possibility exists (the coagulase-negative staphylococci). The lumbar puncture should be performed as part of the sepsis workup except in the infant with cardiovascular instability or significant thrombocytopenia. Nearly one third of neonates with proven sepsis will have concomitant meningitis.[37] A small but significant number of infants with meningitis have negative blood cultures.[38] Although the value of the urine culture is questionable in the early neonatal period, this procedure should become a routine part of the sepsis workup beyond 1 week of age.[39]

Rapid Diagnostic Tests

White Blood Cell Counts

The peripheral white blood cell count and differential is one of the easiest and most routinely available laboratory tests to perform (Table 10.2). Fortunately, it may be one of the most useful tests to identify neonates at risk for bacterial infection. In the past, studies examining total leukocyte counts and percentages of individual forms have found them to be of limited value in the diagnosis of neonatal infection.[40,41] Recognizing these problems, several more recent authors have examined additional neutrophil parameters (total neutrophil counts, total immature neutrophil counts, and immature/total neutrophil ratios) in newborn infants during the first month of life. In a very large study of over 400 neonates, mostly at term, Manroe and co-workers[42] determined reference ranges for absolute total neutrophils/mm^3, absolute immature neutrophils/mm^3, and the ratio of immature/total neutrophils during the first 28 days of life. In addition, this study defined the perinatal conditions involving the mother or infant that may have a significant effect on neutrophil dynamics. These conditions included maternal hypertension, maternal fever, asphyxia, periventricular hemorrhage, meconium aspiration, neonatal hypoglycemia, and hemolytic disease, among others.[42] When these indices were evaluated in infants with infection, neutropenia was the single most accurate predictor of bacterial disease. The association of neutropenia and respiratory distress was highly predictive (84%) of bacterial sepsis.[42,43] Elevations of either the total band, immature or total neutrophil counts were much less useful in predicting the presence of bacterial infection.[31,43]

In response to a stress, such as infection, neutrophils are released from the bone marrow. As the stimulus continues, younger and younger cells are released

TABLE 10.2. Rapid diagnostic tests.

White blood cell counts
Antigen detection methods
Acute-phase reactants

into the peripheral blood stream, as reflected by an increased absolute number of immature cells and an increased ratio of immature/total neutrophil forms.[44,45] Because of the unreliability of absolute band counts in the detection of bacterial disease, Manroe et al.[42] and coworkers have also examined the ratio of band to segmented neutrophils or immature/total neutrophil ratios in peripheral blood. In the study by Manroe et al.,[42] normal infants had immature/total neutrophil ratios up to 0.16 during the first 24 hours of life, which fell to 0.12 by 60 hours of age. Values above 0.2 were highly predictive of bacterial disease, identifying 80% to 90% of infected infants.[42,46]

There are limitations, however, in the use of white blood cell counts in the diagnosis of infection. Reinterpreting the preceding predictive values, one may find that infected infants may have totally normal white blood cell indices, particularly early in the course of bacterial disease. In a recent retrospective study, Rozycki et al.[47] demonstrated that 21% of infected infants have initially normal white blood cell parameters. This information has suggested that the initial screening white count may not identify all infants who require further diagnostic workup and antimicrobial therapy. Additional information may be obtained from repeat counts at 12 and 24 hours. In conclusion, a single white blood cell count in the infant suspected of sepsis should be interpreted with caution. When used selectively and appropriately, however, neutrophil indices may be highly sensitive for the detection of bacterial disease.

The premature infant is at increased risk for the development of bacterial infection, and the mortality from infection is also significantly higher in this weight group.[34,35] Data on neutrophil indices in preterm infants are limited, however. In our laboratory, we have recently determined reference ranges for total neutrophils, immature neutrophils, and the ratio of immature/total neutrophils prospectively over a 2-year period in noninfected preterm infants with birth weights less than 1500 g.[48] Although total neutrophil numbers were similar, noninfected preterm infants demonstrated increased numbers of immature neutrophils and increased immature/total neutrophil ratios when compared to term infants. In this study, although numbers were small, four of five infected neonates demonstrated significant neutropenia and increased immature/total neutrophil ratios during the first 36 hours of life. Future studies should evaluate the usefulness of these indices in large numbers of preterm infants with proven bacterial disease.

Antigen-Detection Methods

Because of the difficulty in differentiating infected from noninfected neonates, several investigators have developed auxillary tests to provide a rapid, presump-

tive diagnosis of infection before culture results are available. Immunoassays to detect bacterial antigens have been used to provide a specific, etiologic diagnosis in neonates infected with group B streptococcus, pneumococcus, meningococcus, and *Hemophilus influenzae*. These techniques include counter immunoelectrophoresis, latex agglutination, and staphylococcal coagglutination tests.[49] The latex particle agglutination test (LPA) has the advantages of simplicity, rapidity, somewhat greater sensitivity than counter immunoelectrophoresis, and greater specificity than coagglutination.[49] When used for the detection of group B streptococcal antigens, the urine LPA test has generally been found to be both sensitive (92% to 100%) and specific (84% to 100%) for the diagnosis of group B streptococcal infection in newborn infants.[49,50] More recently, the monoclonal antibody sandwich enzyme assay has been used to detect group B streptococcal antigen in infected neonates.[51] This assay detects nanogram quantities of antigen and may offer promise as a detection method even more sensitive than those currently available.

In a recent study of neonates evaluated for sepsis in our nurseries, we have noted a high (18%) incidence of positive urine LPA tests, often without corroborating cultural evidence of infection.[52] We have also demonstrated, using sterile and nonsterile urines and urine and perirectal cultures, that local contamination of the perirectal skin or urinary tract was an unlikely source of these positive LPA reactions. At the present time, we are uncertain whether these positive LPA reactions represent true antigenuria without positive blood cultures or apparent false-positive LPA reactions. As with other diagnostic information, the results of LPA testing should be interpreted with caution and in conjunction with other available clinical and laboratory information.

Acute-Phase Reactants

In response to an inflammatory stimulus, the liver synthesizes large quantities of proteins called *acute-phase reactants*. Among them are C-reactive protein; fibrinogen, the major component of the erythrocyte sedimentation rate; haptoglobin; and α_1-acid glycoprotein. Recent investigations have suggested that these proteins, used either singly or in combination as part of a sepsis screen, may be helpful in the diagnosis of bacterial infection.[27,53] Although the exact function of these proteins is unknown, they are believed to be components of nonspecific host defense mechanisms.

C-reactive protein has been detected in the blood of healthy pregnant women,[2] and elevations in this protein have been reported in mothers with chorioamnionitis and premature rupture of membranes.[54] Elevations of C-reactive protein have also been demonstrated in 50% to 90% of neonates with bacterial sepsis.[53,55,56] Despite these favorable results, a number of false-positive and false-negative reactions occur, and C-reactive protein, therefore, may be most useful as part of a sepsis screen. Additional studies have used this protein to follow the course of disease and to determine the response to treatment and duration of antimicrobial therapy.[57]

The erythrocyte sedimentation rate has also been used as an adjunct in the diagnosis of neonatal infection. Several studies have found the erythrocyte sedimentation rate to be markedly elevated in the presence of infection[58,59]; the major factor producing this increase is an elevation in plasma fibrinogen. The sedimentation rate, however, may be normal, particularly early in the course of bacterial disease, and falsely low values have been demonstrated in infants with disseminated intravascular coagulation.[58] Normal infants with Coombs'-positive ABO incompatibility may also demonstrate marked elevations of the erythrocyte sedimentation rate.[60] As with C-reactive protein, therefore, this index is perhaps best used as part of a sepsis screen.[53,61]

Although a number of other nonspecific screening procedures have been advocated, including haptoglobin, α_1-acid glycoprotein, analysis of gastric aspirates, and examination of the umbilical cord, none has proved sufficient to identify the infant with early-onset sepsis. To increase the precision of this diagnostic testing, Philip and Hewitt[53] suggest using a battery of these nonspecific diagnostic tests to provide an increased predictive accuracy for the diagnosis of the infected and noninfected infant. Philip and Hewitt[53] incorporated five tests into their sepsis screen, using the following as abnormal values: band/total neutrophil ratio >0.2, white blood cell count $<5000/mm^3$, C-reactive protein positive, haptoglobin positive, and an erythrocyte sedimentation rate ≥ 15 mm in the first hour. Any two or more abnormal tests were considered a positive sepsis screen. Using this screen, Philip and Hewitt correctly identified 28 of 30 cases of proven infection (93%). The positive predictive accuracy (the frequency the disease is present when the test is positive) of this screening panel was 40%, while negative predictive value (the frequency the disease is absent when the test is negative) was 99%.[53] Gerdes and Polin[61] recently incorporated fibronectin into a four-part sepsis screen consisting of total white count, immature/total neutrophil ratio, C-reactive protein, and erythrocyte sedimentation rate. While fibronectin may play an important role in the pathogenesis of infection, it was not a useful diagnostic marker. In summary, given the high negative predictive value of the sepsis screen, its greatest value is to exclude infection when uncertainty exists in the first week of life. Although Philip[62] has reported decreased use of antibiotics following the use of this screening technique, the clinical evaluation of the infant should remain the most important factor in the decision to begin antimicrobial therapy of potentially infected infants.

Treatment

Antimicrobial Therapy

Because of the continued high mortality associated with bacterial infection in newborn infants, treatment should begin immediately after cultures of blood, cerebrospinal fluid, and urine have been obtained.[1,2,63] Lumbar puncture may be postponed in the unstable infant; however, this should not delay the initiation

of therapy. All infants with suspected bacterial sepsis should initially receive broad- spectrum antimicrobial coverage (Table 10.3). During the first week of life, therapy should include a combination of penicillin or a penicillin derivative plus an aminoglycoside antibiotic. This combination will provide broad-spectrum coverage for both gram-positive bacteria, particularly the group B streptococcus and gram-negative enteric organisms.[63,64] Beyond the first week of life, antibiotic therapy should also include coverage for nosocomial pathogens such as *Staphylococcus aureus, Serratia SP, Pseudomonas SP,* and the coagulase-negative staphylococci.[7,8] Because the coagulase-negative staphylococci, particularly *Staphylococcus epidermidis*, are currently the most common hospital-acquired pathogens, initial therapy for nosocomial sepsis should include vancomycin in combination with an aminoglycoside, such as gentamicin or netilmicin. This initial therapy should be reevaluated after culture results and sensitivities are available.

The duration of therapy depends on the clinical status of the infant, the organism isolated, the portal of entry and the organ system involved, and the initial response to therapy.[1,2,65] For documented sepsis, treatment should be continued for 10 to 14 days, and for meningitis secondary to group B streptococcus or *Listeria monocytogenes*, treatment should be continued 14 days beyond a negative cerebrospinal fluid culture. The optimal therapy for infants with gram-negative meningitis is uncertain at the present time. Treatment modalities consisting of either intravenous antibiotics, third-generation cephalosporins, or a combination of intravenous and intraventricular antibiotics should be individualized, based on the specific organism isolated and antibiotic sensitivity patterns.[66-68]The minimal duration of therapy for infants with gram-negative meningitis is 21 days.

Because of the rapid progression and high mortality from bacterial sepsis in the neonate, early and aggressive therapy is most important. Antibiotics are only part of the management of the newborn infant with infection; additionally vigorous supportive therapy should be provided. In neonates with early-onset disease and respiratory distress, the need for ventilation should be anticipated. Pulmonary hypertension and shock should be vigorously treated. Careful attention should also be paid to the maintenance of fluid and electrolytes and metabolic balance.

Adjunctive Immunotherapies

Despite recent advances in neonatal care and the introduction of several new antimicrobial agents, the mortality rate from neonatal sepsis remains unacceptably high. Recent studies, therefore, have examined the immunocompromised neonatal host defense system and have suggested immunotherapeutic modalities for use during neonatal sepsis (Table 10.4).[10,36,69] These adjuncts to antimicrobial therapy include exchange transfusion, granulocyte transfusion, and the use of intravenous immunoglobulins. The rationale for each of these therapies is to provide immune factors that are deficient or functionally immature in the newborn infant. All of the

TABLE 10.3. Antibiotics that may be employed for treatment of neonatal sepsis or meningitis.

Agent	First week of life or premature			Full-term infant over 1 week of age		
	Dosage	Route	Schedule	Dosage	Route	Schedule
Amikacin	15 mg/kg/day	IM, IV	q12h	22.5 mg/kg/day	IM, IV	q8h
Ampicillin	100–150 mg/kg/day	IM, IV	q8h or q12h	150–300 mg/kg/day	IM, IV	q6h or q8h
Carbenicillin	225 mg/kg/day	IM, IV	q8h	300 mg/kg/day	IM, IV	q6h
Cefotaxime	100–150 mg/kg/day	IV	q12h	150–200 mg/kg/day	IV	q6h or q8h
Ceftazidime[†]	60 mg/kg/day	IV	q12h	60 mg/kg/day	IV	q12h
Ceftriaxone	Not established			50–100 mg/kg/day	IV	q12h
Cephalothin	50 mg/kg/day	IM, IV	q8h	50–100 mg/kg/day	IM, IV	q6h
Chloramphenicol	25 mg/kg/day	IV	q8h	50 mg/kg/day	IV	q6h
Clindamycin	20 mg/kg/day	IV	q8h	30 mg/kg/day	IV	q6h
Colistimethate	5 mg/kg/day	IM	q12h	8 mg/kg/day	IM	q8h
Erythromycin	Not established			40 mg/kg/day	PO	q6h
Gentamicin	5 mg/kg/day	IM, IV	q12h	7.5 mg/kg/day	IM, IV	q8h
Kanamycin	15 mg/kg/day	IM, IV	q12h	25 mg/kg/day	IM, IV	q8h or q12h
Methicillin	100 mg/kg/day	IM, IV	q8h	200 mg/kg/day	IM, IV	q6h
Mezlocillin	150 mg/kg/day	IM, IV	q12h	300 mg/kg/day	IM, IV	q6h
Moxalactam	100 mg/kg/day	IV	q12h	150–200 mg/kg/day	IV	q8h
Nafcillin	100 mg/kg/day	IM, IV	q12h	200 mg/kg/day	IM, IV	q6h
Neomycin	50–100 mg/kg/day	PO	q6h	50–100 mg/kg/day	PO	q6h
Nystatin	200.000–400.00 units	PO	q6h	200.000–400.000 units	PO	q6h
Oxacillin	100 mg/kg/day	IM, IV	q12h	200 mg/kg/day	IM, IV	q6h
Penicillin	100.000–150.000 units/kg/day	IM, IV	q8h or q12h	100.000–300.000 units/kg/day	IM, IV	q6h or q8h
Polymyxin B	3 mg/kg/day	IM, IV	q12h	4 mg/kg/day	IM, IV	q8h
Ticarcillin	150–225 mg/kg/day	IM, IV	q8–12h	225–300 mg/kg/day	IM, IV	q6h or q8h
Tobramycin	4–5 mg/kg/day	IM, IV	q12h	5–7.5 mg/kg/day	IM, IV	q6h or q8h
Vancomycin	20–40 mg/kg/day	IV	q12h	30–60 mg/kg/day	IV	q6h or q8h

Source: Adapted by permission from Feigin et al. Postnatal bacterial infections. In: Fanaroff AA, Martin RJ (eds). *Neonatal-Perinatal Medicine*. 4th ed. St. Louis, Mo: The CV Mosby Co; 1987;769–770.

TABLE 10.4. Adjuntive immunotherapies.

Exchange transfusion
Granulocyte transfusion
Intravenous immunoglobulin

preceding adjunctive immunotherapies should be reserved for the most critically ill infants after conventional therapies have failed.

Exchange Transfusion

Exchange transfusion traditionally has been used for the management of infants with hyperbilirubinemia. This therapy, however, has been used in Europe since the 1970s for the treatment of severe neonatal septicemia.[70-72] The many potential benefits of this therapy include the removal of bacteria, endotoxins, and other bacterial toxins; improvements in peripheral and pulmonary oxygenation and perfusion; a decrease in hemorrhagic complications; and the enhancement of neonatal immune mechanisms, including increases in serum immunoglobulin G (IgG), IgA, IgM, and complement.[70] Although these studies are retrospective and uncontrolled, each suggests that in septic infants treated with exchange transfusion the outcome may be improved. Vain reported the treatment of a group of critically ill, scleremic newborn infants with exchange transfusion.[73] Acidosis, hypotension, and urine output improved, and serum IgA and IgM concentrations increased. Seven of 10 infants that received one to four exchange transfusions survived. In a recent study, Hall and co-workers[74] administered exchange transfusions to 41 infants with proven group B streptococcal disease. Seventy-three percent of the infants survived. In the survivors, the mean pretransfusion opsonic activity against the infecting strain of group B streptococcal was significantly greater than in nonsurvivors. Following transfusion, however, no significant increase in opsonic activity was observed in either group. The authors also observed a significant increase in peripheral neutrophil counts following exchange transfusion in the infants who survived, compared to those who died. Hall et al. suggested that exchange transfusion might enhance neutrophil release from the bone marrow.[74]

At the present time, no prospective, randomized, controlled studies of exchange transfusions in the treatment of neonatal sepsis have been conducted. Although exchange transfusions may theoretically benefit critically ill, infected newborn infants, serious adverse effects may also occur. The potential complications of this therapy include electrolyte and acid–base imbalance, thrombocytopenia, infection, and graft versus host disease.[10] Until further knowledge is acquired, this therapy should be reserved for critically ill neonates in whom conventional treatments have been unsuccessful.

Granulocyte Transfusion

Granulocyte transfusion has also been proposed as an adjuvant form of therapy in overwhelming neonatal sepsis, particularly in infants with neutropenia.[75]

Christensen and co-workers[76-78] have demonstrated quantitative deficiencies in myeloid cells from neonatal rats and human infants, which probably explain the frequent occurrence of neutropenia in septic neonates. The abnormalities include the diminished size of the neutrophil storage[76] (consisting of neutrophils, band forms, and metamyelocytes) and proliferative pools[77] (consisting of myeloblasts, promyelocytes, and myelocytes) in the bone marrow; the decreased stem cell proliferative rate following bacterial challenge[78]; and the disturbed regulation of marrow neutrophil release in the neonate.[79] Qualitative deficiencies include functional abnormalities of neutrophil chemotaxis and killing, which are further depressed during periods of severe stress or infection.[80] Additional studies have demonstrated the high mortality in septic neonates with neutropenia and depletion of the marrow neutrophil storage pool.[45] Studies from adults, moreover, have shown that transfused white blood cells retain functional properties, such as chemotaxis and phagocytosis. To date, although most studies demonstrate an improved outcome in infected neonates, relatively few randomized, controlled trials of the use of granulocyte transfusions in the treatment of neonatal sepsis have been performed.

Christensen et al.[81] evaluated the use of granulocyte transfusions in infants with sepsis, neutropenia, and severe neutrophil storage pool depletion. In this randomized, controlled study, infants received either supportive care plus granulocyte transfusion or supportive care alone. All infants who received a single granulocyte transfusion lived, while all but one infant who received supportive care alone died. No complications of white cell therapy were noted in these patients. Laurenti and associates[82] reported the successful use of neutrophil transfusions in a controlled but nonrandomized study of 20 neonates with gram-negative sepsis. Cairo and co-workers[83] also demonstrated a significant improvement in survival between infants randomized to receive white cells versus controls (95% survival in transfused infants vs. 64% in the nontransfused group). Positive blood cultures were obtained in 80% of infants in both groups. The infants received five white cell transfusions each, despite a return of neutrophil counts to normal within 48 hours of the initiation of therapy. Although most studies have supported the value of white cell transfusion, Baley et al.[84] found no improvement in survival using stored buffy coat neutrophils. Two infants in this study had a fall in partial pressure of oxygen, arterial (Pao_2), following their third white cell transfusion.

In summary, granulocyte transfusions have been used successfully in a limited number of infants. Numerous potential risks exist, however, including fluid overload, shock, graft versus host disease, pulmonary sequestration producing hypoxemia and respiratory distress, and transmission of hepatitis, cytomegalovirus, or human immunodeficiency virus.

Administration of Intravenous Immunoglobulin

The use of intravenous immunoglobulin has also been suggested as an adjunct immunotherapy for severe neonatal septicemia. Several rationales for the use of this treatment exist. First, the presence of opsonic antibody is critically

important in killing many infectious pathogens in vitro.[85] In addition, studies have demonstrated the role of type-specific antibody in the protection of the newborn infant from invasive group B streptococcal disease.[86] The successful use of immunoglobulin therapy has also been demonstrated in several septic neonatal animal models.[87]

IgG is transferred across the placenta by the processes of passive diffusion and active transport. This transfer of IgG is limited before 30 to 34 weeks' gestation, so that preterm infants demonstrate a relative deficiency of this antibody.[88] At term, levels of this immunoglobulin are greater in fetal than maternal plasma. In addition, the maternal immunoglobulin transferred to the fetus will be protective only against the specific etiologic agents to which the mother has been exposed. As a consequence of these factors, several studies have investigated the efficacy of the administration of intravenous immunoglobulin in neonatal sepsis.

Several studies of animals have demonstrated that immunoglobulin could correct some of the immunologic defects of septic premature and term newborn animals. In neonatal rats, Harper et al.[89,90] demonstrated that the administration of intravenous immunoglobulin decreased the mortality rate in animals infected with *Escherichia coil* or group B streptococcus. In premature human neonates, Conway and associates[91] recently reported the prophylactic use of intramuscular immunoglobulin and demonstrated fewer infections in the group receiving immunoglobulin. Sidiropoulos and co-workers[92] treated infants suspected of sepsis with either antimicrobial therapy alone or conventional therapy plus intravenous immunoglobulin. Overall, the differences in mortality were not significant. When only preterm infants were considered, however, mortality was significantly decreased following intravenous immunoglobulin therapy. Chirico et al.[93] also demonstrated the safety and efficacy of intravenous immunoglobulin, observing a significant reduction in the incidence, severity, and mortality from infection in infants < 1500 g who received immunoglobulin prophylaxis. At present, larger efficacy studies are in progress.

In summary, adjunctive therapies, such as granulocyte or exchange transfusion, and immunoglobulin administration may improve survival in infected neonates. Until these therapies receive further evaluation, however, they should be reserved for critically ill newborns in whom other therapies have failed. On a practical level, in the absence of equipment to isolate granulocytes, a double-volume exchange transfusion with fresh heparinized blood will provide a similar quantity of functional phagocytes. If pending studies demonstrate efficacy, intravenous immunoglobulin may ultimately be the most practical and effective adjunctive therapy because it is routinely available in most hospital pharmacies.

Conclusion

The neonate, particularly the premature infant, is at increased risk for the development of invasive bacterial disease. In addition, despite advances in neonatal care and the use of broad-spectrum antimicrobial agents, the mortality rate for

neonatal sepsis remains unacceptably high. A further reduction in mortality should result from advances in diagnostic techniques that allow the improved recognition of infected neonates. Additional help may come from therapeutic strategies to replace or enhance neonatal host defense mechanisms.

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11
Clinical Applications of Neonatal Pulmonary Function Testing

VINOD K. BHUTANI

Neonatal pulmonary function testing has achieved a level of remarkable sophistication. It provides important clinical information and helps define the pathophysiology of a variety of respiratory diseases. Pulmonary function evaluation also assists in determining effective modes of therapy and ventilatory intervention. Standard pulmonary function testing, the basis of evaluating the newborn with any manifestation of respiratory distress, includes the assessment of overall gas exchange, distribution and pattern of ventilation, pulmonary mechanics, and the evaluation of airflow. Physiologic principles, extensively described in the literature, provide the framework for neonatal pulmonary evaluation. The significant merits and controversies of the physiologic basis for pulmonary function testing have also been previously addressed. Technical limitations for optimum data acquisition have included the size of the patient, absence of the appropriate technology or equipment, and the cumbersome, slow process of analysis. These factors have delayed the use of pulmonary function testing in routine clinical practice. With the advent of microprocessor technology and sophisticated, noninvasive equipment, on-line and bedside pulmonary evaluation have become increasingly acceptable. Nevertheless, investigators are continuing to weed out the physiologic and technical factors that can distort accurate measurements necessary for clinical care.[1]

Adequate pulmonary function is best determined by optimum matching of alveolar ventilation with pulmonary perfusion. In routine clinical practice, this is usually assessed by the overall gas exchange as determined by blood gas analysis. The assessment of ventilation has thus far been empirical; it is in this area that significant advances have been made. The evaluation of pulmonary perfusion remains a difficult clinical technique. In this chapter, the clinical determination of airflow mechanics during neonatal respiration is described from a physiologic viewpoint as well as from that of technical instrumentation. The accuracy, precision, and reproducibility of the measurements are discussed with particular attention to routine clinical use.

The components of pulmonary and airflow evaluation are those of standard dynamic respiration: tidal volume, frequency, minute ventilation, and the change in the driving pressure to achieve the tidal volume. The graphic analysis of the

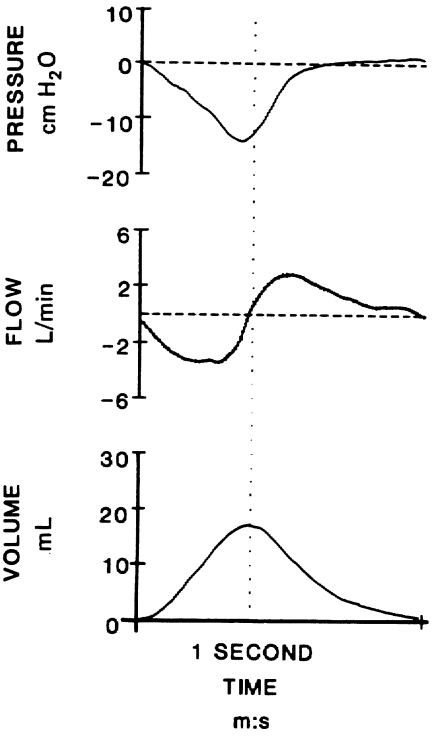

FIGURE 11.1. Pressure, airflow, and volume signals during a respiratory cycle.

respiratory pattern provides an objective view of the interrelationships of these components that provide the basis for clinical diagnosis. The graphic evaluations include tidal pressure–volume relationship; tidal flow–volume relationship; and the scalar record of simultaneous signals of tidal volume, airflow, and driving pressure (Fig. 11.1). The physiologic analysis of these signals to obtain values of dynamic mechanics (compliance and resistance) further provides objective data for quantification.

