The Utility of Contrast Echocardiographic Techniques in the Care of Critically Ill Infants with Cardiac and Pulmonary Disease

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SUMMARY In order to assess the utility of contrast M-mode echocardiography in an intensive care nursery population of critically ill newborns with cardiac and pulmonary disease and to validate contrast echo methods, we performed 200 serial contrast echoes on 40 infants via umbilical arterial or venous catheters which had been placed into these infants for clinical indications. The resulting contrast echoes recorded from the precordium or the suprasternal notch allowed the delineation of intra- and extracardiac right-to-left and left-to-right shunting patterns. Patterns identified and validated by cardiac catheterization (in cardiac patients) were: right-to-left atrial shunts, right-to-left ventricular shunts, and left-to-right patent ductus arteriosus shunts. The studies were without complication. Serial application of these echocardiographic techniques was extremely important in assessing changing physiology in these neonates. Contrast echocardiography adds physiologic flow information to the anatomical information available from M-mode echoes and is quite important in the diagnosis and sometimes in the management of critically ill newborns.

caused by rapid injection of contrast material (indocyanine green dye, saline or the patient’s own blood) is due to turbulence or the formation of microscopic bubbles. Recent modeling experiments, however, have suggested that this opacification effect is produced when an ultrasonic wave encounters microcavitation at a catheter tip. These cavitation microbubbles do not appear to traverse the pulmonary capillary bed and the technique has therefore been used for the evaluation of intracardiac shunting and valvular incompetence in children.

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CONTRAST ECHOCARDIOGRAPHIC TECHNIQUES, initially developed by Gramiak and coworkers1 have been utilized extensively in echocardiography for the validation of echocardiographic structure identification. At present, uncertainty exists as to whether echo opacification

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in the postoperative period using indwelling left-sided catheters, many studies have utilized peripheral venous injections. Only one previous study has documented the application of these techniques to the newborn infant for differential diagnosis of cyanosis.

Because of the importance of noninvasive serial echo studies in critically ill newborns, questions about the fluid volumes required for these techniques in newborns and the unknown effects of lateral resolution errors on the accuracy of these techniques, we have developed and evaluated a comprehensive approach to serial contrast echo evaluation of intracardiac shunts in babies. The technique is performed during, and as an adjunct to, M-mode echocardiography from sites on the precordium and from the suprasternal notch at the bedside in the intensive care nursery. Serial echo findings regarding the application of contrast echo techniques in premature infants for the detection of left-to-right shunts through a patent ductus arteriosus are reported elsewhere. The purpose of this paper is to review the utility of these serial techniques for detection of right-to-left intracardiac and left-to-right ductal shunts in full term infants with severe lung disease or congenital heart disease.

Methods

Patients

Contrast studies (128 serial venous and 72 serial arterial studies are reported herein) were performed in conjunction with echocardiography in 40 infants, age 4 hours to 6 days (mean 54 ± 3 hours (SE)), weight 1600 to 3600 g (mean 2200 ± 135 g). Of these infants, nine (group A) had severe cyanosis secondary to persistent fetal circulation. All of these infants had severe hypoxia despite artificial ventilation, constant positive airway pressure (CPAP) and 100% oxygen. Right-to-left ductal shunts were documented by arterial blood gases. Mean descending aortic PO₂ was 31 ± 5 torr (100% O₂), mean temporal artery PO₂ was 42 ± 7 torr.

Thirteen infants (group B) were studied as a control group and had hyperbilirubinemia requiring exchange transfusion for which umbilical venous catheters had been placed. These infants had no clinical evidence of hypoxia in room air (mean PO₂ 51 ± 5 torr in room air by heel stick).

Additionally, 18 infants (group C) were studied who had severe cyanosis resulting from cardiac disease, which was subsequently verified at cardiac catheterization; of these, six had tetralogy of Fallot, one had truncus arteriosus, three had pulmonary atresia with intact ventricular septum, eight had d-transposition of the great vessels. Of these last eight, six had intact ventricular septum and two had ventricular septal defects.