Physiologic Background

Evaluation of Pulmonary Ventilation

Ventilation Volumes

The following parameters characterize the dynamic features of the ventilatory volumes:

1. Tidal volume (VT): The volume of air inspired with each breath. The usual range in a healthy neonate is 6 to 8 mL/kg.

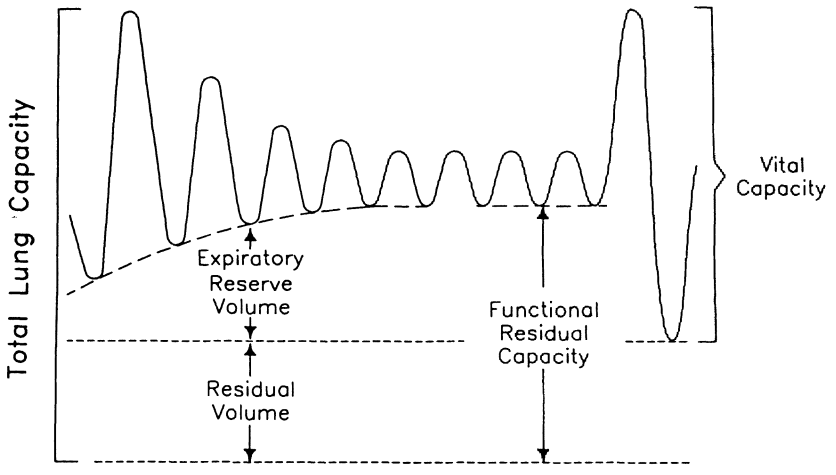

FIGURE 11.2. Static lung volumes.

2. Breathing frequency (f): Represents the number of tidal volume taken per minute. The usual range in the neonate is 40 to 60 breaths per minute.
3. Minute ventilation (MV): The product of tidal volume and breathing frequency. The usual value is 200 to 400 mL/min/kg.
4. Dead space (DS): Represents that component of the lung volume in which there is no gas exchange. This value is usually 2 mL/kg of the tidal volume.
5. Alveolar volume (V_A): Represents the volume in which gas exchange takes place ($V_A = V_T - DS$).
6. Alveolar ventilation ($\dot{V}_A$) is the product of breathing frequency and alveolar volume. The usual value in a term neonate is 110 to 160 mL/kg/min.

These measurements may be obtained by pneumotachography, plethysmography, impedance pneumography, and other techniques.[2,3] The determination of the anatomic dead space remains a difficult clinical procedure in the nursery.[4]

Static Lung Volumes

The static lung volumes are illustrated in Figure 11.2. The classic definitions that are relevant for neonatal applications follow:

1. Residual volume: Volume of air remaining in the respiratory system at the end of maximum possible expiration.
2. Functional residual capacity (FRC): Volume of air in the respiratory system at the resting level or at the end of tidal volume expiration that is in continuity with the airways.
3. Expiratory reserve volume (ERV): Volume of air that is the difference between FRC and residual volume.
4. Thoracic gas volume (TGV): Lung volume that is the total amount of gas in the

TABLE 11.1. Static lung volumes in term healthy neonates.

Residual volume	10–15 mL/kg
Functional residual capacity	25–30 mL/kg
Thoracic gas volume	30–40 mL/kg
Total lung capacity	50–90 mL/kg

lung at end expiration; irrespective of whether or not the gas is in communication with the airways.

5. Total lung capacity (TLC): Volume of air in the respiratory system at the end of maximum possible inspiration.

These volumes are measured by a combination of spirometry, helium dilution technique,[5] and nitrogen-washout technique.[6] Unfortunately, these are not currently available for routine neonatal clinical application. These may be measured by neonatal research equipment, and the normal values are listed in Table 11.1.

Evaluation of Pulmonary Mechanics

Elastic Properties of Lungs (Compliance of the Lung)

Elasticity is the property of matter that causes it to return to its resting condition after some external disturbance. Lungs, airway, and thorax are elastic. These tissues stretch by the changes in pressure during inspiration; when the pressure change ceases, the tissues return or recoil to their resting positions. Thus, compliance of a tissue is equivalent to the change in volume for the change in the pressure.[7]

Pressure–Volume Curve

Contraction of the diaphragm results in a decrease in the intrapleural pressure; this in turn causes the lungs to expand and change their volume. The pressure, when held for a brief time, allows the lungs to come to rest. Such a systemic change in both pressure and volume during inflation and deflation allows a pressure–volume curve of the lungs to be plotted (Fig. 11.3). The curves that the lungs follow during inflation and deflation are different. This physical property of the lungs is known as *hysteresis*. It is to be noted that the lung volume at any given pressure is greater during deflation than during inflation. Surface tension and the tissue properties define the hysteresis.

Lung Compliance

Static pulmonary compliance, considered an accurate determinant of lung elastic properties, is the change in volume for a given pressure at static conditions. Sufficient equilibration period is allowed to ensure that the actual pressure change is recorded. Dynamic compliance is the determination of the change in

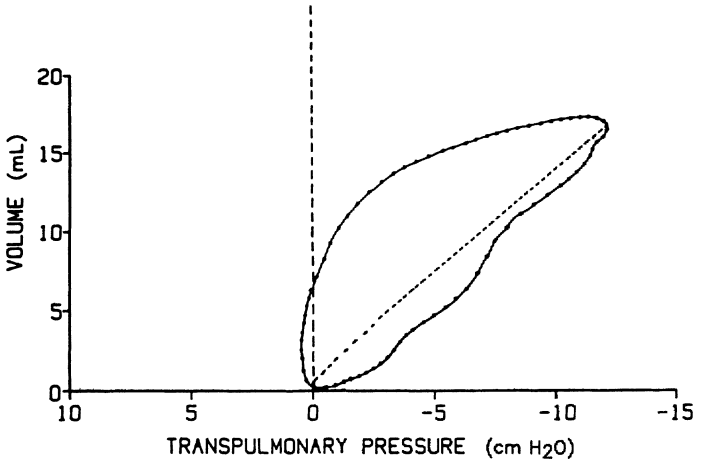

FIGURE 11.3. Pressure/volume relationship in a respiratory cycle. Dots on inspiratory and expiratory limb indicate data sampling at 75 Hz.

volume/pressure during the respiratory cycle (Figure 11.4) and is predominantly influenced by breathing frequency. During rapid breathing, equilibration time may not be sufficient to accurately determine the actual change in pressure.

The site of sampling of the change in pressure during tidal volume is determined by the dynamic compliance that is being measured:

$$\text{TLC} = \frac{\Delta\ V_T}{\Delta\ \text{Airway pressure}}$$

$$\text{Dynamic lung complicance} = \frac{\Delta\ V_T}{\Delta\ \text{Transpulmonary pressure}}$$

$$\text{Chest wall compliance} = \frac{\Delta\ V_T}{\Delta\ \text{Intrapleural pressure}}$$

Nonelastic Properties of the Lung (Resistance to Airflow)

Pulmonary resistance results predominantly from the frictional resistance to airflow. Airflow requires a driving pressure generated by the changes in alveolar pressure. When alveolar pressure is less than atmospheric pressure, air flows in (inspiration). Thus, resistance to airflow is equivalent to the pressure gradient between alveolar gas and the atmospheric pressure divided by airflow value (Fig. 11.4).

The airway resistance, which may be responsible for as high as 80% of the total pulmonary resistance in a normal lung, is influenced by the velocity and pattern of airflow, geometry of the airways, and the density/viscosity of the gas itself.[7] The tissue resistance normally would account for about 20% of the pulmonary

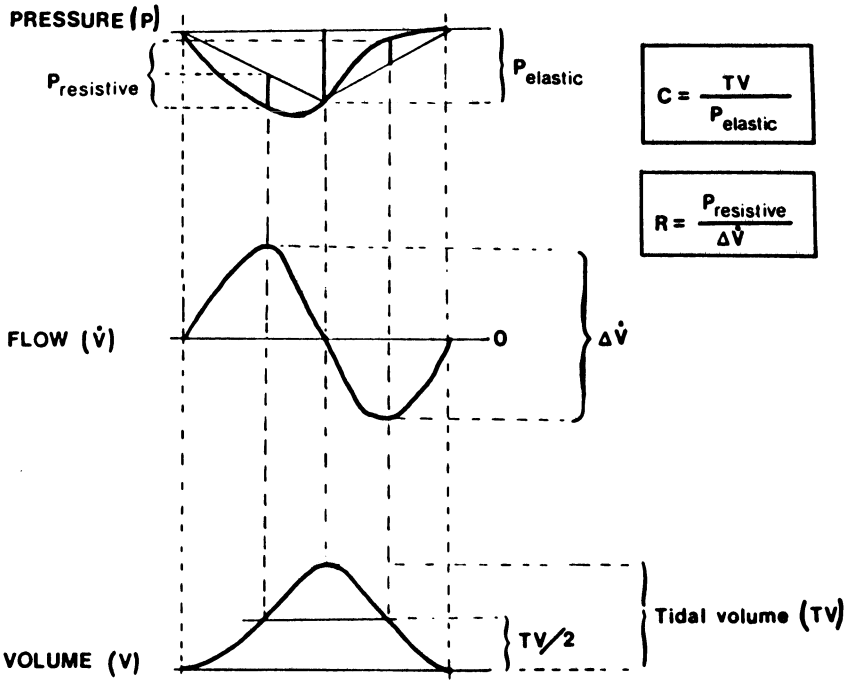

FIGURE 11.4. Scalar record of pressure, airflow, and tidal volume defines calculations of pulmonary compliance (C) and pulmonary resistance (R).

resistance. In a normal lung both tissue resistance and inertia resistance have a relatively small effect. The tissue resistance is influenced by the configuration of the chest wall and the lung as well as by the fluid content of the pulmonary tissue. Thus, in a neonatal diseased lung, the tissue resistance is expected to be higher. Inertial resistance, $<1\%$ of pulmonary resistance, depends on the breathing frequency and the density of the gas.[7]

Pressure Changes During Respiratory Cycle

Both the intrapleural and alveolar pressure change during a respiratory cycle. Before the commencement of inspiration, the intrapleural pressure is subatmospheric (-4 to -6 cm H_2O) because of the elastic recoil of the lung. The alveolar pressure is atmospheric zero, because there is no airflow and no pressure drop along the conducting airways. To establish inspiratory airflow, the alveolar pressure must fall during spontaneous breathing so as to initiate a driving pressure. The magnitude of the change in the alveolar pressure depends on the airflow rate and the airway resistance. The value of alveolar pressure is normally about 1 cm H_2O but is markedly increased with air trapping or airway obstruction.

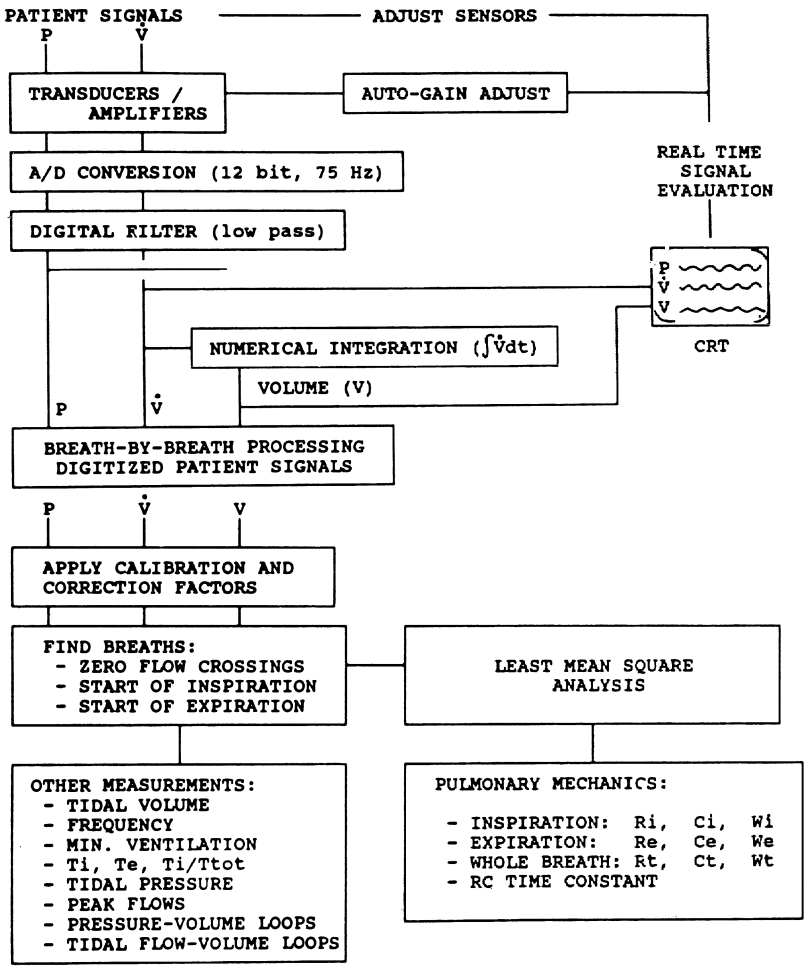

FIGURE 11.5. Patient signal processing of pressure and flow data for computerized analysis of pulmonary function profile. (A/D, Analog to digital; Ci, Inspiratory compliance; Ce, Expiratory compliance; CRT, Cathode ray tube; Ct, Total compliance; P, Pressure; Ri, Inspiratory resistance; Re, Expiratory resistance; Rt, Total resistance; Te, Expiratory time; Ti, Inspiratory time; Ttot, Total time for respiratory cycle; V, Volume; $\dot{V}$, Airflow; We, Expiratory work; Wi, Inspiratory work; Wt, Total work).

The intrapleural pressure falls during spontaneous inspiration. The pressure change is due to an elastic component[7] and therefore the elastic recoil of the lung. It is also due to the resistive component. Thus, at any instant in the respiratory cycle, the intrapleural pressure is the sum of the elastic pressure and the resistive

pressure. The vertical distance between the elastic component and the total pressure therefore represents the resistive pressure component and also reflects the alveolar pressure (Fig. 11.4).

During expiration, the alveolar pressure is positive. The intrapleural pressure is therefore less negative. The resistive component of expiration is thus represented by the difference between the actual total expiratory and intrapleural pressure and its expected elastic component. With forced expiration, the intrapleural pressure exceeds atmospheric pressure.

Under several conditions, the intrapleural pressure is equal to the elastic pressure. First, with a very slow inflation such that airflow is zero, there is no resistive pressure and the inflation pressure will be the elastic pressure. Second, during dynamic breathing, the airflow is zero at the end of inspiration/expiration. Conversely, when the airflow is maximum (usually midrespiratory cycle), the resistive pressure is the largest.

Clinical Calculation of Pulmonary Mechanics

Pulmonary mechanics are determined by simultaneous measurement of the airflow, volume, and driving pressure for consecutive breaths. The calculation of compliance and resistance are based on the assumption of a linear model[8]:

$$P = EV + RV$$

where, P = driving pressure, E is the elasticity (inverse of compliance), V is the volume, R is the resistance, and $\dot{V}$ is the airflow signal. Thus, the driving pressure is always the sum of the elastic and resistive pressure. The calculations may be determined by the traditional or "chord" analysis, as shown in Figure 11.4.[9] Alternatively, the mechanics data may be determined by least mean squares analysis using a three-dimensional model for the pulmonary signals.[10] The theoretic basis of this analysis has been described extensively elsewhere.[11] This mode of analysis is computerized as is the determination of tidal volume, breathing frequency, minute ventilation, peak-to-peak esophageal pressure, time constants and I/E (inspiratory/expiratory) ratio (Fig. 11.5). More importantly, the computerized scanning and record provide a real-time analysis of pressure–volume and flow V_T evaluation of individual breaths.

A technique to measure passive respiratory mechanics without the use of esophageal pressure measurements involves the analysis of the passive expiratory flow–volume relationship and the airway pressure.[12,13] It is assumed that the subject is in a relaxed state such that the expiration is purely passive. Occlusion of the airways, either at end of inspiration or during expiration, has been used with the assumption that the ensuing expiratory phase is entirely passive.[14,15] Expiratory volume clamping,[16] multiple occlusions (interruption) at different levels of exhalation,[17,18] and occlusion at end inspiration[19] have been used by several investigators and hold future clinical application.

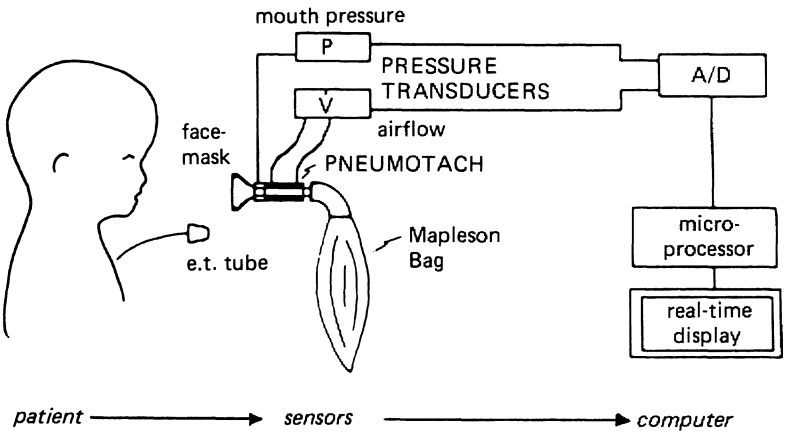

FIGURE 11.6. Schematic of apparatus for data collection. (A/D, Analog to digital; e.t., Endotracheal; P, Pressure; $\dot{V}$, Airflow).

Bedside Collection of Data

The neonates are supine with the head in a neutral position. Data are obtained while they are resting quietly, either during spontaneous breathing (on continuous positive airway pressure [CPAP]) or while receiving ventilatory support. Sedation is seldom indicated. Simultaneous signals of airflow and transpulmonary pressure are recorded and used to calculate pulmonary mechanics and energetics (Fig. 11.6). Transpulmonary pressure is defined as the difference between the intrapleural and mouth pressure (or airway pressure); the changes in the intrapleural pressure during a respiratory cycle are approximated by the esophageal balloon technique. Airflow is measured during the respiratory cycle by a pneumotachometer. The volume change is determined by the digital integration of the airflow signal. The equipment used and their characteristics are described in the following section.

Instrumentation

Esophageal Balloon

The balloon is 40 mm long with a wall thickness of about 0.04 mm and a maximum inflatable diameter of about 7.5 mm. This polyvinyl balloon is attached to an 8-french catheter (Mallinckrodt®). In vitro studies in our laboratory have demonstrated that an appropriate balloon volume of 0.15 mL provides a linear output pressure response to applied pressures over a range of -50 cm H_2O to $+30$ cm H_2O. The frequency response of the balloon is flat to 5 Hz. These data

describe an effective means to determine the pressure signal and are similar to that described by Beardsmore et al.[19]

Catheter Placement

The positioning of the catheter is such that the balloon is placed in the distal esophagus. The length of the catheter insertion is determined by the sum of the distance between the angle of the mouth and the tragus of the ear and the distance between the tragus and the xiphisternal angle. Thus, the distal end of the balloon is predominantly in apposition to the xiphisternal angle.

Pressure Transducer

The proximal end of the catheter-balloon is connected via a threeway stopcock to one side (positive port) of a differential pressure transducer (Celesco P7D). To measure airway pressure, the negative port of the differential transducer is connected via tubing to a pressure sideport between the endotracheal tube and the pneumotachometer.

Pneumotachometer

Airflow is measured by a pneumotachometer (Fleisch 00) and a validyne (MP45) differential pressure transducer. The pneumotachometer is linear for gas flows ranging from 0 to 0.15 L/s. A specially designed adapter is used to connect the pneumotachometer to the endotracheal tube. The resistance and DS of the apparatus have been calculated to be 13.2 cm H_2O/L/s and 1.7 mL, respectively. The pneumotachometer is placed directly in series with the endotracheal tube and the ventilator in an infant receiving ventilatory support. The pneumotachometer is attached to a face mask for a nonintubated infant. Preliminary evaluation did not show any changes in the transcutaneous partial pressure of carbon dioxide (Pco_2) while the pneumotachometer was attached for the duration of the study ($\sim$3 min).

Procedure

Once the balloon is placed and the infant is calm, the infant is prepared for further instrumentation. Using a glass syringe (1.0 mL), the balloon is filled and emptied several times with 0.4 to 1.0 mL of air to remove any bends or folds in the balloon. A volume of 0.15 mL is left in the balloon for the actual pressure measurement. Care is taken that none of the tubing attachments are pressurized during the procedure. The on-line display of the transpulmonary pressure signal on the computer is studied to monitor cardiac artifacts, esophageal contractions, and overdistention of the balloon. As long as no end-distending pressure is being applied, the pressure signal is subatmospheric and exhibits changes concomitant with respiratory cycle. Additional techniques to determine the accuracy of placement of the esophageal balloon may also be used; the airway-occlusion technique

has frequently been recommended.[20] Though this technique is successful in some infants, a large number may be too sick to tolerate this procedure.

After the neonates are appropriately instrumented, the signals are recorded while the neonates are calm and resting. The infants who are studied with ventilatory support are provided the same support during the study unless they are on low respirator rates (< 30 c/min). In these infants, data are obtained only on CPAP during spontaneous breathing.

Calibration

The pneumotachometer (Fleisch 00) should ideally be calibrated using a Tissot spirometer. If this is not available, an accurate variable-area–type flowmeter may be used. A water manometer is used to calibrate the pressure transducer.

Technical Considerations

The analysis technique described subsequently necessitates the determination of driving pressure. In infants on ventilatory support, the airway pressure itself may be used to determine mechanics of the entire respiratory system. To evaluate lung mechanics, determination of the driving pressure requires an accurate measurement of the intrapleural pressure. Its assessment by the esophageal balloon technique has been a subject of frequent criticism.[21] When used judiciously, however, it remains a simplified and noninvasive means to approximate the intrapleural pressure. Alternatively, a saline-filled catheter, an esophageal pressure transducer, or any other alternative technique to measure intrapleural pressure may be used in determining transpulmonary pressure. Concurrent evaluation of breath by breath pulmonary graphics (especially pressure–volume relationships) aids in identifying breaths where the pressure signal is distorted either during inspiration or expiration. These breaths may be excluded from the averaged data at the investigator's discretion. Neonates on CPAP (2 to 3 cm H_2O) exhibited infrequent distortion as compared to premature infants who breathe spontaneously.

On-line scalar display of the pressure signal also is useful in determining the placement of the esophageal catheter. In addition, the dimensions of the balloon are optimal and similar to those defined by Beardsmore et al.[19] after extensive in vivo and in vitro testing for both dynamic and static measurements. Furthermore, the selection process for the breaths included in data analysis are rather rigid and enforce a strict selection criteria.

Accuracy and Precision of Clinical Neonatal Pulmonary Function Testing

The accurate determination of a pulmonary variable would mean that there is a "correct" value, about which repeated measurements will have a standard Gaus-

sian distribution. The closer the measured mean value is to the "correct" value, the greater the accuracy of measurement.

However, as reviewed extensively in the neonatal literature, physicians and physiologists often have had to compromise with not-so accurate measurements. Perhaps the most controversial has been the estimation of pleural pressures by the esophageal balloon-catheter system. Although it is well appreciated that such measurements will not accurately represent the diversity of pressures found in the pleural space, if standard methodology is adhered to and the same methods used in both defining normal and diseased states data, then the measurements are of considerable clinical value.

For an accurate, physiologic measurement, mathematical or mechanical models are constructed to assess the accuracy of the measuring device. It is hoped that these models withstand pathologic diseased states. Physical changes alone, such as humidity, temperature, and gas concentration may provide direct assessment of any pulmonary variable. Thus, maximal accuracy is the goal, but that goal is often difficult and limited by the models and substitutes used. For example, accurate determination of partial pressure of oxygen (Po_2) values by the currently available blood gas analysis has yet to take into account the complexities of hemoglobin dissociation curves in the in vitro state.

Precision, on the other hand, refers to the reproducibility of repeated measurements. The standard deviation of repeated measurements is commonly used as an estimate of precision. The smaller the value of standard deviation, the greater the precision. In neonatal practice, we have considered standard deviation $< 15\%$ the mean value as indicative of optimal precision. Values of $> 15\%$ may reflect a diseased state or a technically poor study.

Precision determination is an important aspect of quality control. Repeated technical evaluations using a model are easy (i.e., simulated lung model). Physical factors may still remain unaccounted however; for example, dry air in the model may not simulate the humidity of the expired breath. It must be recognized that the precision of an instrument, as determined from measurements using devices or products that substitute, may differ from that obtained in the clinical testing condition. The inherent variability of most physiologic measurements in the neonate must always be kept in mind.

In addition to systemic and random errors related to calibration, faulty sampling techniques aggravate accurate and precise data acquisition. Obtaining accurate and precise data is a reasonably achievable goal that requires painstaking, tedious, and meticulous methodologic techniques; no compromises may be made. The only compromise the clinician must make is the acceptance of the current physiologic model that gauges the accuracy.

The final step in the interpretation of the results is accepting the measured value for valid clinical decision making. This process necessitates the ultimate interaction of physiology knowledge base, technique of measurement, the normal data for the appropriate age and gestation, and the statistical relationship of the measured value to disease.

TABLE 11.2. Clinical indications for neonatal pulmonary function evaluation.