Saline Contrast Techniques

Echocardiograms were performed with a 5 MHz 1/4-inch nonfocused transducer and a Smith Kline Ekoline 20A ultrasonograph interfaced with a Honeywell 1856 fiberoptic recorder. At the time of injection, a pencil mark was placed onto the strip chart paper as it emerged from the recorder. An arrow was then placed on the paper approximately 2 inches to the right of the pencil mark since this represented the portion of the record actually being imprinted fiberoptically at the time of injection. The upward pointing vertical or slanting arrows placed toward the bottom of all of the echo figures represent this portion of the record and mark the time of injection. A modified right angle 5 MHz transducer was used for suprasternal notch echo studies. The following types of saline contrast studies were performed in these infants:

Venous Studies. Informed parental consent was obtained under an approved human subjects protocol for infants with clinically indicated umbilical venous catheters (groups A & B) and also for infants with these catheters placed specifically for this study (groups A & C). The catheter tip was placed in the portal venous system, duc tus venosus or inferior vena cava just above the diaphragm. Except for the one injection performed during catheter placement, no catheters were in the right atrium or superior vena cava. A total of 1–3 cc of sterile D5-O.2 normal saline was utilized for the first two or three injections followed by 1 cc of the patient's own blood for subsequent injections during any one echo study. The saline or blood was rapidly hand injected using a 10 cc syringe while the echocardiogram was performed. Injections for the evaluation of right-to-left shunts were performed while the echocardiogram was recorded at a) the level of the mitral valve in a plane passing through the right and left ventricular cavities, b) in a plane passing through the right ventricular outflow tract, aortic root and left atrium, and c) in a suprasternal notch plane passing through the transverse aortic arch, right pulmonary artery and left atrium in a superior-inferior axis.

Arterial Studies. Saline contrast injections were performed after obtaining informed parental consent in infants in all groups who had umbilical arterial catheters placed for clinical indications. One to two cc of saline or blood was injected by hand into the descending thoracic aorta through catheters which were placed so that the tip was at the level of the fourth to sixth thoracic vertebrae; the injection was performed during a suprasternal notch echo cardiogram for the evaluation of left-to-right ductal shunting.

Catheter Positioning. The position of all catheters was checked radiographically upon placement and periodically checked as clinically indicated.

Criteria for Interpreting Echocardiograms. Echocardiograms were qualitatively evaluated for the presence or absence of shunting. Contrast echocardiograms were considered negative for right-to-left shunting if only the right ventricular body, right ventricular outflow tract and right pulmonary artery (except in transposition) were opacified during a venous injection study. Right-to-left atrial shunting was suggested if left ventricular opacification occurred from behind the mitral valve (fig. 1) and if left atrial opacification occurred behind the aortic root in the precordial echo and under the right pulmonary artery in the suprasternal notch echo. Right-to-left ventricular shunting was diagnosed if contrast traversed directly across the ventricular septal echo appearing in the left ventricular cavity in front of the mitral valve (fig. 2). Left-to-right ductal shunting was diagnosed on arterial injections if not only the transverse aortic arch but also the right pulmonary artery was seen to opacify.

Figure 3 shows diagrammatically the suprasternal notch transducer imaging the transverse aortic arch, right pulmonary artery and left atrium while 1 cc of contrast
FIGURE 1. Right-to-left atrial shunting. After injection of contrast material into the inferior vena cava (left panel), not only does the right ventricle (RV) opacify but the left ventricle (LV) opacifies from behind the mitral valve (MV). The shunt is at the atrial level. Further documentation of the site of the shunt can be obtained if the contrast injection is repeated while the M-mode echo is performed at the level of the aortic root. In the right panel, the left atrial (LA) opacification occurs along with opacification of the right ventricular outflow tract (RVOT) and prior to aortic (Ao) opacification. The upward pointing unlabelled arrows in all figures mark the moment of injection.