Acute lung disease
1. Diagnostic evaluation
2. Evaluation of mechanical ventilatory support
3. Evaluation of therapeutic intervention
4. Resolution of acute lung disease
5. Prediction of chronic lung disease
Chronic lung disease
1. Sequential follow-up
2. Evaluation of pharmacological intervention
3. Evaluation of extent of pulmonary dysfunction
4. Evaluation of airway injury
5. Predischarge evaluation of pulmonary status
Outpatient follow-up
1. Low birthweight neonates
2. Infants with chronic lung disease
a Resolution of pulmonary dysfunction
b Discontinuation of pharmacologic intervention
c Evaluation of airflow limitation
3. Assessment of reactive airway disease

Clinical Indications

The clinical usefulness of neonatal pulmonary functions is that they define the magnitude and pattern of respiratory compromise. The data assist the clinician to achieve the following:

1. Differentiate abnormalities in the elastic or resistive components during an acute or chronic disease process.
2. Define the inspiratory and expiratory airflow and the factors that limit or alter the airflow pattern.
3. Determine the effort, the work, and the driving pressure generated by the neonate and whether these are sufficient to maintain an optimum minute ventilation.
4. Determine the time constants of the total lung and to use the information to define some of the variables of mechanical ventilatory support.
5. Study the pattern and effect of mechanically ventilated breath to provide appropriate ventilation measured and minimize inadvertent overdistention of the lungs.
6. Determine the magnitude of the measured abnormalities as compared to data in appropriately matched neonates.
7. Define the sequential change to monitor the progress of disease or the effect of maturation and natural resolution.

TABLE 11.3. Clinical interpretation of pulmonary function data.

1. Pressure–volume relationship
2. Evaluation of airflow
(Tidal flow–volume relationship)
Normal
Extrathoracic airflow limitation
Intrathoracic airflow limitation
Inspiratory airflow limitation
Expiratory airflow limitation
Multiple airflow limitation
3. Evaluation of scalar record
4. Assessment of ventilation parameter
Tidal volume
Minute ventilation
Peak-to-peak esophageal presssure
5. Mechanics: Mean ± SD values:
Dynamic pulmonary compliance
Pulmonary resistance
Resistive work of breathing
Respiratory time constants
6. Other techniques to assess airflow limitation
Forced Expiratory maneuvers
Bronchoprovocation

SD, standard deviation.

Based on the potential indications listed previously, the currently used indications for pulmonary function testing in the intensive care nurseries are listed in Table 11.2. Additional indications are being defined as clinicians become familiar with neonatal pulmonary technology.

Clinical Interpretation

The clinical relevance of the measured variables is listed in Table 11.3 and described individually in the following subsections.

Normal

Pressure–volume relationships should be constructed for individual sampled breaths. The change in the transpulmonary pressure (or driving pressure) is presented on the horizontal axis, and the tidal volume, on the vertical axis (Fig. 11.3). The slope of this loop approximates the pulmonary compliance; the hysteresis represents the resistive work of breathing. The dashed line separates the inspiratory and expiratory components, which are usually of equal magnitude. To evaluate any abnormalities, the following characteristics are studied:

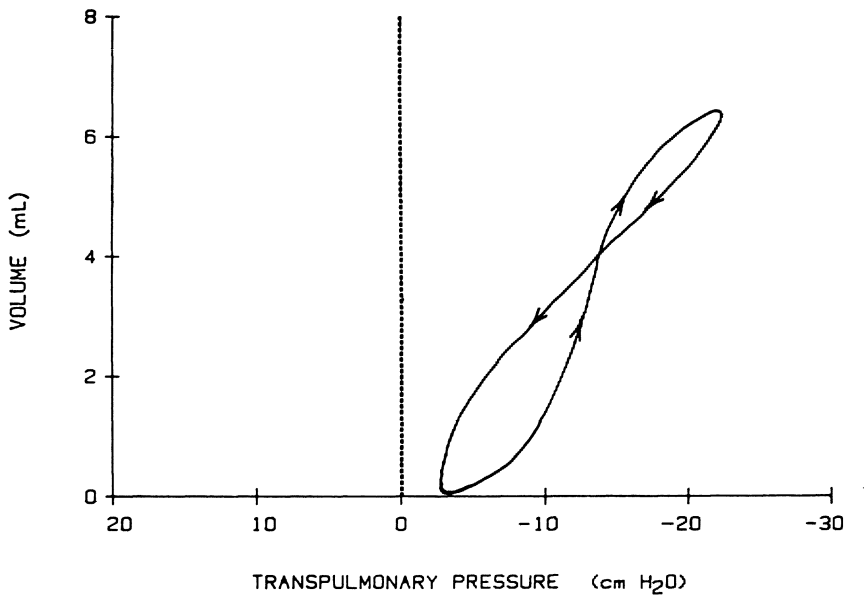

FIGURE 11.7. Inversion of pressure-volume relationship.

1. Tidal volume
2. Driving pressure
3. Positioning of the inspiratory loop to the expiratory loop
4. Size of the hysteresis
5. Slope of the entire loop
6. Slope of the terminal portion of the loop as compared to the proximal
7. Evidence of pressure distortion

Effect of Chest Distortion

In the presence of chest distortion or the highly compliant nature of the thoracic cage, the intrathoracic pressure changes during inspiration or expiration are not uniformly distributed. The pressure–volume loop (with pressure determined from an esophageal pressure) will manifest as either inversion or reversal of the pressure signal (Fig. 11.7). Similar loops may also appear if an esophageal catheter is used and is partially displaced in the stomach.

Effect of Acute Lung Disease

In acute neonatal lung disease, irrespective of the etiology, the primary mechanical component affected is the elastic property. There is an extreme reduction in the pulmonary compliance. This is evident in hyaline membrane disease, pulmo-

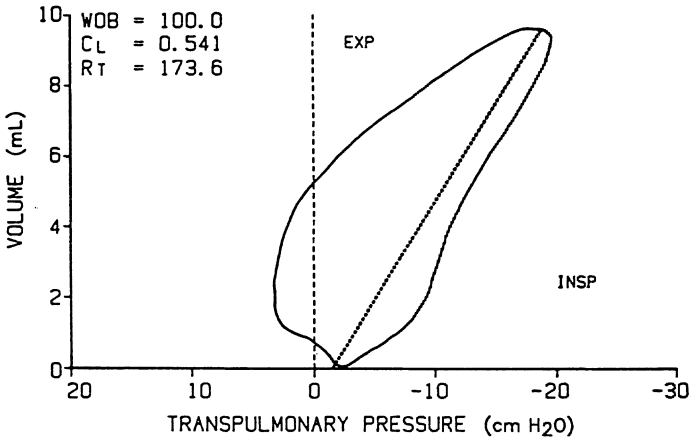

FIGURE 11.8. Pressure/volume relationship of a respiratory cycle in an infant with bronchopulmonary dysplasia. Values of pulmonary compliance (Cl), pulmonary resistance (Rt) and resistive work of breathing (WOB) are calculated.

nary edema, pulmonary hemorrhage, pneumonia, and congestive heart failure. The slope of the pressure–volume loop is decreased, the hysteresis loop is diminished, and the tidal volume is lessened. Generally, the neonate also is unable to generate a sufficient driving pressure, and this usually precedes the onset of respiratory failure and hypoventilation.

In the event of aspiration syndrome or an airway disease process, the air trapping may lead to changes in the resistive mechanical components. The resistive changes are evident by a widening of the hysteresis loop, which is due to a predominant increase of the expiratory component.

Effect of Chronic Lung Disease

The mechanical changes of chronic lung disease are characterized by healing, growth, and the effects of scarring on the respiratory tissue. The slope of the loop may be improved, the tidal volume made more appropriate to normal, and the driving pressure increased by the adaptation of the baby (Fig. 11.8). In fact, the driving pressure is larger than the usual 5 to 7 cm H_2O and may be as high as 20 to 25 cm H_2O. The ability to achieve this is a function of the severity of the disease process and the ability of the infant to achieve optimum ventilation spontaneously. The pulmonary hysteresis is widened because of an increased pulmonary resistance during both inspiration and expiration. Air trapping may be evident by a disproportionately widened expiratory component of hysteresis. More commonly, the neonate has an active expiratory component that is associated with obstructive airway disease. The widened hysteresis also reflects the increased resistive work of breathing during spontaneous breathing.

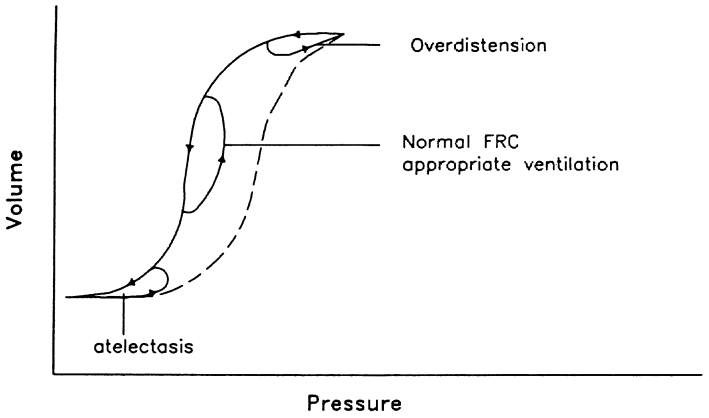

FIGURE 11.9. Pressure/volume relationship indicating areas for tidal volume ventilation. Tidal volume at low functional residual capacity (FRC) (atelectasis) is associated with lower volume of dynamic compliance; high FRC (overdistention) is also associated with low dynamic compliance.

Effect of End-Distending Pressure

The distending pressure increases the lung volume; the mechanical effects are variable and depend on the change in the lung volume (Fig. 11.9). The effect of end-distending pressure (EDP) on the pressure–volume loops and the pulmonary mechanics at both high and low CPAP is shown in Figure 11.10. Observations of pressure–volume loops and incremental levels of EDP provide a means to determine the optimum level of support.

Effect of Mechanical Ventilation

During mechanical ventilation, the early detection of lung overdistention is feasible. At different stages of the disease or with different pathologies, the usual peak inflating pressure used may cause an inadvertent overdistention of the lung. These situations are particularly common with air trapping: aspiration syndrome, airway pathology, or pulmonary interstitial emphysema. Alternatively, these may occur with pathologically low lung volume: pulmonary hypoplasia or severe lung disease. Figure 11.9 illustrates the flattening of the terminal portion of the pressure–volume loop. When such pressure–volume relationships are noted on a real-time basis with bedside, on-line, data-monitoring systems, reduction in the driving pressure (or peak inflating pressure) may show demonstrable change in pulmonary hysteresis and reduction in overdistention with no appreciable change in tidal volume.

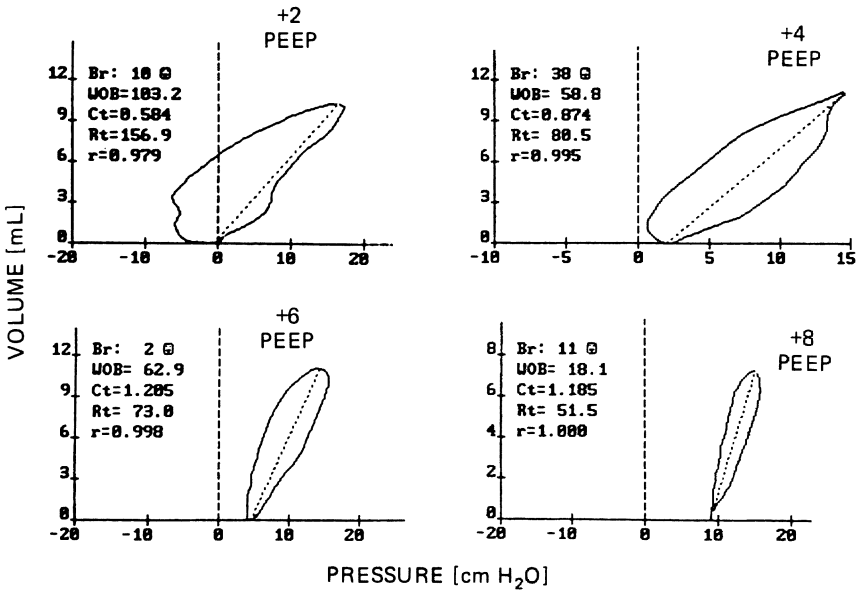

FIGURE 11.10. Effect of end-distending pressure on pulmonary mechanics in infant with bronchopulmonary dysplasia.

Br	Breath number
Ct	Total compliance
PEEP	Positive end-distending pressure
Rt	Total pulmonary resistance
WOB	Resistive work of breathing

Effect of Manual Ventilation

Manual ventilation, or handbagging, is a common resuscitive procedure in the neonatal intensive care nursery. It has been shown handbagging technique among nursery staff varies widely with a tendency for hyperventilation and the use of excessive airway pressures. Inadvertent pulmonary overdistention may occur during manual ventilation.[22] During handbagging, the on-line pressure–volume loops confirm the overdistention, which is related to either a higher airflow rate (and larger tidal volume) or inadvertent EDP (Fig. 11.11). Thus, on-line evaluation of pressure–volume loops, inflating pressure, inspiratory/expiratory airflow, and tidal volume are useful means to minimize inadvertent barotrauma.

Tidal Flow–Volume Relationship (Assessment of Airflow)

The tidal flow–volume loop illustrates the change in tidal volume to both inspiratory and expiratory flow (Fig. 11.12a). In addition to defining the peak values of

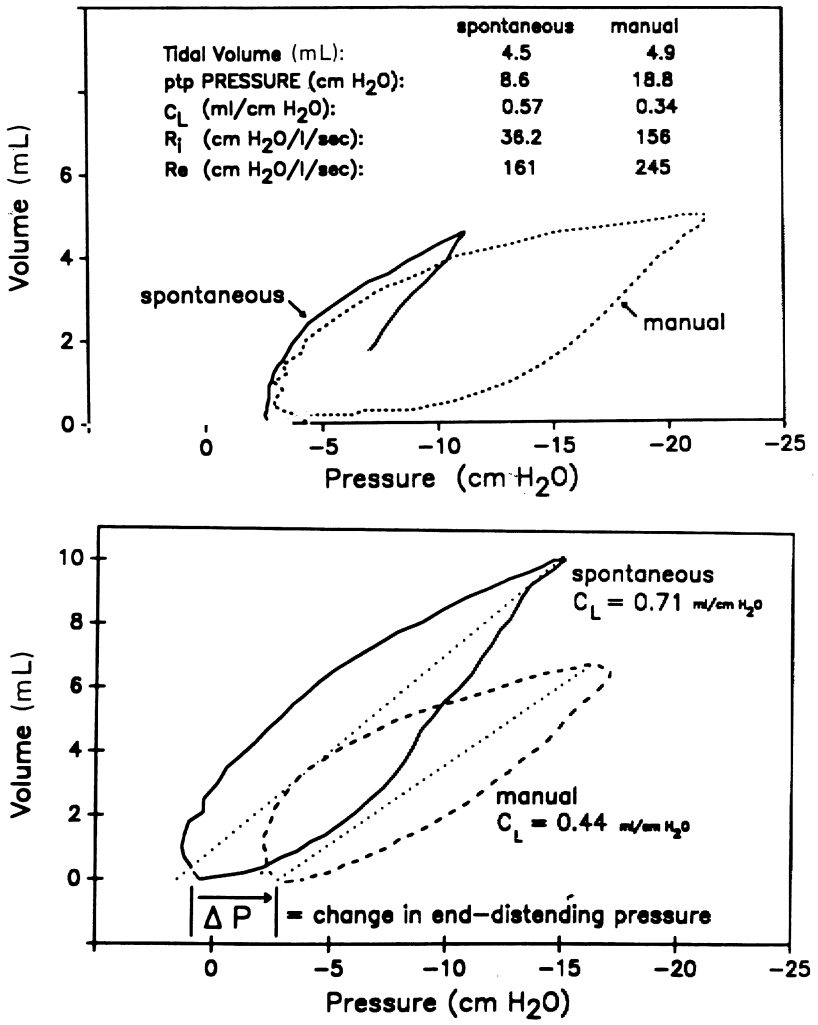

FIGURE 11.11. Effect of pulmonary overdistention with mechanical ventilation (manual ventilation). (A) Overdistention and changes in pulmonary mechanics as compared to a spontaneous breath in the same neonate. (B) The effect of inadvertent change in end-distending pressure and the change in pulmonary compliance (Cl) as compared to the spontaneous breath.

Ptp Peak transpulmonary pressure
Ri Inspiratory resistance
Re Expiratory resistance

both inspiratory and expiratory flow rates, the location of these peaks in relation to the origin of inspiration is also calculated. The pattern of airflow with turbulence or flow limitation may also be visualized. In our laboratory, when the airflow signal shows 80% to 100% flow limitation during a respiratory cycle and is followed by the same phase of the respiratory cycle, it is considered as complete flow limitation (Fig. 11.12b). When the flow rate is only limited to 40% to 80% of the peak value, it is considered an incomplete flow limitation, and this may be either a single or multiple event (Fig. 11.12c). In our experience, flow limitation is an important indication of obstructive airway disease such as plugging, mucosal lesions, necrotizing tracheobronchitis, or tracheomalacia. The characteristics used to define tidal flow–volume loops are listed in Table 11.4.

Scalar Evaluation

A typical scalar record of pulmonary function for individual breaths is illustrated in Figure 11.13; this has been the traditional means of data evaluation. The changes in pressure and concomitant changes in airflow and tidal volume are described during inspiration and expiration. The pressure tracing provides a means to evaluate the magnitude and pattern of change during each respiratory cycle. These records best illustrate the normal variability that is present during neonatal breathing. The consecutive values of tidal volume and driving pressure differ. The data are only constant in a paralyzed infant during mechanical ventilation.

Evidence of swallowing, esophageal peristalsis, and active expiration are evidenced by the positive deflection of the pressure signal (Fig. 11.13). The magnitude of inspiratory and expiratory flow signals are evident. The individual respiratory cycles are usually demarcated by the crossings of zero flow. Interruption to flow signals and turbulence are also apparent. The volume signal defines the tidal volume; it also indicates evidence of air leaks during data collection or even pulmonary air leaks. Though scalar evaluation provides meaningful data, pressure and flow distortion are best visualized with pressure–volume and tidal $\dot{V}$–V loops.

Assessment of Ventilation Parameters

The clinically relevant parameters are the ability of the infant to maintain minute ventilation and the driving pressure that is being generated. Thus, values of minute ventilation, tidal volume, and breathing frequency gauge the infant's ability to maintain appropriate ventilation. The peak-to-peak pressure change (measured in the esophagus) is the indirect assessment of the infant's capability to achieve that minute ventilation.

Mean Data on Pulmonary Mechanics

The mean data on the pulmonary mechanics provide an objective parameter of the infant's pulmonary well-being or compromise. Because of the inherent

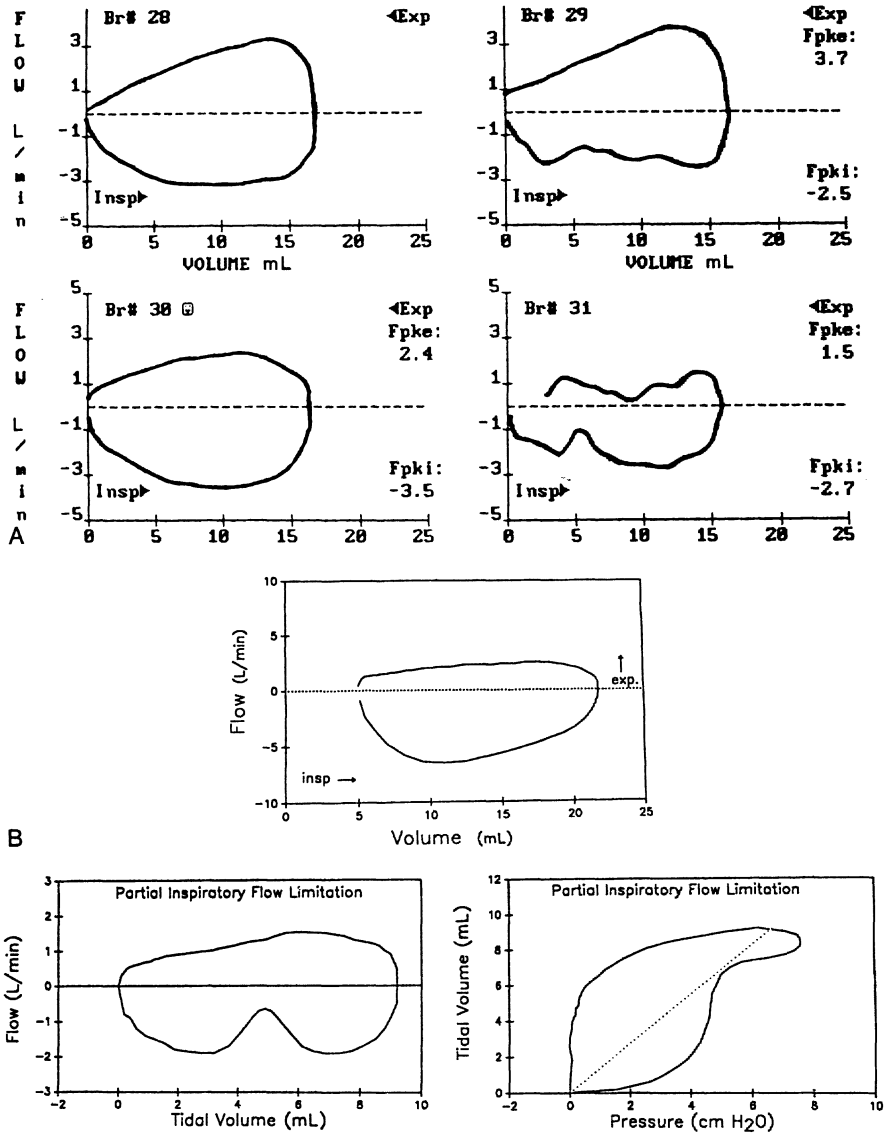

FIGURE 11.12. (A) Tidal flow–volume relationships. Normal loop (breath [Br] 28, 30); multiple inspiratory partial obstruction (Br 29); inspiratory and expiratory obstruction (Br 31). Values of peak inspiratory flow (Fpki) and peak expiratory flow (Fpke) are listed. (B) Complete expiratory flow limitation in tidal flow–volume relationship. (C) Tidal flow–volume and pressure–volume relationship in infant with partial inspiratory flow limitation.

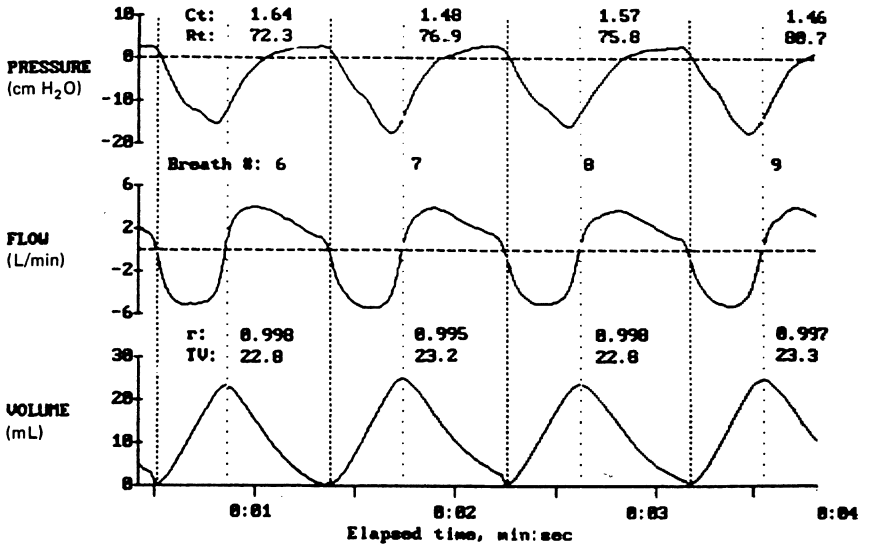

FIGURE 11.13. Scalar record of consecutive respiratory cycles with values of tidal volume (TV), total compliance (CT) and total pulmonary resistance (RT).

neonatal respiratory variability, it is crucial to sample a large number of breaths. Usually 100 to 150 breaths must be sampled. Pulmonary mechanics data evaluation is based on the accurate determination of pressure, flow, and volume; because pressure measurements may not be accurate during chest distortion,[23] these breaths are excluded from the calculation of compliance and resistance. It is preferred that at least 25 to 40 breaths are used for calculation of mechanics. All sampled breaths need to be seen in all graphic forms before their inclusion in the pulmonary mechanics data.

TABLE 11.4. Characteristics of tidal flow–volume loops.

1. Peak inspiratory flow rate
2. Peak expiratory flow rate
3. Tidal volume
4. Timing of peak inspiratory/expiratory flow
5. Airflow at midinspiration and midexpiration
6. Incomplete airflow limitation (40%–80% reduction of peak flow)
7. Complete airflow limitation (80%–100% reduction of peak flow)
8. Percentage of breaths with airflow limitation
9. Repeated evidence of flow limitation (e.g., after suctioning)
10. Reversal of flow limitation with end-distending pressure

TABLE 11.5. Frequently observed values in normal term infants, those with acute RDS (<7 days age), and in infants with BPD (at 4 weeks postnatal age).

	Newborn	RDS	BPD
Pulmonary compliance ($mL/cmH_2O/kg$)	2–2.5	<0.6	<1.0
Pulmonary resistance (cm $H_2O/L/s$)	20–40	>40	>100
Resistive work of breathing (g-cm/kg)	20–30	30–40	>40

BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome.

Classically, both lung disease and mechanics have been categorized as restrictive or obstructive disorders. Many different lung diseases lead to a "restrictive" disorder such as hyaline membrane disease, pneumonia, pulmonary edema, pulmonary hypoplasia, and so on. Obstructive lung diseases have been studied extensively; these have fairly characteristic functional abnormalities. Air trapping with meconium aspiration syndrome, pulmonary interstitial emphysema, and chronic lung disease with bronchopulmonary dysplasia are a few of the examples. A general difficulty, however, is that the pathologic changes are often unevenly distributed. Thus, the determination of pulmonary mechanics does not imply a homogenous disease process. Similarly, normal mechanics may not necessarily reflect lack of a subtle disease process.

Pulmonary mechanics for normal term neonates have been extensively studied and reported.[2,3] Recently, Abbasi and Bhutani[24] reported values for pulmonary mechanics and energetics in normal, nonventilated, low birth weight infants. Table 11.5 lists the commonly determined values of compliance, resistance, and resistive work of breathing in normal and sick neonates with acute (restrictive type) or chronic (obstructive pattern) lung disease. Values of mechanics may be

TABLE 11.6. Pulmonary functions at 4 weeks' postnatal age in infants with and without BPD.

	No BPD	BPD
Birthweight (kg)	1.2 ± 0.1	1.2 ± 0.1
Gestational age (weeks)	29 ± 0.5	29 ± 0.5
Tidal volume (mL/kg)	7.4 - 0.5	5.2 ± 0.5
Minute ventilation (mL/min/kg)	646 ± 60	323 ± 76
Dynamic compliance (mL/cm H_2O)	1.85 ± 0.17	1.25 ± 0.14
Pulmonary resistance (cm $H_2O/L/s$)	87 ± 12	112 ± 12
Resistive work of breathing (g-cm/kg)	21 ± 6	44 ± 6
Peak to peak esophageal pressure (cm H_2O)	5.4 - 1.1	9.7 ± 2.1

Data are mean ± SD for low birthweight infants (< 1500 g) with BPD and matched normal neonates.
BPD, bronchopulmonary dysplasia.

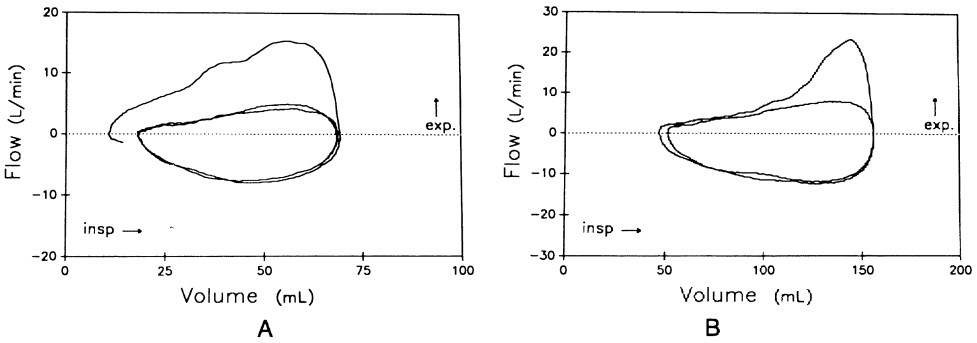

FIGURE 11.14. Partial expiratory flow/volume relationship as determined by rapid thoracic compression technique: (A) normal, (B) infant with bronchopulmonary dysplasia.

determined for the inspiratory and expiratory phases of the respiratory cycles in addition to the usual total breath. The changes in pulmonary mechanics in normal low birth weight infants to those with bronchopulmonary dysplasia are compared at 4 weeks of postnatal age in Table 11.6.

Techniques to Assess Airflow Limitation

Airflow limitation is an important aspect of neonatal disease and especially in infants recovering from bronchopulmonary dysplasia. The pathophysiologic basis for airflow limitation may be related to the airway lumen, mucosal and submucosal wall, tracheal wall, or it may be due to extramural compression. Neonatal airway diseases such as inspissated plug, airway edema, necrotizing tracheobronchitis, mucosal granulomatous lesions, bronchospasm, tracheobronchiomalacia, and elevated intrathoracic pressure account for airflow limitation. These may be evident by changes in tidal flow–volume loops (as described previously).

Airflow limitation that may not be apparent from tidal flow–volume loops may be detected by simulating forced expiratory maneuvers. These tests are usually performed in the postneonatal period. Rapid thoracic compression has been described by Taussig et al.[25] and modified by other investigators.[26] As described by Morgan[27] and in Figure 11.14A, the partial expiratory flow–volume loop illustrates the rapid rise in peak flow, with RTC (Rapid Thoracic Compression), and is followed by a progressive decrease in flow to a volume point below FRC. The curve is convex, away from the volume axis in a normal infant, and $\dot{V}$max FRC (maximal expiratory flow) is higher than tidal expiratory flow.[27] Tepper et al.[28] have shown the significant flow limitation and $\dot{V}$max FRC in infants with bron chopulmonary dysplasia (Fig. 11.14B).

Induction of bronchoprovocation, either with a pharmacologic agent[29] or cold air challenge,[30] may be used to provoke the bronchial reactivity in infants with bronchopulmonary dysplasia. In addition to flow limitation, there is an increase in pulmonary resistance that may be associated with decrease in pulmonary compli-

ance and minute ventilation. The value of this investigation is being currently researched, especially to consider if these tests are safe in the neonatal population.[31]

Spontaneous Versus Mechanical Breaths

It is well understood (and described previously) that mechanical ventilation can distort the pulmonary functions. This distortion primarily is due to inadvertently higher tidal volume or EDP such that the "mechanical breath" differs markedly from the spontaneous breath (Fig. 11.11). Thus, the determination of the neonate's true pulmonary status is best measured during spontaneous breathing in a nonsedated state. On the other hand, the effect of mechanical ventilation itself may be evaluated by measuring pulmonary functions during mechanical ventilatory support. The technical difficulty remains in sequential comparison of data obtained during mechanical ventilation and subsequent spontaneous breathing. In addition, during sampling at low ventilatory support (mixture of spontaneous and mechanical breaths), the effect of volume history of a mechanical breath on the ensuing spontaneous breath must be considered. Generally, data are collected either during mechanical ventilation or entirely during spontaneous breathing.

On-Line Evaluation of Bedside Pulmonary Function

Infants on mechanical ventilation must be continuously monitored for tidal volume, pressure–volume relationship, and tidal flow–volume relationships. The technical limitation has been the need to use a pneumotachometer to measure airflow and tidal volume. The currently available pneumotachometers have substantial DS volume and resistive load, both of which would comprise the pulmonary status of a sick neonate. In the meantime, intermittent evaluation, especially before a significant change in ventilatory support, is recommended.

Rationale for Post-Intensive Care Nursery Follow-up

Low birth weight neonates and neonates who have been ventilated for >7 days have consistently shown that they are likely to have abnormal pulmonary functions at the time of discharge from the nursery.[32-34] Some of these neonates do not meet the existing criteria to be defined as having bronchopulmonary dysplasia. We, however, have previously reported that the pulmonary mechanics of the infants who met the criteria of bronchopulmonary dysplasia did not differ from those who did not.[24,35] In view of the relatively high incidence of respiratory infections, airflow limitation, and bronchial reactivity, we follow these infants in the manner outlined in Table 11.4.

Future Clinical Applications

The diagnostic procedures being investigated include the determination of static pulmonary compliance (as by occlusion or interrupter techniques), functional residual capacity, and ventilation–perfusion matching. These parameters would thus complete the basic pulmonary functions that are necessary to assess a neonate with respiratory dysfunction.

Conclusions

Comprehensive evaluation of the pulmonary function profile involves the analysis of a wider spectrum of breaths. There is an easier recognition of distorted breaths, which may be excluded from the analysis of pulmonary mechanics. Importantly, there is a real-time evaluation of the pulmonary status that would provide guidelines for therapeutic intervention and assess prognosis. These data are significantly useful as they relate to growth: both somatic and pulmonary, intercurrent diseases and respiratory support. Pulmonary function testing is an integral component in understanding the pathophysiology of the neonate with respiratory distress.

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12
High-Frequency Ventilation of Infants

J. BERT BUNNELL

Introduction and History

Mechanical ventilation has proven to be a tremendous tool for the critical care of newborn infants. Many more infants survive their prematurity, meconium aspiration, and other forms of respiratory distress, thanks in large part to mechanical ventilators. Conventional ventilators, however, do have their limitations.

High pressures and oxygen concentrations often must be applied to infants' lungs to provide adequate ventilation and oxygenation. These high pressures and oxygen concentrations take their toll by contributing to the iatrogenic disorders that are all too familiar to anyone who works in this environment: pulmonary air leaks, damage of the airways and mucosal membranes, elevated intracranial blood pressure and intraventricular hemorrhage, compromise of the cardiovascular system, and so on. Thus, new and better techniques of providing mechanical ventilation are always being sought.

High-frequency ventilation is a new technique that promises to add to the success of using mechanical ventilation in the treatment of infants in respiratory distress. The use of smaller tidal volumes and lower pressures, which are inherent in at least some high-frequency techniques, is proving to make the critical difference in cases when conventional mechanical ventilation has previously fallen short.

This chapter will present some of the theoretical background of this technique and the clinical implications of these theories. It will examine the various types of high-frequency ventilators that are now available for general or investigational use. The Food and Drug Administration (FDA) regulations that control the introduction of new devices of this type into the US marketplace will also be discussed. Finally, examples of the data gathered during clinical trials used to garner FDA approval for one high-frequency ventilator will be presented.

Forced Oscillations

In 1956, DuBois and co-workers[1] published their theory of the natural or resonant frequency of the respiratory system. This theory serves as a basis for understanding the potential benefits of high-frequency ventilation.

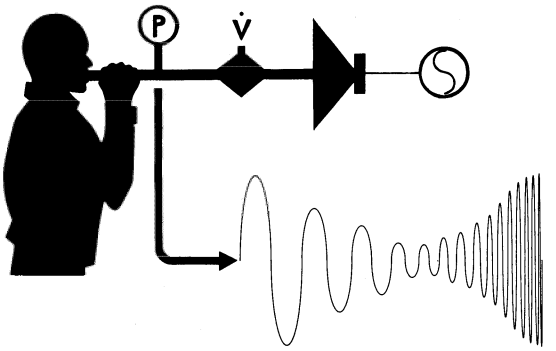


FIGURE 12.1. Forced oscillations and resonant frequency. The respiratory system has a natural or resonant frequency at which the energy necessary to push gas in and out of the lungs is minimized. This phenomenon can be demonstrated using a loudspeaker and a pressure transducer (P). A flow sensor ($\dot{V}$) allows measurement of airway resistance.[1]

Three elements make up the impedance (i.e., the total opposition) to gas flow in and out of the lungs: compliance of the lungs and chest wall, airway resistance, and inertance. Inertance is normally considered to be negligible, because it is related to changes in momentum. Changing the momentum of the gas that moves in and out of the lungs and the tissue that moves with it at normal breathing rates is very easy because the mass involved is so slight.

Momentum is equal to mass times velocity. While the mass of the gas and tissue in the lungs is small and will not change, velocity will rise with frequency. As one increases the frequency of gas movement in the lungs beyond that which the subject could produce on his or her own, the effects of increasing velocity will cause inertance to become increasingly significant.

When a small volume of gas is forced in and out of the lungs using a piston or loudspeaker, an oscillating pressure waveform can be measured at the subject's mouthpiece (Fig. 12.1.) As the frequency of the induced constant volume oscillations is increased with an adult subject, the amplitude of the pressure oscillations will diminish in the range of 1 to 4 Hz (1 Hz = 1 cycle/s), will encounter a minimum in the range of 4 to 8 Hz, and will increase as frequency is further increased. The frequency at which the pressure oscillations become minimal is recognized to be the natural or resonant frequency of that subject's respiratory system.

The resonant frequency of the lungs is encountered when the energy required to overcome the inertance of getting gas to move into the lungs is equal to the energy required to overcome lung and chest wall compliance. These two components of impedance are encountered sequentially; thus, the energy embodied in the momentum of the incoming gas and moving tissue is transferred and absorbed by the tissues whose stretching composes the compliance element of impedance. The elasticity of the lungs and chest wall then provides the energy necessary to reverse the momentum of the incoming gas. Its recoil forces serve to send the gas back out of the lungs. The timing is perfect at resonance, and a minimum of energy is required to effect gas movement in and out of the lungs.

Once resonance is achieved, the only element of impedance remaining is airway resistance or friction between the moving gas and tissues. Thus, the amplitude of the pressure waveform at its minimum over this frequency spectrum provides the pressure drop in the numerator of the airway resistance equation:

$$R_{aw} = \frac{\Delta P}{\dot{V}}$$

where R_{aw} = airway resistance, ΔP = the minimum pressure amplitude, and $\dot{V}$ is the volumetric flow rate at that frequency where the minimum pressure drop is measured.

While this theory leads one to the conclusion that gas movement in and out of the lungs can be produced with a minimum of outside applied energy, it does nothing to ensure that this gas movement will provide gas exchange. The equation for alveolar ventilation ($\dot{V}_A$) predicts that alveolar gas exchange will occur only to the extent that tidal volume (V_T) exceeds dead space volume (V_{DS}):

$$\dot{V}_A = (V_T - V_{DS})f$$

where f = breathing frequency.

Is it possible to achieve normal gas exchange at the resonant frequency of the respiratory system? At first glance, the alveolar gas equation leads one to predict that extraordinary minute volumes would accompany any attempt to use frequencies from 4 to 8 Hz. If the use of lower airway pressures is our goal in this type of mechanical ventilation, could this goal be reached while achieving normal gas exchange?

Infrasound

In 1973, Colonel Daniel L. Johnson of the Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio, delivered a treatise on the various effects of infrasound.[2] Infrasound is low-frequency sound of 1 to 10 Hz which may be experienced in everyday life while riding in an automobile at high speed with a window down. The lay literature of the time occasionally published an article on the harmful effects of infrasound including symptoms akin to drunkenness. Johnson discovered that infrasound could be used for mechanical ventilation when a subject is encased in an airtight container.

Johnson's experiments involved placing dogs in an airtight chamber where sound was generated by a piston placed in one of the walls. As the dogs were bombarded with sound at higher and higher amplitudes, Johnson found that they stopped breathing. Upon further thought and examination, he realized that he had created something similar to an iron lung. In this case, however, the subject's head was inside the chamber.

The sound-generating piston created changes in pressure within the chamber as it oscillated back and forth. The anesthetized animal accommodated these pressure oscillations by allowing air to enter and leave its lungs when the pressure around it was increased and decreased. This movement of air served to keep the

gas inside the animal's thorax at atmospheric pressure. Johnson calculated that the animals stopped breathing when the sound-induced pressure changes in the chamber reached a level that produced volumetric changes roughly equivalent to the animals' normal minute volume.

The fact that Johnson used "breathing" frequencies in the range of the resonant frequency of human lungs was most intriguing. Even more intriguing was the possibility that normal gas exchange was being accomplished at these high frequencies at what appeared to be normal minute volumes. When I queried Johnson about the adequacy of the animals' ventilation using infrasound, he responded that blood gases and tidal volumes were never measured.

The tidal volumes used in Johnson's experiments were approximated by converting the decibel values noted at the time of the animals' onset of apnea into changes in pressure. These pressure changes were then converted into volumetric changes (i.e., tidal volumes) using Boyle's law. The tidal volumes calculated in this way were in the range of 1 to 2 mL/kg body weight.

Anatomic dead space of mammalian lungs is approximately 2 mL/kg body weight.[3] If Johnson's sonic tidal volumes were equal to or less than that value, it was improbable that the animals were being adequately ventilated.

Early Animal Experiments Using High-Frequency Positive-Pressure Ventilation

Bunnell et al.[4] sought to determine the tidal volumes necessary to achieve normal ventilation in anesthetized and paralyzed rabbits at frequencies from 1 to 10 Hz and reported their findings in 1978. They constructed a simple high-frequency positive-pressure ventilator (HFPPV) using quick-acting solenoid valves and incompressible tubing. Tidal volumes were measured by collecting all exhaled gas and dividing by the number of exhalations.

A series of rabbit experiments revealed that the tidal volume necessary to achieve an arterial partial pressure of carbon dioxide ($PaCO_2$) near 40 mmHg decreased as ventilator frequency was increased from 1 to 10 Hz (i.e., 60 to 600 breaths per minute). A tidal volume limit of 1 to 2 mL/kg body weight was approached in the upper rate range. The corresponding minute volume rose with increasing frequency but not nearly as much as would have been suggested by the alveolar air equation. The investigators concluded that normal ventilation could be achieved using tidal volumes equal to or less than anatomic dead space.

Theories of Gas Exchange During High-Frequency Ventilation

Although numerous investigators have demonstrated that ventilation could be accomplished using very small tidal volumes,[4,8,10,11] few have explained how it actually happened.[9] Some research groups[4,6] attempted to explain these results

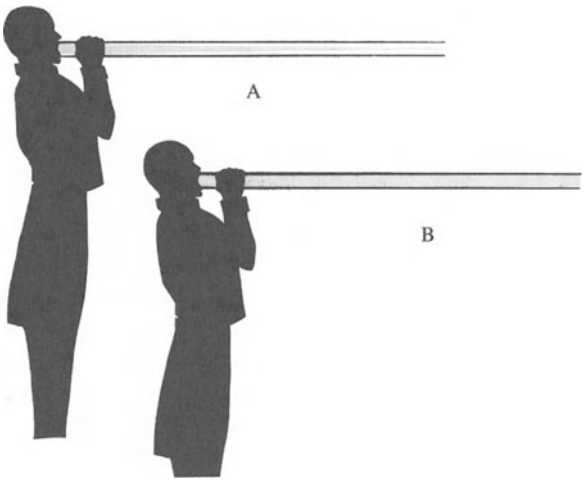


FIGURE 12.2. Henderson's smoke convection/diffusion experiment. A sudden burst of tobacco smoke into a glass tube creates a long sharp spike (A), which dissipates by diffusion at the instant the flow stops (B).[5]

based on theories related to enhancement of diffusion. The enhancement of diffusion caused by cardiac motion in an apneic subject had been previously described,[47] and some felt that the vibrations induced during high-frequency ventilation must have a similar effect.[8] However, the distances over which significant diffusion may take place are quite short, and the time available for diffusion during high-frequency ventilation is so limited that different mechanisms related to the *convective* movement of gas in and out of the lungs must be considered.

One of the best theories related to the enhancement of convection was proposed by Henderson et al. in 1915.[5] Henderson was intrigued by the apparent shallow breathing of panting dogs. To explain how these animals could pant indefinitely without becoming hypoxic, he demonstrated flow streaming using tobacco smoke and a glass tube 1 m long and 2 cm in diameter. Filling his mouth with smoke, Henderson blew a very brief, sharp breath of smoke into the tube. His associates observed that the smoke streamed through the center of the tube as a very long, sharp spike (Fig. 12.2). The faster he blew this single mouthful of smoke, the greater the distance down the tube the thin spike progressed. The instant he stopped the flow by applying his tongue to the upstream opening, the smoke filled the tube axially by diffusion.

This classic experiment demonstrates the relative importance of convection and diffusion in high-frequency jet ventilation. Convection can carry fresh oxygen long distances very quickly and deeply into the lungs. Once the flow stops, the two gases mix by diffusion. Diffusion also occurs very quickly but over much shorter distances.

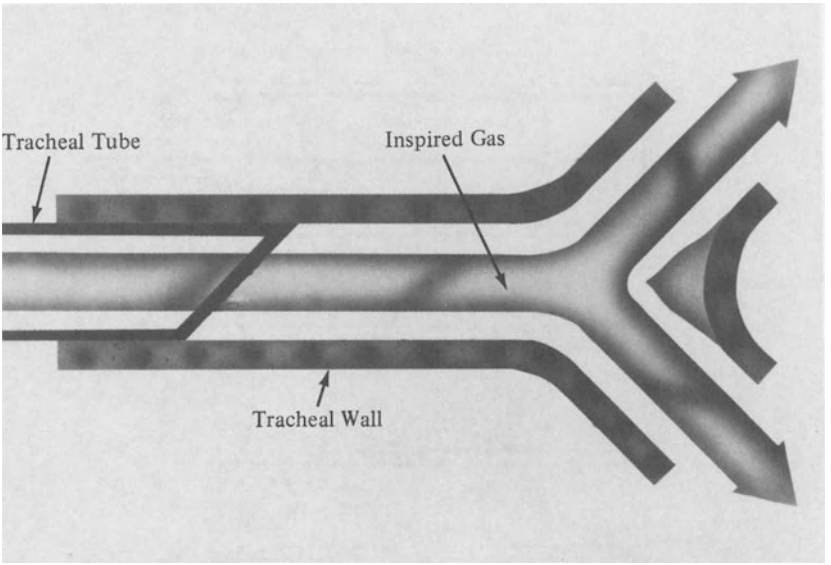


FIGURE 12.3. Gas swirls into the lungs down the center of the airways during high-frequency ventilation.

Diffusion in the airways during high-frequency ventilation is counterproductive because it dilutes the incoming gas with carbon dioxide and enriches the exhaled gas with oxygen. The more incoming oxygen can remain separate from the resident dead space gas, the more oxygen will be available for diffusion once it reaches the alveoli. Only at the level of the alveoli and respiratory bronchioles is diffusion helpful during high-frequency ventilation.

Turbulence in the airways is likewise counterproductive. It breaks down the boundaries between the fresh gas streaming into the lungs and causes mixing of the incoming and dead space gas. High-frequency ventilation and the architecture of the lungs discourage turbulence during inhalation. They promote flow streaming, which keeps incoming oxygen separate from the outgoing CO_2-rich dead space gas.

Gas coming into the lungs during high-frequency jet ventilation is propelled at high velocity for sufficiently short duration so that turbulence is avoided. The flow is not actually laminar, at least in the trachea and large airways, but the briefness of the incoming pulses does not allow time for fully developed turbulence. The gas probably begins to swirl and spiral with its abundance of kinetic energy, but the pulse is stopped before these swirls can become chaotic and disorganized. Thus, the incoming gas holds together and streams as a unit (Fig. 12.3).

The architecture of the lungs is such that the cross-sectional area of the tubes going into the lungs continuously increases with each bifurcation so that the flow rate of incoming gas decreases as it penetrates. On exhalation, the outgoing gas

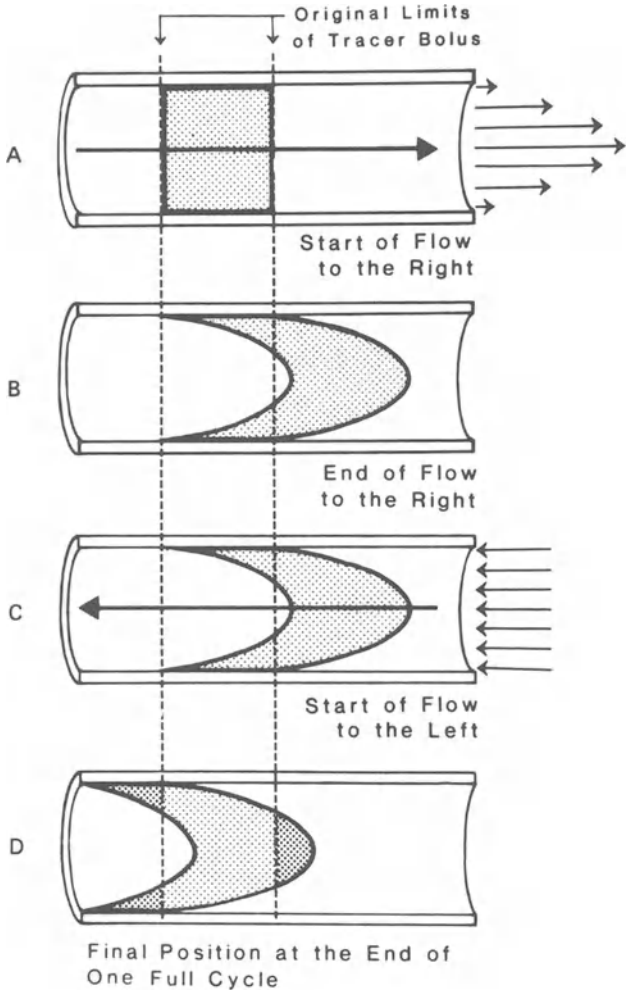


FIGURE 12.4. Inhalation and exhalation flow-velocity profiles. (A) Laminar flow with its parabolic velocity profile is promoted by the architecture of the lungs during the inhalation phase of high-frequency oscillation. (B) At the end of one high-frequency inspiration, a tracer bolus is distorted and displaced downstream in proportion to the viscous forces applied. (C) Turbulent flow with its blunt-velocity profile is promoted during the exhalation phase. (D) At the end of one complete cycle, the tracer bolus remaining at the end of inspiration has been displaced uniformly upstream, maintaining the distorted shape. The net effect of one oscillation is the displacement of axial gas downstream and wall gas upstream. (*Source*: Modified with permission from Haselton FR, Scherer PW: Bronchial bifurcations and respiratory mass transport. *Science*. 1980;208:69. Copyright 1980 by the AAAS.)

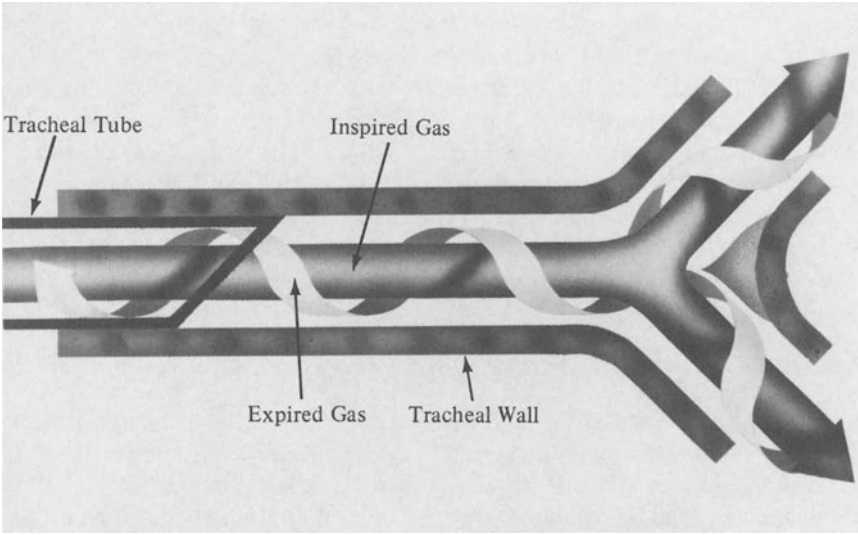


FIGURE 12.5. The mathematical model of Ellis predicts counter-current swirling gas flow in the lungs during high-frequency ventilation.[7]

is accelerated by this architecture, and turbulent flow results. Haselton and Scherer[6] described how this slowing of gas on inhalation and acceleration of gas on exhalation supports the concept of flow streaming by promoting laminar flow on inspiration and turbulent flow on expiration.