material is injected into the descending thoracic aorta at the level of the fourth to sixth thoracic vertebrae. Retrograde opacification of the transverse aorta (as a control for adequate injection) is observed. In the presence of left-to-right ductal shunting not only does the transverse aortic arch fill, but the right pulmonary artery fills as well, from the descending aorta. If the right pulmonary artery does not fill, this does not mean that the ductus is not patent, but only that the left-to-right shunting is too small to be detected. No technique has yet been devised for echo diagnosis of right-to-left ductal shunting. We have relied on temporal artery vs umbilical artery blood sampling of arterial blood gases to detect right-to-left shunting at this level. Figure 4 shows the actual preoperative (positive) and postoperative (negative) suprasternal notch arterial contrast echoes from a premature infant who underwent ligation of a large patent ductus arteriosus.

Spillover echoes, a "smear" artifact from too forceful an injection, were a potential cause of false-positive opacification of posterior or inferior structures. Figure 5

FIGURE 2. D-transposition with patent foramen ovale and ventricular septal defect. This infant had a small interatrial shunt via the patent foramen ovale. As shown on the right in a suprasternal notch echocardiogram, little left atrial (LA) opacification is visualized underneath the right pulmonary artery (RPA). There is, however, a ventricular shunt with contrast passing directly (left panel) across the ventricular septum from the systemic right ventricle (RV) to the pulmonary left ventricle (LV) in front of the mitral valve. The direct passage of contrast characterizes right-to-left shunts at the ventricular level and accounts for the significant right pulmonary artery fill in the suprasternal notch echo (right panel). TAA = transverse aortic arch.
demonstrates an injection which was performed too forcefully in an infant and appears to obliterate or pass directly through the ventricular septum, obscuring the left and right ventricles and mimicking a right-to-left ventricular shunt; the contrast "front" opacifies the whole cardiac silhouette simultaneously. A second injection, performed less forcefully from the same catheter location, shows opacification of the left ventricle from behind the mitral valve, and faint opacification of the right ventricle anterior to the septum later in the injection. The time differences observed in opacification are the most reliable method of ruling out false positives. Such artifacts result from the detection of off-axis contrast echoes which appear in records to smear across interfaces such as the ventricular septum without interruption. They could usually be avoided by less forceful injections. This smear artifact probably represents a lateral resolution error and as such also appeared more prominently with low reject or high gain settings. The recordings in this paper were all obtained with highest possible reject and lowest possible gain. Since this tended to make the recordings faint, specialized high contrast photographic technique was required to aid in their reproduction, which accounts for the dark background and lack of gray scale in many of the figures.

The same smear artifact caused by lateral resolution errors in venous studies may produce potential false-positive results for the arterial contrast techniques as well (fig. 6). Decreasing injection force and volume will usually allow the interfaces of the transverse aortic arch, right pulmonary artery and left atrium to image clearly on the echocardiogram. The two injections seen in figure 6 were performed one after another and differed only in injection technique.

FIGURE 3. As shown in this diagram, the saline contrast technique could be expected to show opacification of not only the transverse aortic arch (TAA) but the right pulmonary artery (RPA) as well, in this suprasternal notch echocardiogram if there was left-to-right ductal shunting. The insert panel shows the diagrammatic appearance of these suprasternal notch echoes. L-R = left-to-right; PDA = patent ductus arteriosus; LA = left atrium; SSN = suprasternal notch.

FIGURE 4. This 1100 gram infant studied serially had a large left-to-right ductal shunt and congestive heart failure. As evidence of a left-to-right shunting patent ductus arteriosus (left panel), both the transverse aortic arch (TAA) and right pulmonary artery (RPA) opacify after the descending aortic arch injection. The infant underwent surgical ductal ligation after which a negative study (right panel) was obtained. At no time did he have a cardiac murmur.
The infant actually had what appears to be a negative study.