The velocity profile of laminar flow is bullet shaped, whereas the velocity profile of turbulent flow is blunt. This difference in flow profiles encourages gas coming into the lungs to advance down the center of the airways. It encourages the gas going out of the lungs to advance along the walls (Fig. 12.4).

The net effect of these phenomena during high-frequency oscillation is that gas flowing into the lungs in short bursts tends to stay in the center of the airways. The gas going out of the lungs pulses out in the marginal annular space surrounding the incoming gas. A bidirectional, double-helical flow pattern has been suggested by the mathematical model of Ellis[7] (Fig. 12.5).

Although the rapid alterations in direction produced during high-frequency ventilation minimize the amount of counterproductive mixing that can be accomplished by diffusion and turbulence in the airways, they probably enhance diffusion at the level of the alveoli by mechanical vibration. Lunkenheimer and co-workers[8] demonstrated this phenomenon in apneic dogs using high-frequency oscillations.

The overall effect of these phenomena is that the dead space volume of the lungs is reduced. Thus, a fresh look at the familiar equation for calculating alveolar ventilation ($\dot{V}_A$),

$$\dot{V}_A = (V_T - V_{DS})f$$

reveals that if the dead space volume is reduced, the tidal volume necessary for alveolar ventilation may likewise be reduced, and there is really no mystery to this business after all. Weinmann and associates[9] stated the issue as one wherein anatomic dead space exceeds physiologic dead space during high-frequency ventilation, whereas it is commonly accepted that physiologic dead space exceeds anatomic dead space during conventional ventilation. Henderson stated the case in exactly the same way some 69 years previously and concluded that during rapid shallow breathing in man, "there may easily be a gaseous exchange sufficient to support life even when the tidal volume is considerably less than the dead space."[5]

Carbon Dioxide Elimination and Oxygen Uptake

A common observation during high-frequency ventilation is that changes in peak inspiratory pressure or waveform amplitude are much more important in CO_2 elimination than changes in frequency. While the relationship between CO_2 elimination and minute volume is well established in conventional ventilation, investigators have found that the following relationship applies in high-frequency ventilation:

$$\dot{V}_{CO_2} = kfV_T^2$$

where $\dot{V}_{CO_2}$ is carbon dioxide elimination, k is a constant, f is frequency, and V_T is tidal volume.[10,11] A simple clinical or physiologic explanation for this phenomenon has yet to be proposed. Most investigators state that this relationship is the result of numerous effects including flow streaming, pendelluft (gas exchange between alveoli resulting from nonhomogeneity in the lungs and differences in time constants), and direct ventilation of alveoli closest to the trachea. An elegant mathematical analysis of this finding has been presented by Venegas and associates.[12]

Clinical observations of the effects of high-frequency ventilation on oxygenation are not nearly as consistent as those related to CO_2 elimination. After many years of combined clinical experience, however, the following observations seem to be fairly uniform: (1) Oxygenation is directly proportional to mean airway pressure, although the mean airway pressure required during high-frequency jet ventilation may be significantly less than that required for a comparable level of oxygenation during conventional ventilation or high-frequency oscillation. (2) Atelectasis is commonly encountered within hours of the initiation of high-frequency ventilation if no "sighs" or normal-sized breaths are delivered periodically. High-frequency breaths may or may not be "stacked" on top of the sighs or intermittent mandatory breaths.

These observations are, of course, quite similar to those made on patients during conventional ventilation. Sighs are no longer routinely used with conventional ventilation, especially with infant ventilators, but these same clinical observations have led people to use sighs in the treatment of adults in lieu of higher levels of positive end-expiratory pressure (PEEP) for the past 20 to 30 years.[13]

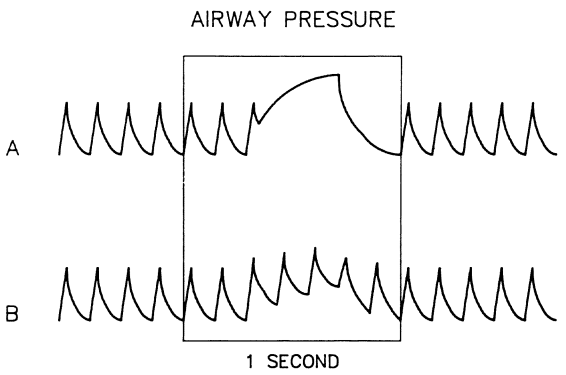


FIGURE 12.6. "Sighs" or infrequent conventional ventilator breaths appear to be beneficial during high-frequency ventilation. These deeper breaths may be programmed to interrupt (A) or not interrupt (B) the high-frequency pressure waveform.

If a high-frequency ventilator is designed to be sufficiently similar in design and nomenclature to conventional ventilators, the approach to its use is remarkably familiar. PEEP, rate, and peak pressure are manipulated to produce changes in mean airway pressure. Alveolar recruitment presumably occurs whenever the high-frequency breaths are interrupted or augmented by conventional breaths or "sighs" (Fig. 12.6).

The possibility that sighs or periodic elevations of the high-frequency pressure waveform are effective during high-frequency ventilation, whereas sighs have been shown *not* to be effective during conventional ventilation, has been explained by Kolton and co-workers.[14] These investigators used sustained inflations of 30 cm H_2O for 15 seconds before conventional and high- frequency oscillatory ventilation (HFOV) in an effort to recruit alveoli. The technique was effective with HFOV but not with conventional ventilation. Their explanation was that the sustained inflation provided the large opening forces that are otherwise absent with the low tidal volume high-frequency ventilation breaths, whereas conventional ventilation provided sufficient opening forces with its larger tidal volumes. Thus, high-frequency ventilation may inherently provide better gas exchange but not without a certain level of already open alveoli.

Clinical Implications of Theoretical Gas Exchange Mechanisms and High-Frequency Ventilator Design

The clinical implications of the concept of resonant frequency in the lungs include but are probably not limited to the following:

1. Compliance is eliminated as a major factor influencing the pressure required to achieve adequate gas exchange.
2. Use of lower distending airway pressures should be possible if mechanical

ventilation is implemented at frequencies that are approximately 10 times normal breathing frequency. Extensions of this implication follow:

a. Pulmonary air leaks may be more effectively treated at higher frequencies.
b. Pulmonary vascular resistance and cardiac output will be less affected if mean airway pressure is lowered.
c. Barotrauma may be avoided if high-frequency ventilation is instituted prophylactically.

The theory that inertia and momentum of flowing gas are of comparable importance to lung compliance infers that gas flow in the lungs during high-frequency ventilation will not necessarily follow the path of least resistance. Thus, one may expect that inspired gas will flow past airway disruptions such as bronchopleural and tracheal–esophageal fistulae.

Streaming of gas through the airways (i.e., inspired gases are directed down the center of the airways, using only a portion of the total tube volume) infers that smaller tidal volumes will penetrate more deeply into the lungs. Thus, "effective" or physiologic dead space volume is reduced. It is further implied that implementation of higher minute volumes and hyperventilation for conditions such as persistent fetal circulation becomes much easier (i.e., less peak and mean airway pressure is required).

Finally, the swirling, wall-hugging flow pattern of exhaled gas during high-frequency ventilation tends to facilitate the removal of secretions and aspirated material from the lungs. As a result, suctioning may be required more frequently during the first hour or two of high-frequency ventilation. Once excess secretions are removed, there is nothing to suggest that any extra secretions are produced. Thus, this phenomenon may be important in the prevention of aspiration and in cases when excessive secretions, mucus plugs, and/or meconium are compromising the patient's well-being.

Gas Trapping

Perhaps the greatest concern related to the clinical use of high-frequency ventilation is the possibility of causing gas trapping. Gas trapping occurs when either the time for expiration is insufficient or when "choke" points develop in the airways of the lungs that seal expired gas off from its exit point at the trachea. If the exhaled tidal volume during high-frequency ventilation is not reduced in proportion to the time allotted for exhalation, gas trapping may occur.

The propensity for gas trapping during high-frequency ventilation differs with ventilator design and operating conditions. The following factors are inclined to *encourage* gas trapping:

1. Inadequate time for exhalation
2. Larger tidal volumes
3. High resistance to exhalation, whether in the patient's lungs or in the exhalation limb of the ventilator circuit
4. High lung compliance

The time allotted to exhalation during any type of mechanical ventilation will be inversely proportional to the ventilator rate and inspiratory/expiratory time ratio (I:E). Obviously, the larger the breath, the harder it will be to get it back out of the lungs. Thus, the higher the rate and the bigger the breath, the more the potential for gas trapping. The longer the expiration time, the less the potential for gas trapping.

The ease with which gas may exit the lungs is also a function of the mechanical properties of the lungs themselves. The stiffer the lungs (i.e., the lower the lung compliance), the faster gas will be pushed out on exhalation. The greater the airway resistance, the slower the gas will exit. These two elements of impedance define the "time constant" for exhalation (TC_e):

$$TC_e = \frac{1}{R_{aw} C_l}$$

where C_l = lung compliance. Lungs with shorter expiratory time constants will trap gas easier than lungs with long time constants. Lungs with shorter time constants must be ventilated with smaller tidal volumes, slower rates, and/or shorter I:E ratios to avoid gas trapping.

Lung mechanics can be manipulated by ventilator management. PEEP increases lung volume, which will decrease airway resistance to exhalation and may decrease lung compliance. Applying negative pressure during expiration or sucking gas from the lungs decreases lung volume, which increases airway resistance to exhalation. This phenomenon makes high-frequency oscillators particularly predisposed to producing gas trapping. High-frequency jet ventilators, however, can produce gas trapping if they are run at inappropriately high rates.[15]

High-Frequency Ventilation Techniques

Various high-frequency ventilation techniques have evolved over the past 30 years. Emerson[16] patented an "airway vibrator" in 1959, which he postulated would enhance gas exchange as well as facilitate chest physiotherapy. This device became the first high-frequency oscillator (HFO). Its value in assisting ventilation, however, was not studied until the early 1980s.[17] Emerson later developed a rotating ball valve device that became known as a high-frequency flow interrupter (HFFI)[18] (Fig. 12.7).

In the late 1960s, a group of Swedish researchers began to explore the advantages of using higher frequencies as they sought a way to remove the artifact imposed by mechanical ventilation on the cardiovascular system.[19] They used fairly standard ventilators with special low-compliance tubing and connectors to maximize their efficiencies at rates up to 120 breaths per minute. Sjostrand[20] coined the term *high-frequency positive-pressure ventilation* (HFPPV) to describe their treatment of thousands of children and adults during surgery and 32 infants with respiratory distress syndrome.[20]

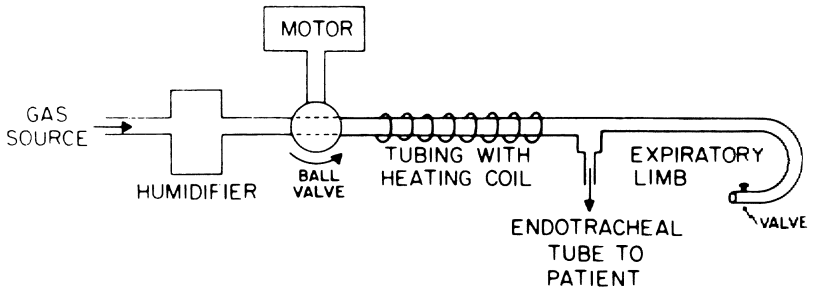


FIGURE 12.7. Emerson high-frequency flow interrupter. A rotating ball valve creates high-frequency pulses that are directed into the patient by frequency-dependent differences in the impedance of the patient versus the impedance of the exhalation limb of the breathing circuit. (Reproduced by permission of *Pediatrics*, vol. 71, page 484, copyright 1983.)

Lunkenheimer and co-workers[8] introduced the concept of using very high-frequency oscillations to enhance diffusion in the lungs in 1972. In Toronto, Bohn et al.[10] and Marchak et al.[21] followed this work with an HFO that has been used extensively in animal and clinical work (Fig. 12.8).

Klain and Smith[22] improved the concepts of HFPPV and HFFI in the early 1970s by introducing the concept of high-frequency "jet" ventilation (HFJV). This technique eliminates practically all of the mechanical dead space associated

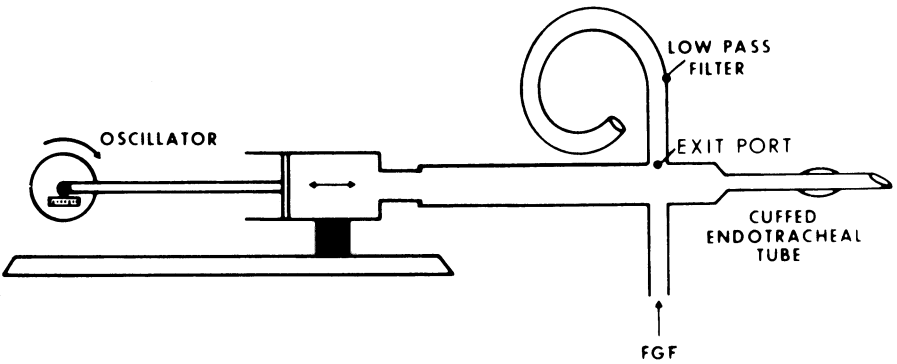
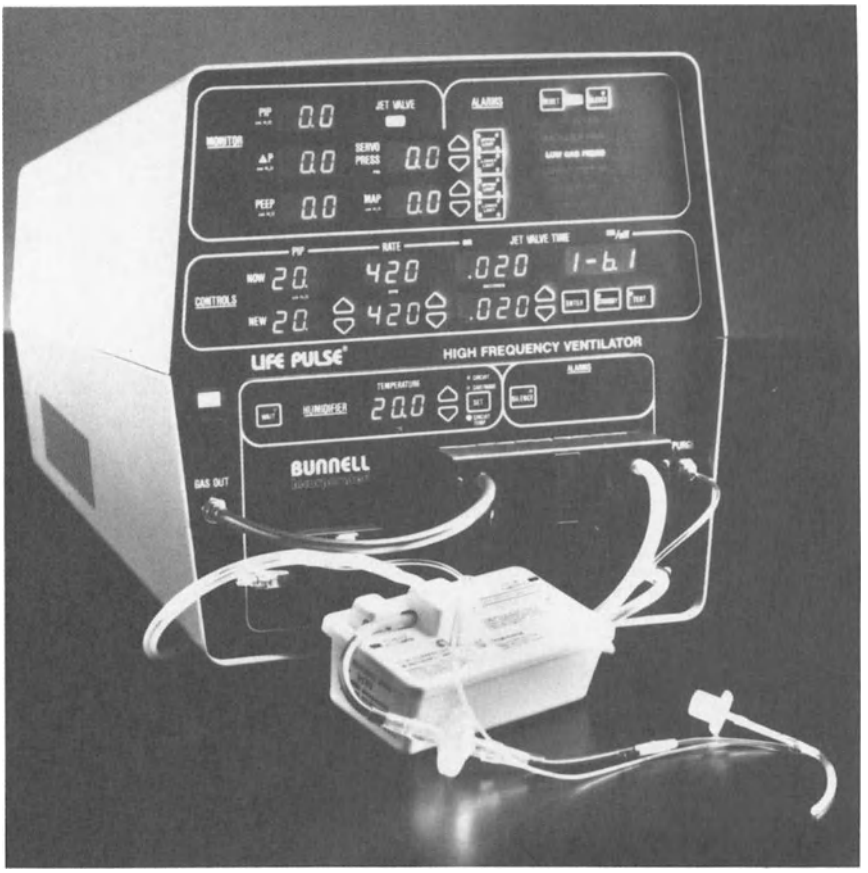


FIGURE 12.8. High-frequency oscillatory ventilator. A piston creates high-frequency pulses that are directed into the patient by frequency-dependent differences in the impedance of the patient versus the impedance of the exhalation limb of the breathing circuit. Fresh gases enter the system just proximal to the tracheal tube (FGF). Excess fresh gas and mixed gases that are oscillated out of the lung exit via the low-pass filter. (*Source*: Reprinted with permission from Marchak BE, Thompson WK, Duffy P, et al. Treatment of RDS by high-frequency oscillatory ventilation: a preliminary report. *J Pediatr.* 1981;99:289.)



A

FIGURE 12.9. Life Pulse high-frequency jet ventilator. (A) Picture of ventilator, (B) diagram of front panel, (C) block diagram of key elements. (ATM, atmosphere.) The operator specifies the peak inspiratory pressure on the Life Pulse front panel, and the ventilator automatically delivers and maintains that peak pressure. High-frequency pulses are released through an electronic pinch valve into the jet lumen of the Hi-Lo JET tracheal tube. (See Fig. 12.10.) The pinch valve is located in a box close to the infant to minimize compressible dead-space volume. The pressure generated by the jet is measured at the distal tip of the tracheal tube. This measurement is used to feedback control the driving pressure behind the jet.

with all other types of mechanical ventilators and introduces the gas directly into the trachea with low-pressure, small-volume, high-velocity pulses of gas. It has now been refined and used extensively[23-25] and is the basis for the first high-frequency ventilator approved by the FDA (Fig. 12.9).

At least two hybrid high-frequency ventilators have also been developed. Infrasonics Inc. has developed an HFPPV module for its Infant Star® ventilator that produces the effects of HFO as a result of its breathing circuit design. Bird Space

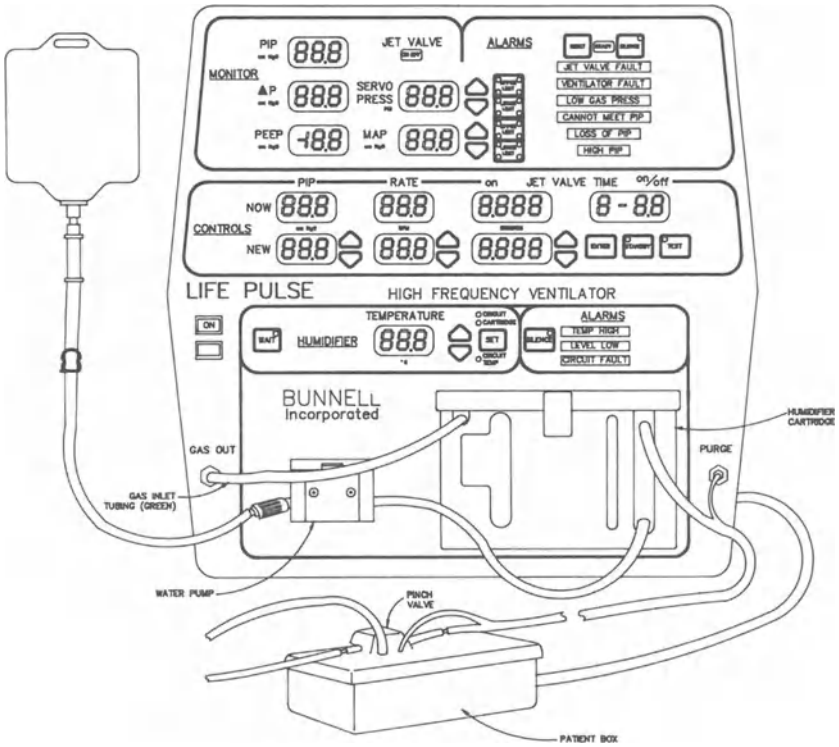


FIGURE 12.9B.

Technology Inc. has developed a jet-type device called the Volumetric Diffusive Respirator® (VDR). Its "jet" is significantly removed from the tracheal tube; thus, some reviewers have referred to the VDR as a "set-back jet."

Each of the high-frequency techniques has its advantages and disadvantages. The following analysis is an attempt to contrast the similarities and differences of the various techniques. (However, I admit to a fair degree of prejudice, resulting from my experience with the Life Pulse® ventilator.)

Similarities

All of the high- frequency ventilator techniques operate, of course, at rates considerably higher than normal breathing rates. The only limitations on rate for the various techniques are due to response times of the mechanisms employed. The impedance of the delivery system versus the impedance of the patient will determine the frequency range for which an individual technique may be effective.

High-frequency oscillators typically operate at the highest frequencies (10 to 40 Hz); high-frequency jets and flow interrupters typically operate at somewhat

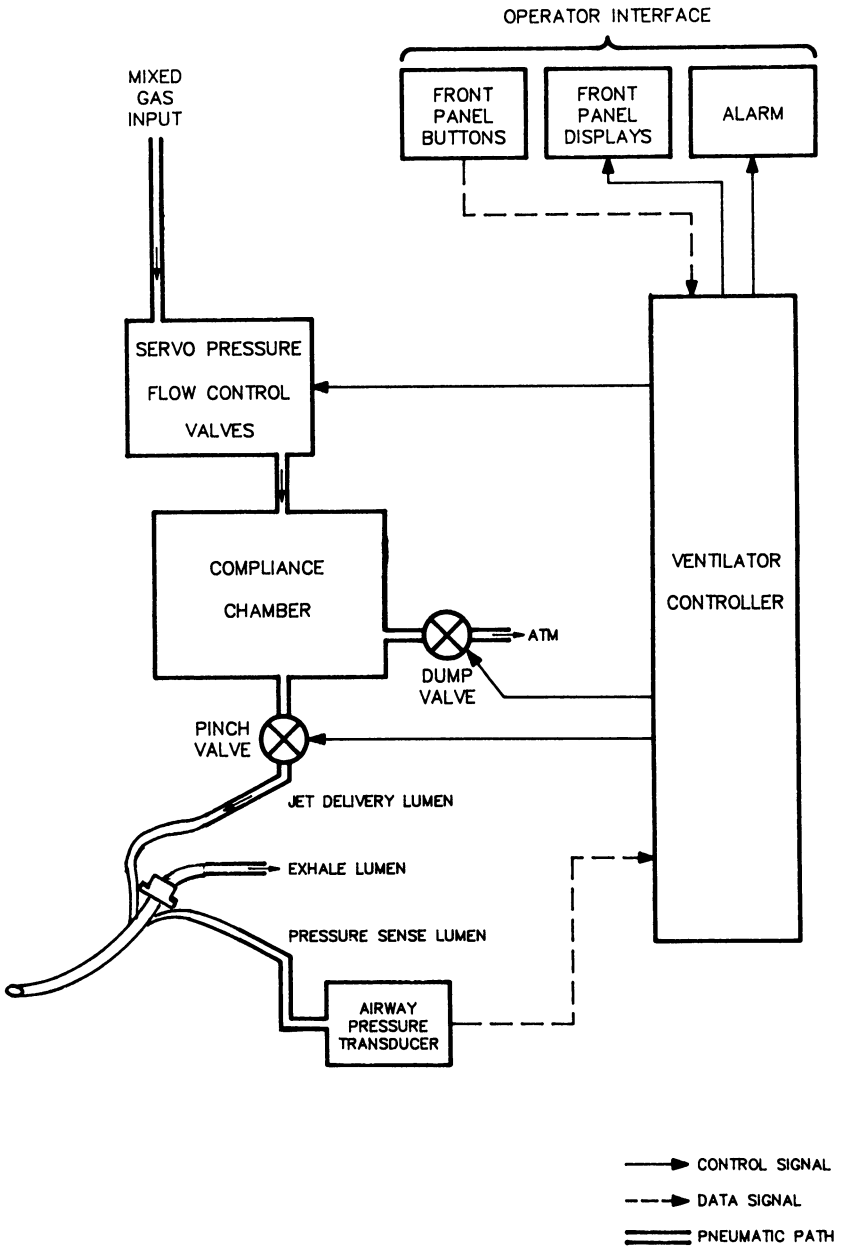

OPERATOR INTERFACE
FRONT PANEL BUTTONS
FRONT PANEL DISPLAYS
ALARM
MIXED GAS INPUT
SERVO PRESSURE FLOW CONTROL VALVES
COMPLIANCE CHAMBER
VENTILATOR CONTROLLER
ATM
DUMP VALVE
PINCH VALVE
JET DELIVERY LUMEN
EXHALE LUMEN
PRESSURE SENSE LUMEN
AIRWAY PRESSURE TRANSDUCER
CONTROL SIGNAL
DATA SIGNAL
PNEUMATIC PATH

FIGURE 12.9C.

slower frequencies (2.5 to 15 Hz), and HFPPVs typically operate at the slowest frequencies (2.5 to 10 Hz). Oscillators typically use either a motor-driven piston or diaphragm to produce gas flow. Jets, flow interrupters, and positive-pressure ventilators typically use solenoid valves. The hybrid Infant Star HFOV uses electronic valves, and the hybrid Bird Space Technology VDR uses a pneumatic oscillator valve.

Differences

The principal differences between the various high-frequency techniques and apparati follow:

1. How fresh gas is delivered to the patient
2. How expired gas is collected from the patient
3. How tidal volume is controlled
4. How high-frequency ventilation is monitored

Table 12.1 illustrates how five currently available types of high-frequency ventilators differ in these four areas. It also illustrates differences in pressure waveforms and typically used ventilator rates.