Site of Injection. We investigated the effects of differences of injection sites on our ability to perform these studies. In general, a more vigorous push of 2 cc or more was required for arterial catheters lying well below the diaphragm or for venous catheters within the hepatic or portal venous system. One-half to one cc pushed quite gently produced adequate opacification from arterial catheters with their tips lying close to the ductus arteriosus or from venous catheters with their tips lying within the ductus venosus or inferior vena cava above the diaphragm; larger amounts produced a smear artifact.

A striking difference in flow patterns was observed in four infants, two with lung disease and two in the control group who had contrast echoes preformed simultaneously from "brachial" and inferior vena caval sites. Satisfactory contrast studies in these babies were obtained by injection through a 21 gauge scalp vein needle inserted into a vein on the dorsum of the hand. In these babies, the venous saline contrast injection performed through the 21 gauge needle demonstrated trivial opacification of the left atrium and did not document significant right-to-left shunting, while larger right-to-left atrial shunts were suggested by dense left atrial opacification on the simultaneously performed subdiaphragmatic injection study. These streaming effects on contrast studies were not unexpected in view of the well known streaming effects on blood distribution in the fetal circulation. This same difference in shunting was noted in one additional group A infant in whom a superior vena caval injection through an umbilical venous catheter was performed just prior to pulling the catheter back to the inferior vena cava. Comparison of these superior and inferior vena

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**Figure 5.** A smear artifact from too forceful an injection (upper panel) obscures the site of right-to-left shunting. Contrast appears to pass directly across the septum (S) from the right ventricle (RV) to the left ventricle (LV). With a less forceful injection, the contrast can be seen more clearly appearing in the left ventricle from behind the mitral valve (AML) preceding the right ventricular opacification (arrow) (lower panel).

**Figure 6.** Smear artifact on an arterial contrast study. After the first injection (left panel) contrast traversed the entire echo smearing across all the interfaces right down through the bottom wall of the left atrium. This is a false positive. When the injection was repeated less forcefully (right panel), adequate opacification was obtained in the transverse aortic arch, but there was no right pulmonary artery (RPA) opacification.
caval injections suggested that the difference in shunting patterns was not merely a result of differences in the force of injection between the central and peripheral injection sites. The detection of this effect in contrast echocardiography suggests that hepatic portal or ductus venosus injections may overestimate the amount of right-to-left atrial shunting whereas brachial or superior vena caval injections may underestimate foraminal right-to-left shunting. In the detection of ventricular septal shunting these changes of injection site appeared to be of no importance.

**Results**

**Venous Studies**

*Group A.* Of the nine infants with persistent fetal circulation, all had intracardiac right-to-left shunting at the level of the atrial septum which appeared to be of significant magnitude. As shown in figure 1, an injection of 1–2 cc of saline into the inferior vena cava or ductus venosus opacified not only the right ventricular cavity but also the left ventricle from behind the mitral valve. As verification of this atrial shunting pattern, contrast was also observed in the left atrium prior to opacification of the right ventricular outflow tract and by subsequent opacification of the aorta on the next beat. All of the infants in group A were artificially ventilated in 100% oxygen and three were receiving i.v. tolazoline. In addition to right-to-left atrial shunting a right-to-left ductal shunt was present as demonstrated by the consistent temporal artery-umbilical artery PO2 differences on arterial blood gases (see Methods). The echoes were interpreted only qualitatively for right-to-left shunting and no correlation between the degree of desaturation, temporal or umbilical, and the extent of right-to-left atrial shunting was attempted.

The echocardiogram from another infant with persistent fetal circulation is shown in figure 7. In this infant, right-to-left shunting existed at the foramen ovale (atrial level). Contrast appeared as opacification of the left ventricle from behind the mitral valve prior to opacification of the right ventricle from behind the tricuspid valve. Opacification of the left atrium and aorta also occurred prior to opacification of the right ventricular outflow tract. Although the right ventricular body was opacified significantly (left panel) the suprasternal notch echo confirmed that the left atrial and transverse aortic arch opacification significantly preceded and exceeded the amount of opacification of the peripheral right pulmonary artery. This difference between right ventricular body and right pulmonary artery contrast was seen consistently in group A and may reflect decreased flow into the peripheral right and left pulmonary arteries.

Six infants in group A survived. The three who died had remained consistently hypoxic and continued to have large right-to-left atrial shunts until the time of their death. Serial studies were performed in four of the six survivors and in all four right-to-left atrial shunting was still present at the time the study was terminated (at a mean age of 97 ± 6 hours). One of the four infants still had right-to-left shunting at a time when he was in 25% oxygen with a systemic PO2 of 64 torr and no temporal-umbilical arterial difference.

*Group B (control group).* Group B infants had no cardiorespiratory distress and served as control group for group A. Umbilical venous catheters were placed in this group of infants requiring exchange transfusion. In five of the infants in this group, capillary blood gases had been performed and were normal (mean PO2 was 51 torr in room air). (This is normal at Tucson’s 2500 ft. elevation for infants less than 24 hours of age.) None of the infants were considered to be desaturated at the time of the initial study. Nonetheless, nine of the thirteen infants, even when lying quietly, had unsuspected right-to-left atrial shunts. Seven of these were studied serially and in all, these shunts had disappeared by 72 hours of age. No ventricular shunts were noted.

The appearance of right-to-left atrial shunting in groups A and B was quite similar and it was present in all infants with severe lung disease and in almost 75% of the control infants. Nevertheless, the time of resolution for the foraminal shunting was different in the two groups (less than 72 hours in the normal group, greater than 72 hours in the infants with lung disease).

**Cyanotic congenital heart disease (group C).** Eighteen patients with congenital heart disease were studied and in all the anatomical diagnosis and sites of shunting were verified by cardiac catheterization and angiography.

![Figure 7](image_url)

*Figure 7.* In this infant with persistent fetal circulation, a large right-to-left atrial shunt can be seen behind the mitral valve (left panel), behind the aorta (AO) in the left atrium (middle panel) and with opacification of the transverse aorta (TAA) following left atrial opacification in the suprasternal notch view (right panel).
Eight infants had transposition of the great vessels, six with intact ventricular septum. In two of these latter six infants with transposition, oxygenation was adequate before palliation (PO₂ values were 33 and 36 torr, respectively, in 100% oxygen) and the contrast injections (fig. 8) suggested that they had large right-to-left interatrial shunts. Cardiac catheterizations showed large atrial septal defects and good systemic-pulmonary mixing. In both infants, the atrial septal defect appeared to have a diameter of at least 1.5 cm when sized before balloon septostomy with a 5 French balloon catheter. The other four infants with transposition of the great vessels and intact ventricular septum had a small interatrial mix before cardiac catheterization with a mean PO₂ of 19 torr in room air and 25 torr in 100% oxygen (fig. 9). In three of these infants, the PO₂ rose after balloon septostomy to a mean of 36 torr in 100% oxygen with a significant increase in right-to-left atrial mix seen on contrast echocardiograms, paralleling this rise in PO₂. In the last infant, despite an increase in the left atrial echo contrast opacification after balloon septostomy, the PO₂ did not rise above 24 torr in 100% oxygen. The infant subsequently underwent an open surgical septectomy with no improvement in systemic oxygenation despite persistence of left atrial contrast after venous injection. The right-to-left atrial shunt in this infant did not reflect good interatrial mixing, even postoperatively, when there was essentially no atrial septum present. None of these infants had pulmonic stenosis.