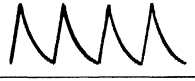
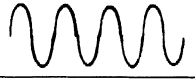
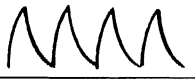
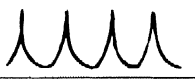
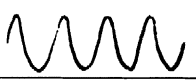
Fresh gas is delivered during high frequency oscillation indirectly. Fresh gas is fed at a steady flow rate into a long, large diameter tube (1 m long, 5 cm in diameter). Oscillatory inspirations are directed into the patient from this tube as a consequence of frequency dependent differences in impedance between the patient and the expiratory limb of the breathing circuit tubing set. Expired gas leaves the large tube through tubing that preferentially allows gas to escape at low frequencies. Thus, gas moving at high frequencies flows preferentially in and out of the patient's tracheal tube from the large tube, and gas flowing steadily or at normal breathing frequencies is preferentially directed in and out of the fresh gas inlet and expired gas outlet tubing, respectively.

Exhalation of gas during high-frequency ventilation is passive with every technique except HFO. Exhalation is "assisted" during HFOV. There is considerable question as to whether the active pulling of gas from the lungs during HFOV is helpful or detrimental. One worries that any attempt to assist exhalation would result in the development of choke points in the airways and gas trapping.[26] The fact that higher mean airway pressures are typically used during HFO compared to those used with conventional and HFJV may be the consequence of this phenomenon.[14,27,28] A higher PEEP may be necessary to keep the airways open during active exhalation.

High-frequency jet ventilators deliver fresh gas directly into the tracheal tube. If the Mallinckrodt Hi-Lo JET® tracheal tube (Fig. 12.10) is used, the fresh gas is delivered about 7 cm from the distal tip of the tube. Other injector devices allow the gas to be delivered at the proximal connector.

All other high-frequency ventilators deliver the fresh gas into the inhalation limb of the ventilator circuit. The Emerson spinning ball valve HFFI raises the pressure in the circuit so quickly that gas flow is pushed into the tracheal tube

TABLE 12.1. Principal differences between five high-frequency ventilators.

Factor	HFJV Life Pulse (Bunnell)	HFO HF-3100 (Sensormedics)	HFFI (Emerson)	Hybrid VDR (Bird Space Technology)	Hybrid Infant Star (Infrasonics)
Fresh gas	Injected directly into Hi-Lo JET tracheal tube	Flows steadily into large tube where oscillations are produced Tracheal tube is attached to large tube	Pulsatile flow into breathing circuit tubing	Injected just upstream of patient's tracheal tube	Pulsatile flow upstream of breathing circuit tubing and humidifier
Expired gas	Passive exhalation into conventional breathing circuit	Active withdrawal out expiratory limb of special tubing circuit	Passive exhalation into "low-pass filter" tubing	Passive exhalation into conventional breathing circuit	Active withdrawal into conventional breathing circuit
Control of tidal volume	Servo control of peak inspiratory pressure Conventional ventilator control of PEEP	"% Power" control of piston stroke	Manual control of upstream driving pressure	Manual control of upstream driving pressure	Manual control of pressure amplitude at proximal end of tracheal tube
Pressure monitoring	Intratracheal pressures monitored and digitally displayed	Proximal monitoring and display of peak, mean, and delta pressures	Must be independently monitored	Must be independently monitored	Proximal tracheal tube pressures monitored and displayed digitally
Typical rate used	420 bpm (7 Hz)	900 bpm (15 Hz)	600 bpm (10 Hz)	600 bpm (10 Hz)	1200 bpm (20 Hz)
Pressure waveform					

bpm, breaths per minute; HFFI, high-frequency flow interrupter; HFJV, high-frequency jet ventilation; HFO, high-frequency oscillator; PEEP, positive end-expiratory pressure; VDR, Volumetric Diffuse Respirator.

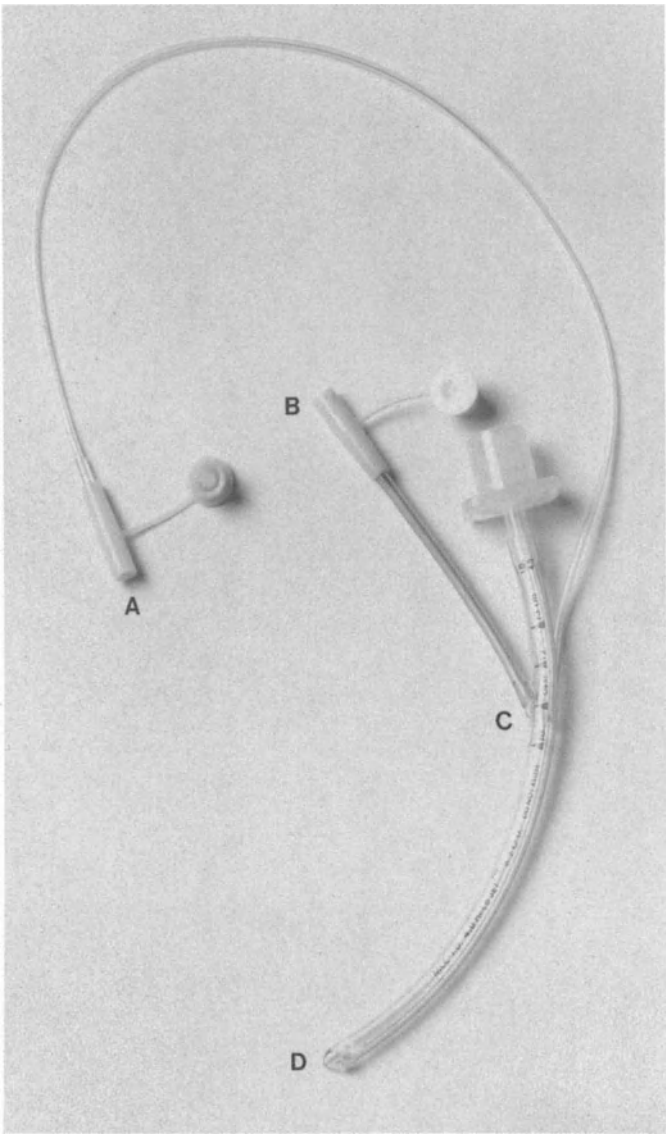


FIGURE 12.10. Hi-Lo JET® tracheal tube. This three-lumen tube is used with high-frequency jet ventilators. The main lumen is used to supply gas for conventional ventilator breaths, spontaneous breathing, and exhalation of all gas. The shorter side tube (B) is used to deliver the high-frequency jet breaths into the main lumen at C. The longer side tube (A) is used to monitor pressure pulses at the distal tip of the tube (D) at frequencies up to at least 24 Hz. (Courtesy of Mallinckrodt Anesthesia Products, St. Louis.)

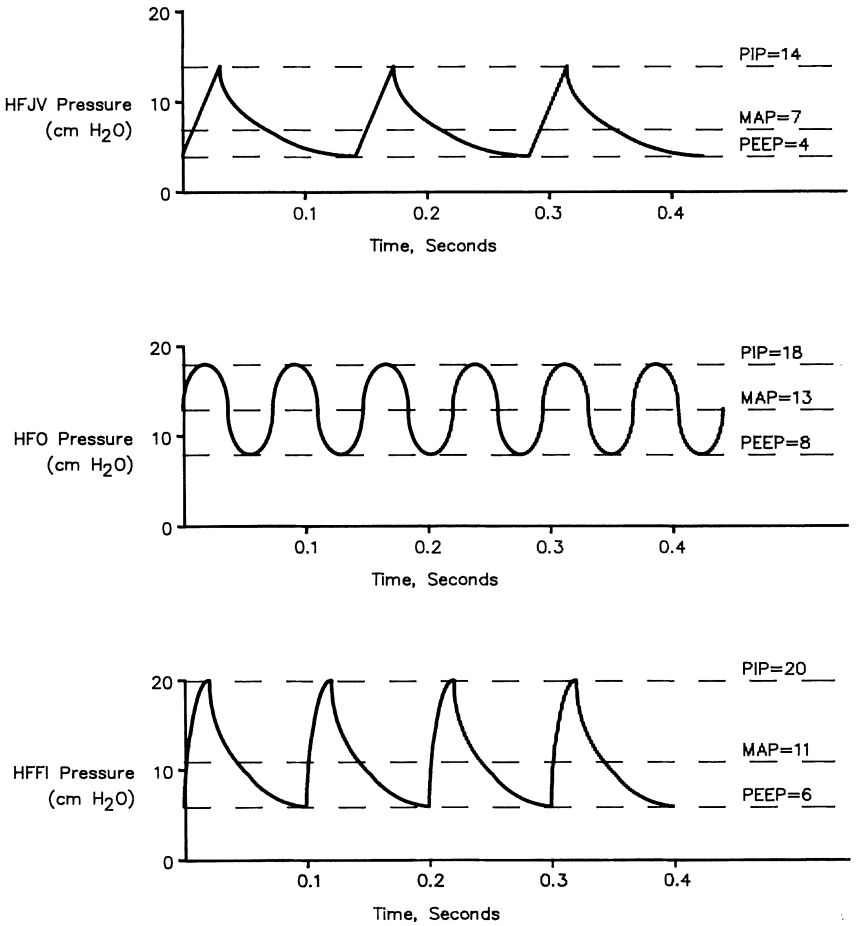


FIGURE 12.11. Idealized pressure waveforms for high-frequency oscillation (HFO), high-frequency jet ventilation (HFJV), and high-frequency flow interruption (HFFI). (MAP, mean airway pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.)

even though the exhalation limb of the circuit is open to the atmosphere (Fig. 12.7). The Infant Star® and VDR® ventilators work in similar fashions with exhalation valve-equipped circuits.

The idealized pressure waveforms developed by conventional ventilators and the various types of high-frequency ventilators are also shown in Figure 12.11. The key differences to note here are the differences in pressure amplitude (the differences between peak inspiratory pressure [PIP] and PEEP or the peaks and the valleys), PEEP, and rate.

The proponents of HFO believed that the minimal amplitudes used with that technique would lead to a reduction in the incidence of bronchopulmonary dysplasia and barotrauma in premature babies. However, a National Institutes of Health-sponsored controlled study found no diminution of bronchopulmonary dysplasia and an increase in intraventricular hemorrhage and pulmonary air leaks.[29] The increased PEEP and mean airway pressure used with HFOV may be the key to that finding.

High-frequency jet ventilation uses a lower mean airway pressure than either conventional or HFOV.[24,30] The PEEP used with HFJV is essentially the same as that used with conventional ventilation, whereas the PEEP used with HFO may be considerably higher.[14,27,29]

The Infant Star® is purported to behave the same as any HFO.[48] The VDR® is purported to behave like an HFFI.[27] The Emerson HFFI has been reported to use lower peak pressures but mean airway pressures comparable to conventional ventilation.[18] The VDR® has been reported to use higher peak and mean airway pressures.[31]

The Importance of Pressure Monitoring

Monitoring pressure during high-frequency ventilation is no easy matter. Monitoring instrumentation must have frequency response capabilities of at least several times the operating frequency of the ventilator in order to ensure proper accuracy.[32] Monitoring at the tubing connector at the proximal end of the tracheal tube can be very misleading. Monitoring distally at the tip of the tracheal tube requires a system for dealing with accumulations of water and mucus. Unfortunately, few of the high-frequency ventilators now in use have adequate pressure-monitoring capabilities. Only the Life Pulse high-frequency ventilator has the capability of accurately monitoring the distal peak, PEEP, and mean airway pressure of the pulses it generates.

The use of a multilumen tracheal tube such as the Hi-Lo JET® for monitoring at the tip of tube is extremely helpful. The differences in pressures monitored at the proximal connector versus the tip are very well demonstrated by the pressure waveform generated by the Infant Star® HFOV (Fig. 12.12).

During some types of high-frequency ventilation, however, even pressure monitoring in or near the trachea can be very misleading. Numerous investigators have discovered that higher mean pressures can be generated in the alveoli during HFO than are measured at the airway as a result of gas trapping.[33-35] In this situation, the lungs can become progressively overinflated as airway pressure is dropped.

High-frequency jet ventilators do not report misleadingly low airway pressure even if gas trapping is occurring, because exhalation is passive. Perez Fontan and associates showed that mean airway pressure overestimates mean alveolar pressure during HFJV.[36] Thus, the pressure in the alveoli only exceeds the pressure in the airway by a modest amount as the alveoli empty during exhalation.

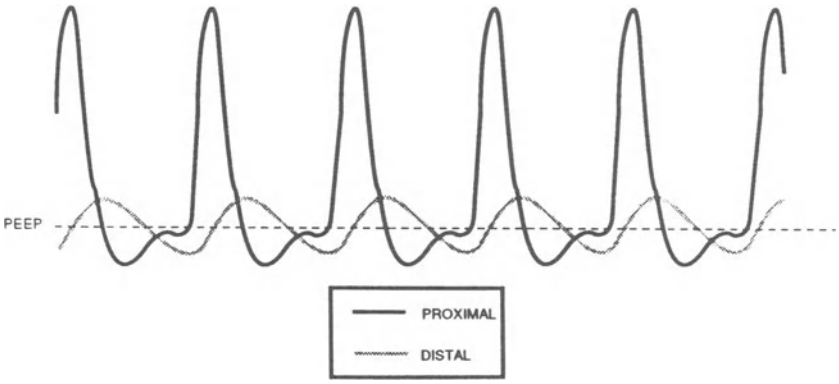


FIGURE 12.12. Difference in pressure waveform from the Infant Star high-frequency oscillatory ventilator measured proximally versus distally. (*Source*: Used with permission of Infrasonics, Inc, San Diego, Calif.) (PEEP, positive end-expiratory pressure.)

Alarms and Safety Features

It is somewhat ironic that a high-frequency ventilator, the Life Pulse,® is the only ventilator of any type certified by the FDA as "safe." (See "Safety" discussion below.) The classification system used by the FDA almost guarantees that this irony will continue because no conventional ventilator must undergo the rigors of a Class III examination.

High-frequency ventilators must have safety features superior to those used with conventional ventilators because the former can generate much faster gas flow rates much quicker. The potential for lung overdistension and inadequate humidification is much higher during high-frequency ventilation. The requirements for FDA approval ensure that these risks are properly managed by any high-frequency ventilator that gains this distinction. The Life Pulse high-frequency ventilator met the safety requirements of the FDA by demonstrating adequate control and humidification of its delivered gas using microprocessor feedback-control mechanisms.

Humidification Systems

One of the advantages of HFO is that adequate humidification is relatively easy to incorporate into the system, and any of a number of readily available systems may be used. High-frequency jet, positive pressure, and hybrid ventilators require humidification systems that will either handle high pressures or will produce humidity without adding significant mechanical dead space to the system. At least one high-frequency ventilator, the Infant Star® HFOV, suffers from changes in delivered tidal volume as a function of the water level in its humidifier.

Chatburn and co-workers[37] designed a humidification system for HFJV that accommodates both high pressure and offers very low mechanical dead space. The Life Pulse Humidifier® is quite similar in design; it is also feedback controlled for maintenance of appropriate temperature, humidity, water level, and prevention of excessive condensation.

FDA Approval of High-Frequency Ventilators

Unlike conventional ventilators, high-frequency ventilators must be *proven* to be safe and effective before they may be marketed in the United States. Products that must be proven safe and effective are labeled Class III devices by the FDA. Class III devices include products described as follows:

1. Devices for which performance standards cannot be written at the present time that would virtually guarantee safety and effectiveness
2. Devices that support or sustain human life

While Class III devices must be proven to be safe and effective before they are allowed to be marketed, Class I and II products are not. Conventional ventilators are considered to be Class II devices because they have been around long enough so that performance standards *could* be written to reasonably ensure that they are safe and effective for their intended use. No such performance standards have yet been written, but the *possibility* of having performance standards for conventional ventilators is readily conceivable. So conventional ventilators are exempt from needing proof that they are safe and effective.

Performance standards for high-frequency ventilators would be impossible to write at this time. So much is unknown about all of the possible indications, contraindications, mechanisms of action, and the like that it will be many years before these devices could be reclassified as Class II.

Class III devices undergo a Pre-Market Approval (PMA) process conducted by the FDA, which includes the following:

1. A "filing review" for administrative and limited scientific completeness of laboratory, animal, and human studies
2. An "in-depth review" for scientific content and compliance with FDA regulations pertaining to the conduct of the studies and readiness of the organization for manufacturing
3. A "panel review" by an advisory panel of appropriate medical and other professional nongovernmental workers
4. Final deliberations, documentation, and notification of the FDA approval decision

The PMA process usually takes several years to complete. One high-frequency ventilator, the Bunnell Life Pulse, successfully completed this process and received FDA approval in 1988. A brief description of the data used to support

the safety and effectiveness of the Life Pulse® for gaining FDA approval is presented in the following section.

Safety

The issues concerning the safety of the Life Pulse high-frequency ventilator included the ventilator's design and safety record and a careful analysis of the adverse effects that occurred during the clinical trials. Exhaustive tests and two types of failure analysis satisfied the FDA that the design was adequate. Four years of clinical trials with hundreds of babies provided data to support claims of reliability and the absence of any increased incidence of adverse side effects.

The adverse effects noted during the treatment of 200 infants diagnosed with severe respiratory distress syndrome complicated by pulmonary air leaks were not uncommon in this patient population. There was a relatively high incidence (71%) of necrotizing tracheal bronchitis (NTB) diagnosed microscopically at autopsy in the first 28 nonsurviving infants. Subsequent nonsurvivors who were treated with an improved humidifier experienced a much lower incidence rate (14 out of 34, or 41%). This incidence is comparable to rates quoted in the literature for similar patients.[38-40] NTB was never diagnosed in surviving infants, several of whom were examined via bronchoscope as a precaution.

Additional animal experiments[41,42] and consideration of the condition of the patients when high-frequency ventilation was initiated have confirmed that the risks of encountering this adverse side effect are outweighed by apparent benefits.[43] One investigator concluded that "NTB appears to be a rediscovered condition related to endotracheal intubation and mechanical ventilation using high mean airway pressures."[44]

The incidence rates of other adverse side effects were either less than or equal to the rates of those complications on conventional ventilation in those same patients before initiation of high-frequency ventilation. The incidence rates of pulmonary interstitial emphysema, pneumothorax, and bronchopleural fistula either appearing for the first time or worsening while on high-frequency ventilation were significantly less than those incidence rates on conventional ventilation.[49]

Follow-up studies were conducted on 87 of 106 survivors. Six short-term (6-month) survivors, all of whom had been on high-frequency ventilation for more than 6 weeks, exhibited no significant airway abnormalities or other evidence of unusual pathology. No unanticipated long-term adverse effects or unusual severity of anticipated adverse effects were noted in the other 81 infants.[49]

Effectiveness

Blood gas and airway pressure data collected from the first 92 infants studied before and after initiation of high-frequency ventilation were analyzed statistically. Significant improvements in ventilation, oxygenation, and arterial pH on

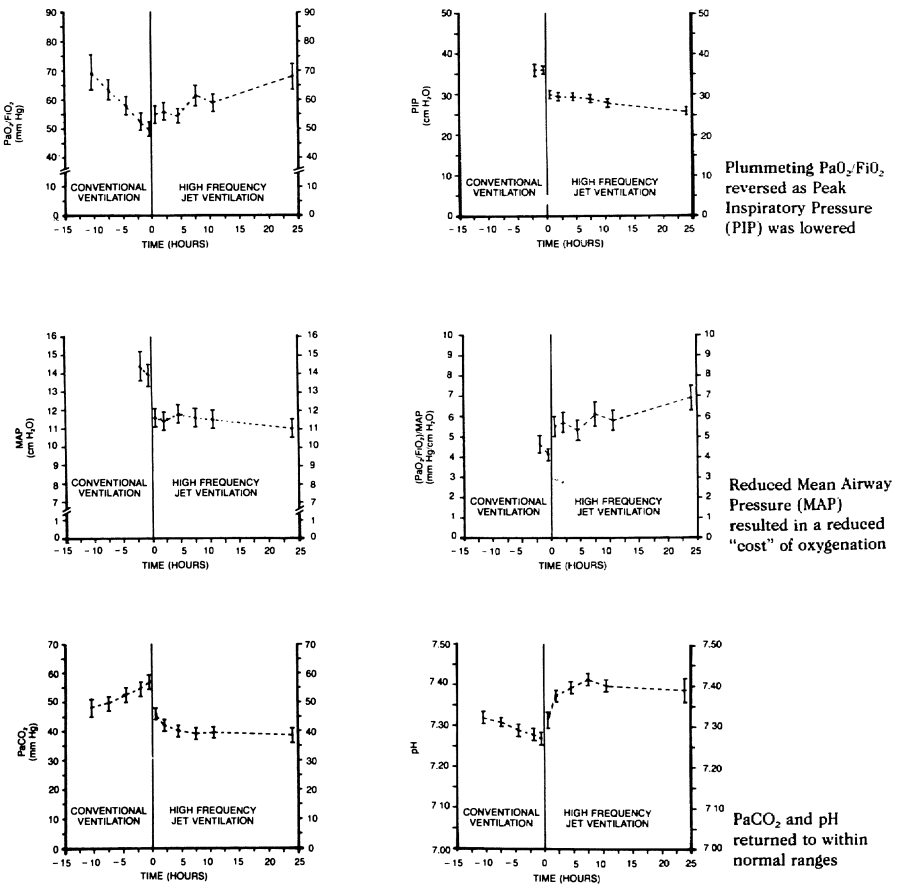


FIGURE 12.13. Arterial blood gas and airway pressure data. Data from 92 infants diagnosed with severe respiratory distress syndrome complicated by pulmonary air leaks who were, in the opinion of their attending physicians, failing on conventional ventilation. Graphs show 12 hours of data collected just before initiation of high-frequency jet ventilation and 24 hours of data immediately thereafter. (FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen, arterial.)

high-frequency ventilation were realized even though statistically lower peak and mean airway pressures were used (Fig. 12.13). Airway pressure data were collected using the Life Pulse in all cases for both conventional and high-frequency ventilation.[49]

Trends in the arterial blood gases 12 hours before initiation of high-frequency ventilation and for the 48-hour period after initiation of high-frequency ventilation were plotted and analyzed (Table 12.2). Comparisons of before and after data and trends revealed statistically positive or neutral results in every case, as shown in Table 12.3.[49]

TABLE 12.2. Absolute values of blood gases and airway pressures statistically improved on high-frequency ventilation.

$Paco_2$	Decreased by 15 mm Hg within 1 h
Pao_2/Fio_2	Increased by 12 mm Hg within 9 h
pH	Increased by 0.11 within 1 hr
MAP	Decreased by 2.5 cm H_2O within 1 h
(Pao_2/Fio_2)/MAP	Increased by 1.6 mm Hg/cm H_2O within 1 h
PIP	Decreased by 6 cm H_2O within 1 h
PEEP	Increased by 0.8 cm H_2O within 1 h

Fio_2, fraction of inspired oxygen; MAP, mean airway pressure; $Paco_2$, partial pressure of carbon dioxide, arterial; Pao_2, partial pressure of oxygen, arterial; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.

Arterial blood pressure and heart rate data from 57 patients and two hospitals were analyzed. Wilcoxon tests were conducted to test for changes in systolic and diastolic blood pressures and heart rate before and after switching to high-frequency ventilation. There were no statistically significant changes in any of these variables.

Leakage through chest drainage tubes was less during high-frequency ventilation than during conventional ventilation in all five of the infants with pneumothorax studied. These reductions were in direct relationship to the significantly lower mean tracheal airway pressures used.[45]

Conclusions

Theories predict many beneficial applications of high-frequency ventilation with few risks of increased adverse side effects if equipment is properly designed and manufactured. These benefits are most easily realized in patients for whom

TABLE 12.3. Time trends of blood gases and airway pressures statistically improved on high-frequency ventilation.

	12-hour trends on conventional ventilation	48-hour trends on high-frequency ventilation
$Paco_2$	Increased with time	Decreased to normal by 3 h
pH	Decreased with time	Increased to normal by 3 h
Pao_2/Fio_2	Decreased with time	Stabilized
MAP	Insufficient data*	Stabilized
(Pao_2/Fio_2)/MAP	Insufficient data*	Increased within 1 h
PIP	Insufficient data*	Decreased slowly
PEEP	Insufficient data*	Stabilized

*Pressure data were not collected with the Life Pulse high-frequency ventilator for more than 3 hours before initiation of high-frequency ventilation required by the critical condition of the patients.
Fio_2, fraction of inspired oxygen; MAP, mean airway pressure; $Paco_2$, partial pressure of carbon dioxide, arterial; Pao_2, partial pressure of oxygen, arterial; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.

conventional techniques are inherently limited: patients with low lung compliance or leaks in the major airways (e.g., bronchopleural fistulae) or patients suffering from conditions that are aggravated by higher mean airway pressures (e.g., pulmonary interstitial emphysema and other air leaks, cardiac insufficiency, persistent pulmonary hypertension, and intracranial hemorrhage).

Most of the risks associated with high-frequency ventilation are proportional to applied airway pressure. However, the propensities for gas trapping resulting from decreased times for exhalation and for providing inadequate humidification are certainly increased with this mode of assisted ventilation. More vague factors related to implementation of new technology also cannot be overlooked.

The benefits of HFJV have already been shown to outweigh risks in some applications with several more currently under examination. The risks of HFO have been shown to outweigh benefits in one controlled study with premature infants. Other applications using different equipment are now being examined with other studies.

One high-frequency ventilator has been awarded Class III FDA approval after 16 years of research including 6 years of clinical trials. At least two other companies are currently pursuing FDA approval for other types of high-frequency ventilators. The Sixth Annual Conference on High-Frequency Ventilation of Infants recently took place in Snowbird, Utah, with an international assemblage of nearly 200 participants. Over 100 hospitals in the United States now use high-frequency jet ventilation in their newborn intensive care units. Who could doubt that this new mode of assisted ventilation is here to stay?