The other two infants with d-transposition had ventricular septal defects identified by contrast echo technique, although the VSD in one of these infants was not initially associated with an audible murmur. As shown in figure 2, this infant with d-transposition and no murmurs had a right-to-left shunt through a ventricular septal defect with opacification of the left ventricle appearing directly across the plane of the ventricular septum and in front of the mitral valve. In the suprasternal notch echo (right panel) there was little left atrial opacification, but right pulmonary artery opacification occurred with shunting across the ventricular septum along with the direct antegrade fill of the transverse aortic arch. The passage of contrast directly across the plane of the ventricular septum and in front of the mitral valve complex (but avoiding smear artifacts) appears specific for detection of right-to-left shunts at the ventricular level. (We have subsequently observed right-to-left ventricular shunting patterns after peripheral venous antecubital injections in four older children with ventricular septal defects and pulmonary vascular obstructive disease.)

Six of the group C infants had tetralogy of Fallot, one had truncus arteriosus and three had pulmonary atresia with intact ventricular septum. In all the tetralogy and truncus patients, right-to-left ventricular shunting was best visualized high up on the septum close to the level of the septal-aortic (truncal) discontinuity. Four of the neonates

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**Figure 8.** D-transposition with large atrial septal defect. A large right-to-left atrial shunt exists before cardiac catheterization in this infant with d-transposition and a large atrial septal defect. The left ventricle fills from behind the mitral valve while the right ventricle fills from behind the tricuspid valve.

**Figure 9.** Pre and post balloon atrial septostomy: injections from the same inferior vena caval site. In this infant, a small interatrial shunt was present before cardiac catheterization (left panel). After the balloon septostomy (right panel) there was an increase in the interatrial mix with a rise in oxygen saturation and an improvement in the infant's overall condition.
with tetralogy of Fallot and the infant with truncus had unsuspected right-to-left atrial shunts demonstrated by contrast echocardiography. The infants with pulmonary atresia, type I, likewise had interatrial right-to-left shunts. The predicted right-to-left atrial and/or ventricular shunting patterns were verified in all group C infants at cardiac catheterization.

**Arterial Studies**

Contrast studies performed from the suprasternal notch view were used to detect left-to-right patent ductus shunts (Fig. 3). Figure 4 shows a suprasternal notch arterial contrast echocardiogram performed in a premature infant without an audible murmur and with a large left-to-right shunt through a ductus arteriosus. Opacification of the transverse aortic arch and the right pulmonary artery was observed preoperatively, whereas only opacification of the transverse aortic arch was seen four hours after operative ductal ligation. The frequency of silent ductus arteriosus and the importance of these studies for monitoring noninvasive attempts to achieve closure of ductus arteriosus have been emphasized recently in a report from a laboratory summarizing 168 serial contrast studies performed on 50 premature infants. This report describes the application of the technique to the detection of left-to-right ductal shunting in the presence of congenital heart disease or severe pulmonary disease in larger infants.

Three of group A infants with persistent fetal circulation had left-to-right ductal shunting, suggesting that in these babies a left-to-right component of bidirectional ductal shunts could be identified despite significant pulmonary hypertension. This finding may be the result of pressure exerted by the injection in the descending aorta which temporarily reversed the shunt but served as documentation of ductal patency in the three infants. None of the control group had arterial catheters and so no injections were performed.

Of the group C infants, six of the eight patients with transposition had arterial injection studies performed with catheters placed above the diaphragm. Three of the six had ductal shunting identified and all three had a small left-to-right patent ductus arteriosus at cardiac catheterization. In two of these three infants, the left-to-right shunt disappeared during the period of serial study, one at 60 hours of age and the other by 75 hours. The third infant still had a positive left-to-right ductal shunt as shown by saline contrast study at the time the catheter was removed at 95 hours of age. Positive studies for left-to-right ductal shunts were found in the three infants with pulmonary atresia and in three of the four tetralogy infants who had high umbilical arterial catheters. All these ductal shunts were verified at cardiac catheterization. The infants with pulmonary atresia and one of the tetralogy patients had what appeared to be very large left-to-right ductal shunts and were indeed ductus dependent for almost all of their pulmonary blood flow. The other two infants who had tetralogy of Fallot and positive arterial contrast studies had less prominent pulmonary opacification on their echocardiograms. Both had antegrade as well as ductal flow supplying their pulmonary bed at cardiac catheterization. The infant with truncus arteriosus type II had faint right pulmonary artery opacification observed on an arterial contrast study which could not be distinguished from a left-to-right duct although opacification occurred with a slight delay. To date, although only two infants have been studied after palliative surgery, our initial experience suggests that this technique will be quite useful in serially studying patency of artificial systemic-pulmonary anastomoses. The two tetralogy of Fallot infants with small ductal shunts had milder forms of tetralogy and did not require palliative surgery. They underwent serial arterial contrast studies and in both the left-to-right ductal shunts appeared to close during the period of study. In these babies, arterial PO2s dropped coincident with ductal closure as identified by the saline contrast study (41 to 32 and 39 to 29 torr, respectively, in room air).