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13
Current Management of Hypoplastic Left Heart Syndrome

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A diminutive, nonfunctional left ventricle with aortic atresia or severe aortic stenosis and hypoplasia of the ascending aorta constitutes the main structural abnormality in hypoplastic left heart syndrome. The syndrome often presents early with catastrophic hemodynamic decompensation. It is the most common cause of cardiac death in the first week of life[1] and usually affects newborns who are otherwise normal.[1,2] Hypoplastic left heart syndrome remains a major medical and surgical challenge.

Pathophysiology

Initial survival of patients with hypoplastic left heart syndrome depends on the presence of foramen ovale or atrial septal defect and patency of the ductus arteriosus (Fig. 13.1). This allows mixing of systemic and pulmonary venous blood at the atrial level and retrograde perfusion of the systemic circulation through the ductus arteriosus. The right ventricle is the only functioning ventricle supplying blood to the pulmonary arteries and to the aorta. The hypoplastic ascending aorta carries coronary blood flow in a retrograde fashion. Because of pulmonary vasoconstriction in the early postnatal period, increased pulmonary blood flow is not an immediate problem. As pulmonary vascular resistance falls, however, symptoms of pulmonary vascular congestion will appear. A restrictive interatrial communication will accentuate the problem. The presence of mitral atresia or severe mitral stenosis and juxtaductal coarctation usually does not affect early hemodynamic changes.[3,4]

Clinical Manifestations and Diagnosis

Most infants will present in the first week of life with tachypnea and mild cyanosis. Two thirds of the patients will present with low cardiac output evidenced by hypotension, decreased peripheral pulses, oliguria, and varying degrees of

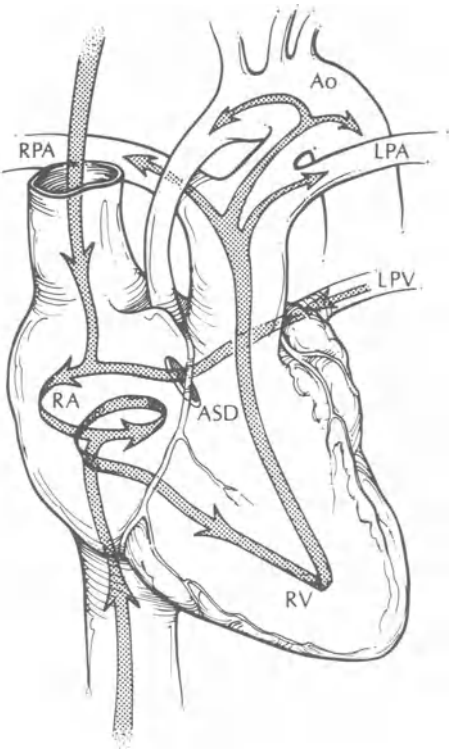


FIGURE 13.1. Systemic and pulmonary blood flows in hypoplastic left heart syndrome. (Ao, aorta; ASD, atrial septal defect; LPA, left pulmonary artery; LPV, left pulmonary vein; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.)

metabolic acidosis.[5,6] Chest roentgenograms usually show cardiomegaly and increased pulmonary blood flow (Fig. 13.2).

Two-dimensional echocardiography is now the main diagnostic tool[5,7] in hypoplastic left heart syndrome. The atresia or hypoplasia of the aortic valve, ascending aorta, left ventricle, and mitral valve can be readily demonstrated (Fig. 13.3). Right ventricular function and tricuspid insufficiency, adequacy of the interatrial communication, and presence of coarctation can be determined. Cardiac catheterization usually does not add to the information provided by echocardiography and may even be harmful in these critically ill infants.

Medical Management

Treatment should be instituted only if subsequent surgical intervention is to be considered. Two main objectives of medical management are maintenance of patency of the ductus arteriosus with prostaglandin E_1 and preservation of pulmonary vasoconstriction by an ambient O_2 environment of room air. Resuscitative measures, such as airway intubation and respiratory support, administration

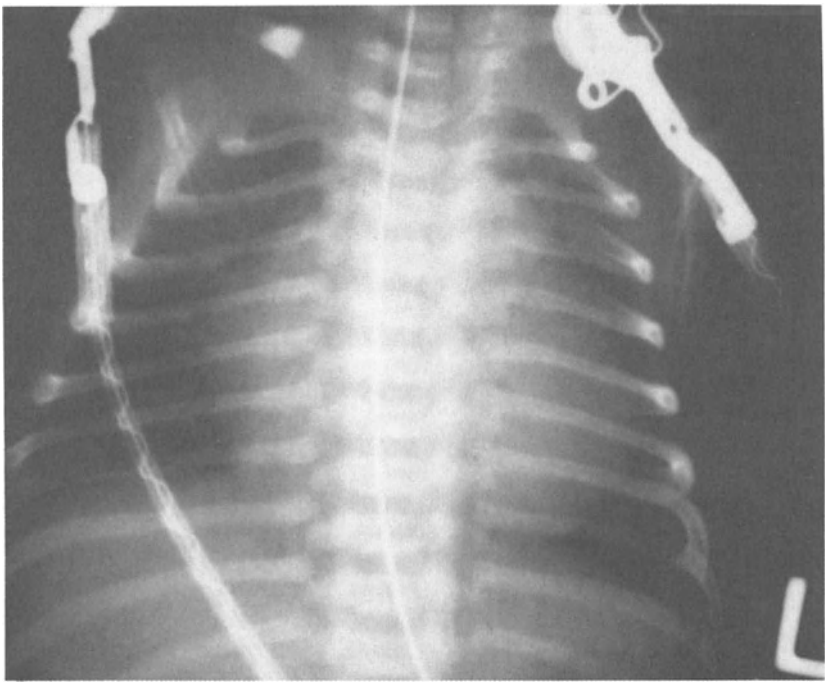


FIGURE 13.2. Chest roentgenogram of a newborn with hypoplastic left heart syndrome showing cardiomegaly and increased pulmonary vascular markings.

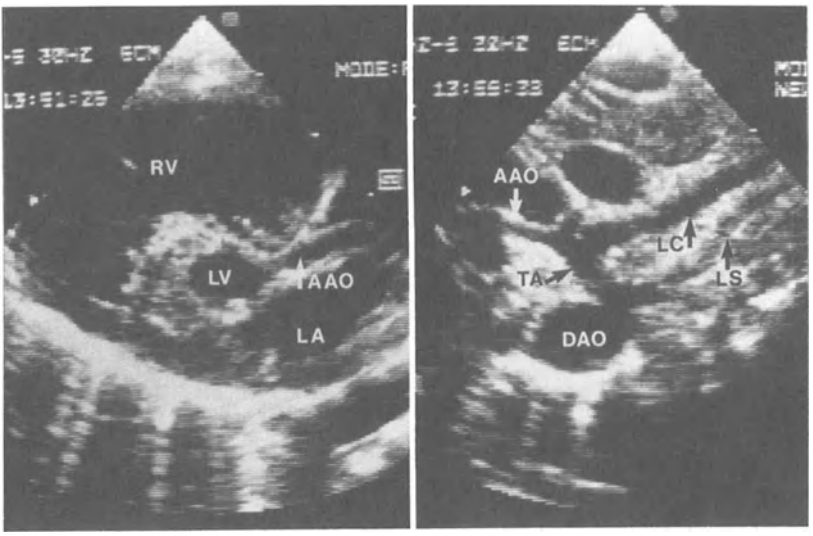


FIGURE 13.3. Two-dimensional echocardiograms showing the hypoplastic left ventricle (LV) and ascending aorta (AAO). The transverse aortic arch (TA), left carotid (LC), and left subclavian (LS) arteries and descending aorta (DAO) are well seen. (LA, left atrium; RV, right ventricle.)

of inotropes (Isuprel [isoproterenol hydrochloride] dopamine, and dobutamine), and correction of metabolic acidosis, are carried out as needed. Ventilatory support should be done with room air rather than oxygen.

Early Surgical Management

The majority of infants will respond to medical management with stabilization of hemodynamics, improvement of right ventricular function, and tricuspid insufficiency allowing surgical intervention. Currently, two initial surgical options available in some centers are first-stage palliation[5,8-10] and orthotopic heart transplantation.[11-13] The choice of procedure varies with the preference of the individual institution. Although the first-stage palliative procedure is more technically demanding than orthotopic heart transplantation, the latter requires a greater commitment of resources.

First-Stage Palliative Procedures

The feasibility of using the main pulmonary artery as an outflow to the aorta is an important concept in the palliation and correction of various complex congenital heart defects. The main pulmonary artery-to-aorta connection has been an integral part in most palliative procedures used for the hypoplastic left heart syndrome.[8,14-17] It has also been successfully used in bypassing various forms of subaortic stenosis in patients with univentricular or single ventricle complexes[18,19] and is part of the Damus-Stansel-Kaye Procedure[20] in the correction of certain forms of transposition of the great arteries.

In addition to establishing a wide open connection between the main pulmonary and the aorta, provisions should also be made to control the pulmonary blood flow and create an unrestricted interatrial communication in the palliation of hypoplastic left heart syndrome. Our current approach involves a midsternotomy, institution of cardiopulmonary bypass through an arterial cannula in the main pulmonary artery with the pulmonary artery branches temporarily occluded, a venous cannula in the right atrial appendage, profound hypothermia of 18 to 20°C rectally, and circulatory arrest. The ductal tissue is completely excised (Fig. 13.4A) with the incision extended to the descending aorta to relieve the coarctation if present.[21] The pulmonary artery is reconstructed with a thin-walled polytetrafluroethylene (PTFE) patch (Fig. 13.4B). Another PTFE patch that eventually will form a tube is used to connect the main pulmonary artery to the aortic arch (Fig. 13.4C). An atrial septectomy is performed and cardiopulmonary bypass reinstituted. While rewarming, a subclavian artery to pulmonary artery shunt is created using a 4-mm PTFE graft.[22] Because of development of pulmonary artery branch stenosis with the subclavian pulmonary artery shunt (Fig. 13.5),[23] we have recently begun using a stented button to separate and control the pulmonary blood flow (Fig. 13.6). This most recent approach appears to minimize distortion of the pulmonary artery branches (Fig. 13.7).

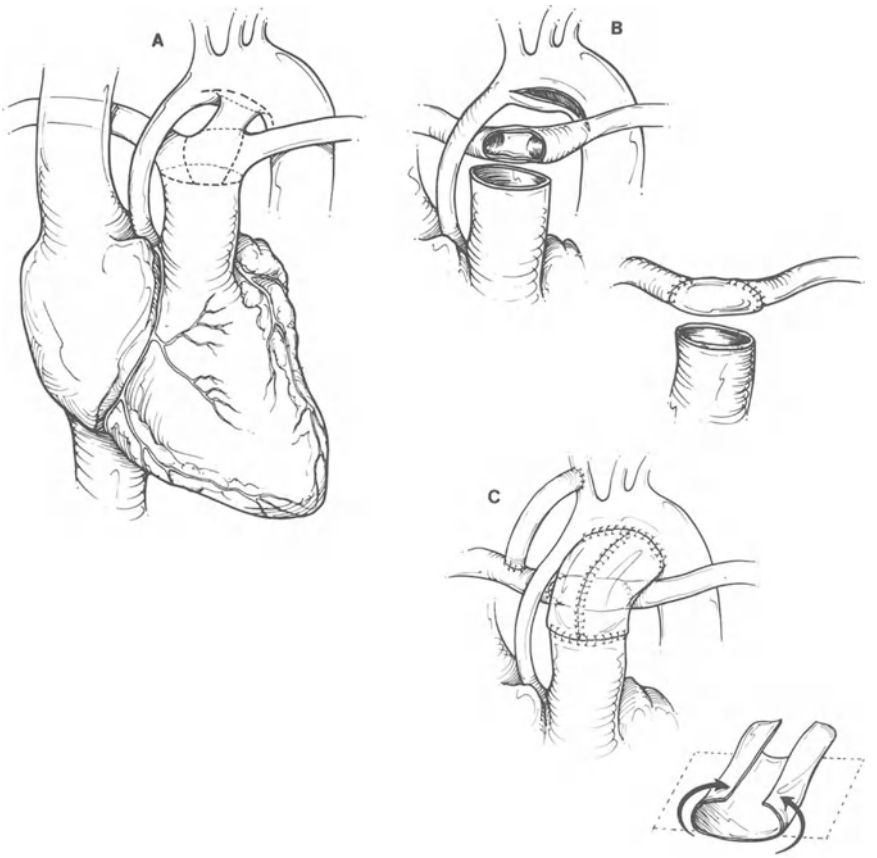


FIGURE 13.4. (A to C) First-stage palliative procedure. (See text for description.)

The largest experience with the first-stage palliative procedure of more than 100 patients have come from Pigott and colleagues[10] from Children's Hospital of Philadelphia and Jonas and colleagues[3] from Boston Children's Hospital. Their early mortality rates have improved from 50% to 30%. We have done 18 patients in the last 3 years with an early mortality rate of 50% (8/16). Only one patient died in the immediate postoperative period, the remaining deaths occurred 1 to 3 weeks later. In all cases, the cause of death could be related to the reconstruction of the distal pulmonary artery and control of pulmonary blood flow. We hope our recent modification using the stented button will provide a more effective way of optimizing pulmonary blood flow while allowing growth of pulmonary artery branches.

Orthotopic Heart Transplantation

Bailey and colleagues[11] (personal communication, 1989) (36 patients), Mavroudis and colleagues[12] (4 patients), and more recently Backer and colleagues[24]

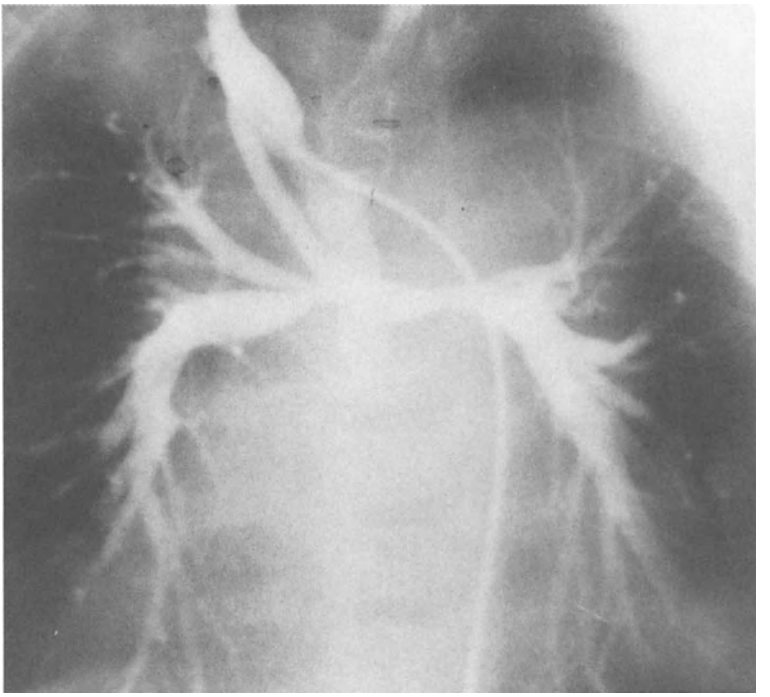


FIGURE 13.5. Innominate artery injection showing the subclavian pulmonary artery shunt. Stenosis of both left and right pulmonary arteris is observed.

(3 patients) have started using heart transplantation for hypoplastic left heart syndrome with early survival rate of 88% (38/43). Although the early result is better than with the first-stage palliative procedure, some patients died while awaiting a suitable donor heart. Additionally, there are serious concerns for repeated rejection and infection, growth retardation, early development of coronary artery obstruction, and malignancy.[25]

Late Surgical Management

The successful application of the Fontan operation (Fig. 13.8) in tricuspid atresia[26] and other forms of univentricular heart complex[27] has made most complex congenital defects amenable for physiologic correction as long as the pulmonary artery size and vascular resistance remain normal. The emphasis on the avoidance of distortion of the distal pulmonary arteries and good control of pulmonary blood flow at the first-stage palliative procedure of the hypoplastic left heart syndrome is designed to make these patients candidates for the Fontan operation. Norwood and colleagues[28] have the most experience with the use of the Fontan operation for the second-stage correction for hypoplastic left heart syndrome (26 patients) with a survival rate of more than 60%.

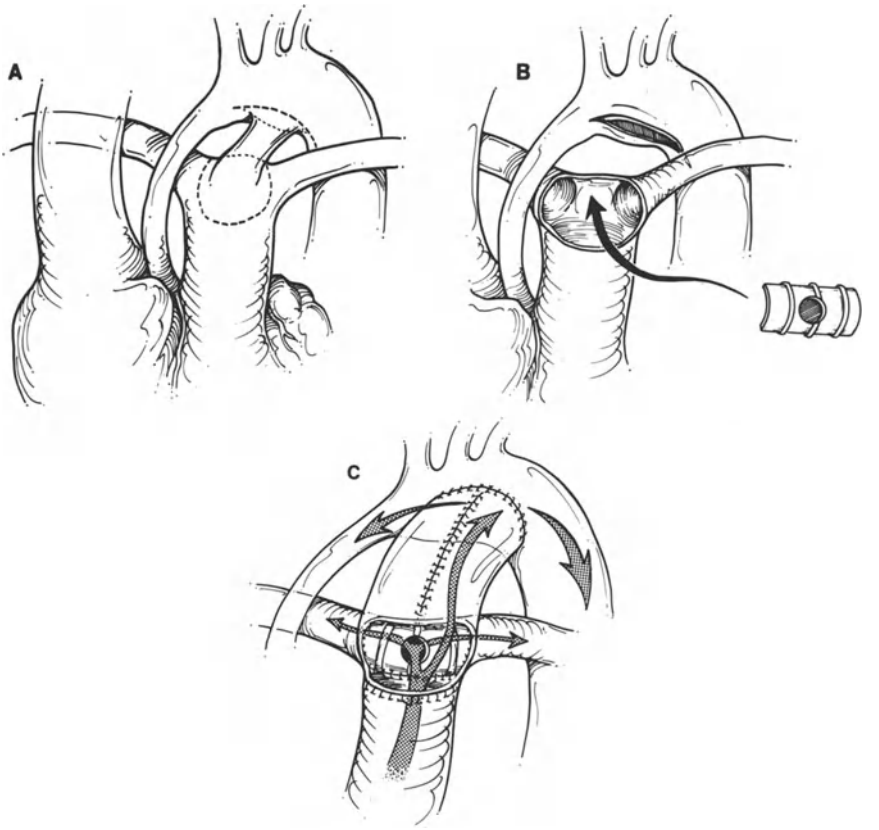


FIGURE 13.6. (A to C) Use of stented button to control pulmonary blood flow. The stent prevents posterior displacement of the button, which might occlude the right and/or left pulmonary artery orifices.

►

FIGURE 13.8. Fontan operation in hypoplastic left heart syndrome. The right atrial (RA) flow is directed to the pulmonary arteries (RPA, LPA) after RA partitioning (arrows). The pulmonary venous blood goes through the atrial septal defect (ASD), tricuspid valve, right ventricle (RV), and aorta (Ao). (LPV, left pulmonary vein.)

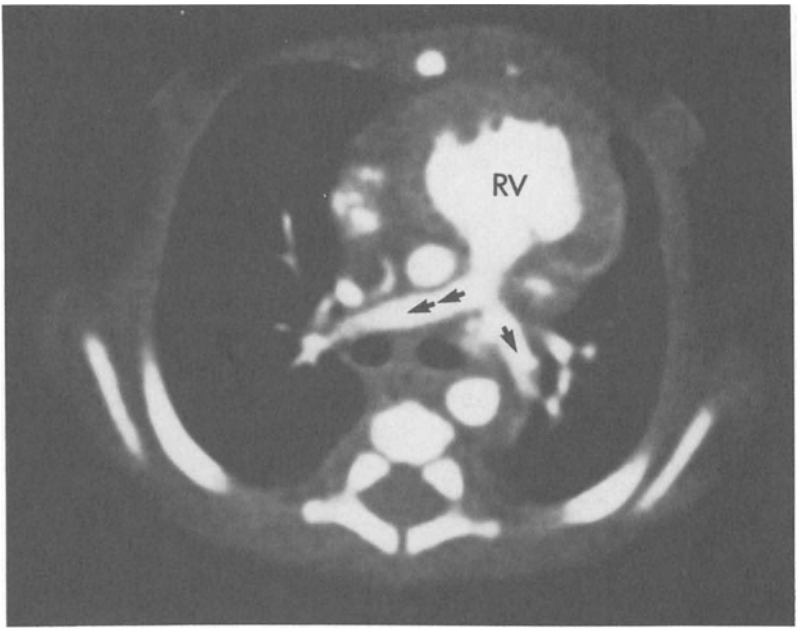
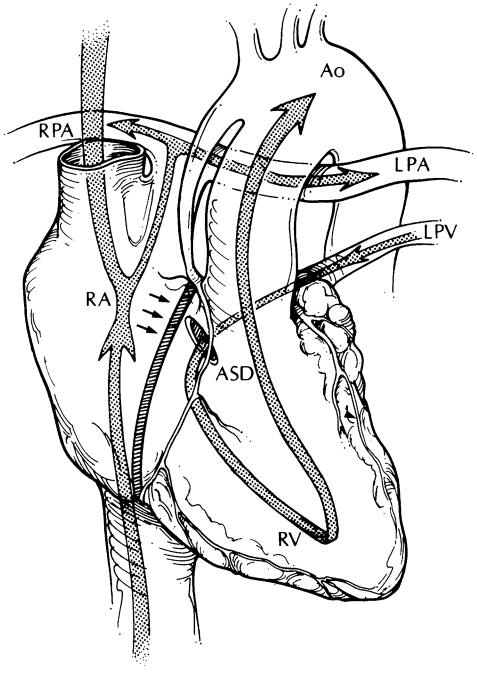


FIGURE 13.7. Ultrafast scan following the stented button technique showing minimal distortion of right (two arrows) and left (one arrow) pulmonary arteries. (RV, right ventricle.)



A dilemma occurs when patients who survived the first-stage palliative procedure may have a dysfunctional right ventricle or pulmonary vascular resistance not suitable for the Fontan operation. Orthotopic heart transplantation may be considered in this group of patients and also in patients undergoing the Fontan operation who subsequently might develop right ventricular failure.

Prognosis

Better understanding of the physiology of the infants, advances in surgical techniques, and application of the Fontan operation have improved the outlook for infants with hypoplastic left heart syndrome. The use of orthotopic heart transplantation has also provided a viable alternative in the early and late surgical management of these patients. The ideal management is not known at this time. We surmise, however, that the sequence of the first-stage palliative procedure followed by the Fontan operation and subsequent heart transplantation in a then-grown child for expected right ventricular failure may prove to be the best approach.

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14
Pain Management in Neonatal Intensive Care

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Recent advances in the area of neonatology have afforded dramatic increases in survival rates of neonates following premature birth and catastrophic illness. Many infants surviving today through use of advanced technology and improved surgical procedures would not have lived 20 years ago. Growth and development of neonatal intensive care units and unprecedented advances in technology have become an integral part of the care we deliver. Rarely has a month gone by over the last 10 years when at least one change in therapeutic interventions did not alter what previously had been considered "state-of-the-art" care. Sophisticated methods for physiologic and biochemical monitoring have necessitated an increase in invasive procedures. Our preoccupation with improved mortality and morbidity may have slanted our focus away from the impact of relentlessly intrusive environment and painful procedures on these fragile infants. Historically, critically ill infants have been exposed to numerous painful medical and surgical procedures without aid of analgesia or anesthesia.

Health-care professionals and health-care consumers are increasingly concerned with potential short- and long-term effects of acute and chronic pain on infant survivors. Painful procedures inflicted on infants without analgesia or anesthesia have sparked controversy with both the news media[1-4] and health-care professionals.[5-8] Until recently, however, medical and nursing literature on the child's experience of pain has been sparse. Specific information on the infant's experience of pain, particularly that of premature infants, also has been meager. Eland and Anderson's[9] search of medical literature from January 1970, to August 1975, produced 1380 articles on pain. Only 33 of these addressed pediatric pain and contained little or no data on behaviors, assessment, or methods of intervention. A nursing literature search was even more bleak, with only one article concerning children's reaction to pain. More recently, Anand et al.[10] presented an excellent review of 201 articles related to the biologic aspects of pain and its effect in the human neonate and fetus. However, as a result of the wide variety of scientific journals in which these articles were published, neonatologists and neonatal nurses would have had to have made a concerted effort to explore this topic. Systematic research in this area is needed.

The Physiology of Pain in the Neonate

In the adult, pain impulses may be traced from both afferent myelinated and unmyelinated fibers to sensory areas in the cerebral cortex. Myelinated A-δ fibers transmit impulses more rapidly than unmyelinated C-polymodal fibers. Sensory fibers transmit pain stimuli to the dorsal horns of the spinal cord where a synapse occurs. The axons of the activated neurons cross to the opposite side of the spinal cord and travel to the thalamus via the spinothalamic tract and finally reach the cortex.[11]

Myelination

In the past, a common rationale for withholding anesthetic or analgesic agents from neonates was the misconception that nerve pathways were not sufficiently myelinated to transmit painful stimuli. Newer studies indicate that cutaneous sensory receptors begin to appear as early as 7 weeks' gestation in the perioral area, spreading to the rest of the face, palms of the hands, and soles of the feet by the eleventh week of gestation. By 20 weeks' gestation, the process is completed, and the fetus has obtained the density of nerve endings similar to those of adults.[10] Progressive nerve myelination occurs during this same period with the myelin sheath, reaching its final thickness during postnatal development. The slower nerve conduction velocities in the fetus and newborn is offset by shorter interneuron and neuromuscular distances traveled by the impulse.[10] Schulte[12] hypothesized that an increasing nerve fiber myelination with age allows nerve conduction velocities to increase concurrently with increasing internodal distances resulting from body growth.

Cortical Maturation

Development of cells in the dorsal horn synaptic interconnections and specific neurotransmitter vesicles appear completed by 30 weeks of gestation.[10] Thus, development of neural pathways for painful stimuli transmission appears to be established early in fetal development.

Thalamocortical connection is also an important factor in perception of pain. For example, if the infant receives a pinprick on the left index finger and only the thalamus is functional, the infant would be able to determine only that the pain originated somewhere on the hand. If the primary sensory cortex is functional, the infant can localize the pain to the precise area on the index finger. Afferent neurons in the thalamus produce axons that arrive in the cerebrum before 20 weeks' gestation. Dendritic arborization of cortical neurons and migration toward the thalamus with synaptic connections is established between 20 and 24 weeks' gestation.[10,12]

Fetal and neonatal electroencephalographic (EEG) patterns as early as 20 weeks' gestation suggest some functional maturity of the cerebral cortex, demon-

strating wakefulness and sleep patterns. Visual- and auditory-evoked potentials can be elicited by 30 weeks' gestation.[13,14] Pain pathways and cortical and subcortical centers required for pain perception do appear to be present and active during fetal development.

Endogenous Analgesic Mechanisms

The discovery of the existence of two separate stereospecific opiate receptors and their endogenous ligands or binding molecules provided an entirely new dimension for pain research. Enkephalins, composed of a 5-amino acid chain, are located in synapses between nerve fibers throughout the central and peripheral nervous systems. They appear to serve as central nervous system neurotransmitters by binding specific receptors and inhibiting release of substance P with nociceptive stimulation. Their duration of action is short, however, as they undergo rapid enzymatic degradation by aminopeptidase and carboxypeptidase.[15] Endorphins, or morphinelike substances, tend to mimic the peripheral and central effects of morphine and other opiate drugs. The strong action of endorphins is widespread and affects mood, endocrine function, respiration, and gastrointestinal motility in addition to pain. These abundant neuroactive peptides have been located in the cognitive areas of the brain as well as in the hypothalamus, amygdala, the periaqueductal gray, nucleus raphe magnus, and the substantia gelatinosa in the dorsal horns of the spinal cord. The location of opiate receptors in brain areas associated with emotions has supported the hypothesis that opiates relieve pain by combining with specific brain receptors to block pain messages and produce analgesia rather than prevent pain.[11,15] β-Endorphin is a 31-amino acid chain peptide and is thought to initiate activity in the descending inhibitory system. It is more resistant to enzymatic degradation with a half-life of at least 2 to 3 hours. Its action has been shown to be 48 times stronger than that of morphine.[15] Thus, both enkephalin and endorphin systems may modulate pain transmission at spinal and supraspinal levels.[11]

Stress and pain both stimulate the endorphin system. Endogenous opiates are released at birth and in response to both fetal and neonatal stress.[16] Infants born vaginally by breech presentation or by vacuum extraction had higher β-endorphin levels than infants born by caesarean section.[10] Negative correlation of plasma β-endorphin concentrations with umbilical-artery pH and partial pressure of oxygen (PO_2) as well as positive correlations with base deficit and partial pressure of carbon dioxide (PCO_2) suggests that birth asphyxia may be a potent stimulus to their release.[10] Although high levels of endorphins have been associated with elevated pain threshold and tolerance levels in adults.[15] It is unlikely that this correlation holds true for neonates faced with stress. The cerebrospinal fluid levels of β-endorphin required to produce analgesia in human adults have been found to be 100,000 times higher than the highest recorded levels in neonates.[10] Further research, however, may produce significant information that will add to our understanding of pain perception and will result in an effective treatment of infant pain.

Hormonal and Metabolic Changes

Evidence is mounting through recent research surgical pain has short-term effects on infants.[17,18] Anand et al.[18] found major hormonal responses (significant changes in plasma adrenaline, noradrenaline, glucagon, aldosterone, corticosterone, 11-deoxycorticosterone, 11-deoxycortisol levels, insulin/glucagon molar ratio, blood glucose, lactate, and pyruvate concentrations) in preterm infants undergoing ligation of a patent ductus arteriosus when nitrous oxide and *d*-tubocurarine were used. With the addition of fentanyl to nitrous oxide and *d*-tubocurarine to the anesthetic regimen, preterm infants had fewer circulatory and metabolic complications postoperatively. They concluded that preterm infants do mount a substantial stress response and suggest that prevention of massive stress responses in preterm infants may be associated with an increased postoperative morbidity and mortality.[10]

Assessment of Pain

The role of the neonatal nurse is to identify and assess the infant's level of pain accurately and determine pain-relief strategies to relieve pain safely and effectively. The International Association for the Study of Pain[19] established a taxonomy that defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Within the context of this definition, pain is a multidimensional, subjective experience, and the person in pain explains the dimensions of the experience. Few clinicians who care for infants daily and witness their flinching or vigorous withdrawal from painful procedures would deny that they do in fact perceive pain. Difficulties arise in attempting to verify and measure the intensity of pain in neonates because of their inability to verbalize painful experiences. The bulk of recent research has focused primarily on attempts to describe various physiologic and behavioral responses to pain.

Lack of a valid and reliable tool to assess or measure pain intensity in the neonate and methods to evaluate the efficiency of pain management has been a frustrating and pressing problem facing health-care professionals and has been a constant hindrance to the study of pain in infants. Adaptations of adult assessment instruments have been used with children but generally require some ability to communicate the painful experience.[20–23] Studies of experimentally induced pain in adults have added to the knowledge base about pain perception[24–26] but have not been conducted on infants because of ethical concerns of subject rights as well as short- and long-term effects of a painful experience. Numerous opportunities exist to study acute pain in premature and seriously ill infants as a result of required medical procedures during hospitalization in the neonatal intensive care unit. These studies are essential, although the data produced may be of limited generalizability to healthy newborns.

Many of these studies were conducted on infants undergoing various surgical procedures, circumcisions, endotracheal intubation, and heel-sticks for blood

sampling. Researchers have examined several variables attributed to the pain response in infants including changes in heart rate, blood pressure, transcutaneous oxygen (t_cO_2) levels, respiratory rate, hormonal, metabolic changes, crying patterns, body movements and palmar sweating.[27-35]

Cardiac Activity

Changes in heart rate may be an important dependent variable in the study of pain response in the infant because it can be easily obtained and is relatively unobtrusive. Changes in heart rate appear to be a sensitive measure of attention and emotion in infants and appear to be bidirectional. Heart rate in infants appears to decelerate consistently in response to mild or moderate levels of non-noxious stimuli, such as eliciting attention or orienting the infant through use of auditory and visual stimuli and appears to accelerate in response to intense or stressful stimuli.[32,36]

Lacey and Lacey[37] have postulated a neurophysiologic feedback system that may explain the bidirectional response of heart rate. Situations that require close attention or orienting result in a slowed heart rate, while situations requiring a reduction of intensity of environmental stimuli such as blocking out painful or noxious stimuli result in an increased heart rate. Noxious stimuli resulting in an increased heart rate cause an increased firing of neurons, leading to the nucleus of the tractus solitarius in the midbrain. The midbrain in turn, has an inhibitory effect on cortical activity. This neurophysiologic interrelationship of attention processes and increased heart rate may assist the infant to psychologically defend himself or herself from strong, noxious stimuli.

Increases in both heart rate and blood pressure in preterm and full-term infants undergoing circumcision, heel lancing, and injections have been reported.[27,30,32,33,38] Johnston and Strada[38] described an initial response following an injection for routine immunization as a long, high-pitched cry followed by a relative period of apnea, a brief bradycardic period, rigidity of the body and limbs, and a facial configuration recognized as an expression of pain. This pattern was followed by a sharp increase in heart rate, lower pitched, but dysponated cries, decreasing rigidity, and a facial expression of pain. The brief bradycardic episode was attributed to possibly an orienting response as described by Lacey and Lacey.[37] Kelly and Finer[39] also reported a significant decrease in heart rate as well as t_cO_2 and a significant increase in mean arterial blood pressure and intracranial pressure (ICP) during nasotracheal intubation. Parasympathetic response to stimulation of the larynx and pharynx or trigeminal region was assumed to be the cause of the rapid onset of bradycardia. This cardiovascular response parallels the response in the newborn lamb with laryngeal chemoreceptor stimulation and to stimulation of trigeminal diving reflex. Thus, the response to nasopharyngeal stimulation with bradycardia may represent a maturational imbalance of parasympathetic over sympathetic tone. The magnitude of the heart rate change may also be related to the intensity and duration of the stimulus. Administration of atropine and pancuronium before intubation was associated

with fewer changes in heart rate (no infant's heart rate fell below 80 beats per minute [bpm]) and a significantly lesser rise in ICP.[39] Full-term infants undergoing circumcision without the benefit of anesthetics demonstrated marked increases in both heart rate and blood pressure during and after the procedure.[27,30,33] Fluctuations in heart rate and blood pressure were prevented with the administration of a local anesthetic.[27,30]

Crying

Crying is the primary form of communication in infants and involves a response higher than a spinal level motor reflex. Its importance as a social behavior has received increased attention in the past decade. Crying is elicited by a variety of stimuli including hunger, anger, and pain. Wolff[40] characterized the pain cry as a high-pitched cry followed by a relatively long period of no breathing, a period of dysphonia, and a gradual return to a rhythmic rising–falling "basic" cry. Wasz-Hockert et al.,[41] however, through an elaborate study found very few of the acoustic attributes of the cry to be predictive of the type of cry. Three types of phonation evolved that reflect an increasing amount of effort-phonated, dysphonated, and hyperphonated cries. Phonated cries do not give the impression of great discomfort and are characterized by harmonic structure and symmetry. Pain cries were of the dysphonated or hyperphonated type. Thus, the amount of discomfort experienced by the infant, despite the reason, causes the difference in type of cry.[41] Additionally, Wasz-Hockert et al.[41] noted that if phonated hunger cries were not responded to for a prolonged period of time, they began to acquire characteristics of dysphonated and hyperphonated cries resulting from increased discomfort.

Wolff[42] also found that numerous infants demonstrated weak replicas of the typical pattern of pain cry, suggesting that either infants were not disposed to cry, the stimuli was relatively weak, or that the infants were "too weak" to cry, as in the case of premature infants. This is supported by the description by Gorski et al.[43] of the cry response of a 33-week's gestation infant to repeated pinpricks as an "evanescent grimace and brief whimper" accompanied with generalized motor activity.

Facial Expression

Facial expressions associated with communication of emotional states has been of great interest to researchers. Izard and Dougherty[44] have used the maximally discriminative facial coding system (MAX) to reliably categorize infant facial configurations associated with various emotional states from both innocuous and painful stimuli. The MAX is a coding system anatomically based on movement units. It was developed as an objective system for identifying the discrete changes in facial appearance necessary for identifying fundamental emotions. It contains 29 movement units or appearance changes in three regions of the face. Judgments are made for each region (brows, eyes/nose/cheeks, and mouth/lips/chin) independently.

During the first 6 months of life, the discomfort–pain (or physical distress) facial expressions include tightly closed eyes; a broadened and bulged nasal root; brows

slanting downward and together; and an angular, square mouth. The same facial expressions were noted in expression of anger, except the eyes were open and staring.[38,44] Similar expressions have been noted in infants being immunized.[38] Difficulty in discrimination between expressions of pain and anger may exist as a result of this subtle difference. Distress expression as an immediate pain response was found to decrease with age.[44] The anger expression as an immediate pain response increased with age. Interobserver reliability of the coding system improved with observer training. The MAX coding system may have value as a tool that neonatal nurses could use in their assessment of pain in infants. Training in use of the coding system could be incorporated into neonatal nurse orientation and training programs.

Body Movements

Although motor responses have been studied as a possible dependent variable in discrimination of infant response to painful experience, no specific overt motor response of infants that characterizes pain has been observed. McGraw's[45] ambitious study consisting of 2008 observations of 75 pin-pricked children found the most common response of the infant was "diffuse body movement." In contrast, other authors[46,47] have described flexion and adduction of upper and lower limbs associated with grimacing in response to painful stimuli in both premature and full-term infants. Neuromaturation of normal infants may proceed in spurts followed by plateaus and even regressions before successive developmental progress is noted.[45] The quality of reflexes and muscle tone of infants with central nervous system damage frequently varies from the responses observed in an intact infant,[43] making evaluation of this variable in the assessment of pain difficult in a large majority of infants in the intensive care unit.

Methods of Pain Management

The role of the nurse caring for infants in pain involves assessing the level of discomfort, collaborating with other health-care professionals to identify and implement appropriate interventions for the relief of pain, and evaluating the effectiveness of the interventions. Although many of these critically ill infants are intubated and paralyzed, or too sick to respond to invasive procedures, we must operate on the assumption that any procedure performed that is known to cause pain in the adult, also causes pain in the infant. This assumption has nursing implications for all surgical procedures routinely performed without the aid of anesthesia and painful procedures performed at the bedside without analgesia such as circumcisions, chest tube placement, lumbar punctures, intubations, and cut-downs for line access. Benefits of both medical and nursing interventions to decrease needless human suffering may also reduce complications such as intraventricular hemorrhage or pulmonary hypertension and improve clinical outcomes.

Nursing Interventions

To effect positive changes in the care of the critically ill infant, the unique capacities and needs of the individual infant must be considered. Reducing or eliminating factors that increase the experience of pain is a basic intervention for all patients experiencing pain. This involves recognizing the unique capacities and needs of the individual infant. Multiple sensory inputs from the environment may cause the infant to respond by physiologic decompensation. Nurses must be astute in their observations of the individual infant's tolerance to the type and amount of stimuli. These observations will aid the infant in developing sufficient physical integrity and internal stability. Our eagerness to maintain biologic survival has resulted in the development of unit routines at times without consideration of the individual infant's tolerance of the noxious stimulation. Clearly, we need to reexamine some of our traditional routines through nursing research.

A walk through any neonatal intensive care unit reveals an environment of space-age technology. Brightly lighted and noisy environments with machines, alarms, radios, and a multitude of persons entering and leaving the room can overstimulate a neonate. Dimming the lights periodically, creating "rest periods" with minimal noise levels maintained have been instituted in several units in an attempt to decrease the amount of continuous noise to which infants are exposed.

Careful repositioning is another important comfort measure. Prone positioning may provide more comfort for some infants. If the supine position is used, placing rolls on each side of the neonate may have a calming effect and provide a feeling of security. Careful attention to eliminating tension placed on tubes secured to the infant decreases discomfort and trauma to insertion sites. Gorski et al.[43] found that gently containing the infant's limbs while slowly turning the baby supine in preparation for an intravenous injection resulted in the heart rate, respirations, and skin color remaining unchanged during the actual procedure. This was in contrast to the marked signs of autonomic liability noted when the infant was abruptly turned with limbs uncontained.

Other nursing measures traditionally used to help alleviate pain in neonates include offering a pacifier, cuddling, tapes of maternal heart beats, limiting painful procedures, allowing more time for uninterrupted sleep, and use of genital massage or therapeutic touch before and immediately following any traumatic procedure. Gently reassuring the infant both before and following the painful stimuli and staying with the infant until there is evidence of relaxation and restoration of homeostasis is often difficult but essential.

Last, a simplistic approach is inadequate. Several methods may be necessary for adequate pain relief. Nurses have relied on our empathy, intuition and experience to form a "gut" feeling that an infant is in pain. Our management techniques have often been a trial and error process. Many of the nonpharmacologic interventions are comfort measures provided to all infants and are not proven to have specific pain-relieving effects. I doubt the effectiveness of these interventions for moderate-to-severe pain. It is imperative that nurses, in conjunction with other

health-care providers, examine the validity of interventions presently used in order to establish a scientific knowledge base of therapeutic techniques effective in pain control measures in the neonate.

Pharmacologic Management

Information on the effective use of analgesics for the relief of pain in the neonate is limited. Routine use of anesthetics and analgesics for surgical procedures or painful procedures was limited as a result of concern that the danger to the unstable infant outweighed possible benefit of pain relief and that infants did not have the cortical function required to have a memory of painful events. The American Academy of Pediatrics[48] in 1987 developed a statement that (1) local and systemic pharmacologic agents are now available that permit relatively safe administration of anesthesia or analgesia to neonates; (2) administration is indicated according to usual guidelines for administration of anesthesia to high-risk, potentially unstable patients; and (3) the decision to withhold medication should be based on the same medical criteria used for older patients and not solely on the infant's age or perceived degree of cortical maturity.

Premedication of infants before painful procedures was not reported as a common practice in the majority of neonatal intensive care units surveyed by Frank.[49] Five percent of respondents related pain medication was never used in their units. Decreased use of narcotic analgesics in pediatric patients has also been reported during the postoperative period in other studies.[50] Neonatal intensive care nurses chose lower doses of narcotics and gave significantly more nonnarcotic analgesics than nurses from either pediatric surgical units or pediatric intensive care units. Fifty percent of the nurses indicated that they felt pain relief needs of their patients were not met.

Neonatal respiratory depression has always been a feared side effect of narcotics. A prolonged or greater respiratory depression following narcotic administration in neonates may result in part from a greater brain penetration of the drug, age-related differences in opiate receptors, and organ system maturation causing slower elimination of the drug from the body.[51–53] Other complications seen with narcotic analgesics include hypotension, bradycardia, and muscle rigidity. Managing pain with narcotic analgesics effectively and safely is a challenge for nurses. It requires a thorough understanding of the pharmacology of the drug, predicting effects of altered physiology in combination with dynamics of human development on both drug disposition and drug activity, and special considerations in administration techniques.

A comparison of selected drugs used in the management of pain in neonatal intensive care units is outlined in Table 14.1. Certain unique factors must be considered in the administration technique of potent narcotics.

Drug Computations

Errors in computations of intravenous drug therapy for infants have been documented to occur as a result of individually calculated doses based on age, weight,

TABLE 14.1. Dosage comparison of selected narcotic analgesics used in the management of pain in neonates.

Drug	Dose	Comments
Morphine	0.1 mg/kg	May increase ICP pressure Respiratory depressions Slower onset of action than fentanyl
Meperidine	1.0 mg/kg	May increase ICP pressure Slower onset of action than fentanyl
Fentanyl	2–4 μ/kg	Rapid onset of action Short duration of action May cause respiratory muscle rigidity with rapid infusion

ICP, intracranial pressure.

or gestational age.[54] Perstein et al.[54] reported an alarming 8% frequency. The similarity in appearance of dosage units (nanogram, ng; microgram, mcg; milligram, mg or mgm; gram, g or gm) adds to the difficulty even when written legibly. Arithmetic errors in calculations can be diminished by having all narcotic doses double-checked by another nurse.

Preparation of Small Therapeutic Dosages

The technique involved in dilution of adult pharmaceutical preparations is also of concern because many preparations are not available in pediatric dosage forms. Dilution intoxication with digoxin has been described in the literature by Berman et al.[55] They measured the amount of digoxin (100 mcg/mL pediatric injection) contained in the calibrated chamber and the dead space of a tuberculin syringe filled to the 0.05-mL level. The amount of digoxin delivered from the calibrated chamber and dead space ranged from 12 to 18 μg as compared with the 5 μg contained in the intended 0.05-mL dosage volume. If the nurse, in an attempt to increase accuracy, further dilutes a medication drawn up in a tuberculin syringe, the medication contained in the dead space of the syringe will be drawn into the actual delivered volume and could result in an inadvertent overdose.[56] Zenk and Anderson[57] described an instance of morphine intoxication in a neonate that resulted from an inappropriate dilution technique. Selected analgesic medications with potential for "dilution intoxication" as a result of concentrations in a commercially available form are listed in Table 14.2. It becomes obvious medications should be diluted before drawing up an infant's calculated dosage to avoid potential dilution errors.

Delivery of Small Dosage Volumes

Delivery of small dosage volumes can be another factor predisposing error in administration of narcotics to infants. Loss of the drug can occur from dead space of large-volume intravenous tubing systems, stopcocks or Y sites and may depend on whether the medication is flushed following injection into these areas or

TABLE 14.2. Potent medications with potential for "dilution intoxication" resulting from concentration in available pharmaceutical preparations.

Drug	*Available concentration	†Calculated individual dose volume (mL)	Dose delivered‡ Amount	Dose delivered‡ With flush	Delivered dose (% calculated)
Morphine	8 mg/mL	0.013	0.1 mg	0.22 mg	220
Meperidine	25 mg/mL	0.04	1.0 mg	1.375 mg	137.5
Fentanyl	0.05 mg/mL	0.04	2.0 μg	2.75 mg	137.5

*Preparation chosen for calculation represents lowest concentration in a commercially available form.

†Calculated dose based on recommended dose for 1-kg infant.

‡Dose delivered by flush determined by combining the desired measured dosage contained in the calibrated chamber of the syringe with the drug in the dead space (0.015 mL) delivered by flushing a 1-mL tuberculin syringe.

Source: Adapted with permission from Roberts JR: Special considerations in drug therapy in infants. In: Roberts JR. *Drug therapy in Infants: Pharmacologic Principles and Clinical Experience.* Philadelphia, Pa: WB Saunders, Co.; 1984; 30 N8B.

simply is allowed to be flushed by the infant's intravenous infusion rate. The use of low-volume tubing, avoidance of traditional Y sites, administration below the level of filters, and flushing injection ports and stopcocks can minimize loss of the drug. Loss of the drug can also occur when parenteral or intramuscular routes are chosen for administration. If the dead space of the nasogastric tube is not appreciated, the dose the infant receives may be less than prescribed. Flushing the nasogastric tube with enough fluid to ensure complete passage of the volume of medication is recommended. Leakage from injection sites in infants resulting from their small muscle mass can be significant. Using a 2-track method by gently retracting the skin laterally with one finger before grasping the muscle mass of the thigh may help prevent leakage of the drug from the injection site if this route is chosen. Thus, it is recommended that units develop uniform protocols to minimize factors that predispose the infant to administration errors.

Administration Time

Complications and side effects may result from too rapid administration of narcotics. Administering drugs slowly may decrease problems of hypotension and respiratory depression. Many neonatal units routinely use a retrograde system for administration of drugs to infants. Nurses must be mindful, however, that drug-delivery time is influenced by both dosage volume and intravenous flow rate. The smaller the dosage volume and the faster the intravenous flow rate, the shorter the drug infusion time.

Precautions

It is generally recognized that infants (especially premature infants) respond to drugs differently from adults. Only limited pharmacokinetics on various narcotic analgesics in the newborn have been published.[52] Lynn and Slattery's[52] study of

infants ≤ 10 weeks of age found a combination of lower clearance and longer elimination half-life in newborns (0 to 7 days). This may explain the prolonged duration of action for morphine that has been observed in very young infants. It may also explain the findings of Burokas[50] that neonatal intensive care nurses chose lower doses of narcotics and gave significantly more nonnarcotic analgesics than nurses from either pediatric surgical units or pediatric intensive care units.

The major concern in administration of narcotics to infants is potential respiratory depression. Because of the severity of this and other potential complications, use of narcotic analgesics in infants should occur in a unit that can provide adequate monitoring. For infants receiving mechanical ventilation (especially those paralyzed for ventilatory management or requiring postoperative analgesia), the benefits of analgesia and sedation outweigh the risks where adequate monitoring and life-support equipment are present.

Morphine, meperidine, and fentanyl are primarily metabolized by the liver, with approximately 10% being excreted as unchanged drug by the kidneys. General guidelines for drug use in hepatic and/or renal dysfunction or failure are difficult to formulate because of the complexity in etiology and pathophysiology. The lack of published information on the use of specific drugs in neonates with hepatic dysfunction demands cautious and individualized therapy based on the known pharmacologic features of the drug, and careful clinical observations of therapeutic effect currently appear to be a reasonable guideline.[56] Clearly, more research into the pharmacokinetic properties of narcotic analgesics in the neonate must be conducted to provide answers to questions concerning distribution, metabolism, and excretion of drugs to ensure safe and adequate dosages.

Evaluation of Pain-Management Techniques

Following pain-management techniques, the nurse should review the infant's baseline assessment data for changes to evaluate whether pain relief was achieved. For example, if the infant was tachycardic and agitated before implementation of pain-management measures, then the expected outcome would include a return of the heart rate to the expected baseline and the infant would appear to be more relaxed. If baseline data remain unchanged, evaluation must be made to determine whether the pain relief measures were inadequate or whether other pathologic reasons exist (such as a change in neurologic function or unstable cardiovascular status) that would explain the abnormal data.

In infants who are intubated and paralyzed with a neuromuscular-blocking agent, both assessment and evaluation become more difficult. Neuromuscular-blocking agents do not produce sedation or analgesia response. Infants with otherwise normal levels of consciousness will continue to be aware of stimuli and sensitive to pain. If one or two probable signs of pain are manifested, however, a test dose of analgesic may be indicated. Narcotic analgesics used in conjunction with neuromuscular-blocking agents blunt the infant's response to noxious stimuli. Nurses may infer that the infant was experiencing pain if the assessed signs abate.

Summary

Evidence strongly suggests that pain pathways as well as cortical and subcortical centers required for pain perceptions are well developed at birth. Although infants are preverbal, the infant's crying activity, increased heart rate, and facial expression seem consistent with signs of distress. The difference between infants and adults may be in the accuracy and maturity of expression of pain by the infant rather than the intensity. Health-care professionals should question former assumptions and promote a more inquiring approach to the assessment and management of pain in infants. Pain in the infant is best viewed as a multivariate event that includes internal and external expressions. The complexity of the concept and the wide range of response systems suggest that a multidisciplinary research is most appropriate to contribute to our treatment of pain in neonates. Increased knowledge of nonpharmacologic and pharmacologic methods of pain relief will provide guidance in clinical practice. Decisions to withhold analgesic agents should be based on the same criteria used in older patients not solely on the infant's age or perceived degree of cortical maturity. Nurses have been and will continue to be a vital link in assessment, intervention, and evaluation of pain in infants. Response to the infant in pain must be proactive and humanistic in both the assessment and relief of pain. The benefits measured by a decrease in needless human suffering may impact the survival of these infants and the quality of their lives.

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