**Discussion**

This study demonstrates that a comprehensive evaluation of intra and extracardiac shunts may be derived from contrast echocardiography in neonates via umbilical artery and venous catheters. These safe and reliable echocardiographic studies may be accomplished in serial fashion to give valuable ongoing information. The shunting patterns determined by this method, in conjunction with the anatomical information provided by M-mode echocardiography provide important information for patient management. The shunt patterns predicted in our patients with congenital heart disease prospectively were all verified at cardiac catheterization as described.

Asphyxiated infants and those with lung disease have long been known to have significant right-to-left intracardiac shunting at the level of the atrial septum. The shunting patterns in our infants with lung disease are similar to those previously described by Pieroni et al., in newborns with persistent fetal circulation. In that study, however, the existence of intracardiac right-to-left atrial shunts in infants with persistent fetal circulation appeared to be an ominous and reliable predictor of patient death. The serial studies in our infants suggested that the temporal resolution of these right-to-left interatrial shunts was often quite slow and lagged significantly behind clinical improvement in oxygenation. As such, these right-to-left shunts at the atrial level may reflect altered diastolic compliance with the right ventricle. While infants with this disease are believed to have intrapulmonary right-to-left shunting as well, this shunting appears to take place at the capillary level as a result of ventilation perfusion imbalance. This type of shunting does not appear to be demonstrable by contrast echocardiography since the pulmonary capillary bed is not anatomically bypassed. Although intrapulmonary shunting through arteriovenous malformations has been demonstrated as a cause of similar contrast echocardiographic findings, it is unlikely that such shunts were present in our group A infants. The detection of right-to-left atrial shunting in a large proportion of our control group is not inconsistent with previous information since right-to-left shunting has been reported in crying newborns with significant hypoxia generated up to 8 days of age and shunting has been assumed to take place at the foraminal level. Shunts at the atrial level have likewise been detected at cardiac catheterization by dye dilution techniques in normal newborns. The shunts detected in our control infants, however,
were present at rest and were not associated with clinically detectable cyanosis by capillary blood gas studies. It is our impression, however, that inferior vena caval injections may overemphasize or exaggerate the degree of right-to-left shunting and the shunted volume may represent only a small portion of systemic venous return.

The detection of significant right-to-left atrial shunting in our infants with d-transposition of the great vessels appeared to be associated with adequate atrial mixing; but there are exceptions, as in the case of the single infant in whom oxygenation did not improve even after subtotal removal of the atrial septum. Nonetheless, those infants with d-transposition who were found to have good right-to-left atrial shunting prior to balloon septostomy were found to have significant atrial septal defects at cardiac catheterization.

Our own criteria for right-to-left intraventricular shunting agree with previous reports, i.e., the appearance of contrast passing directly across the ventricular septum and appearing in front of the mitral valve. One must avoid the smear artifact caused by too vigorous an injection which can mimic this shunting pattern. The illustrations shown by Valdes-Cruz and her coworkers appear to represent meticulously performed studies and their figure 2 suggests that they were well aware of problems of imaging artifacts. In our transposition group, in both of the infants with ventricular septal defects, the right-to-left shunt at the ventricular level was proven at cardiac catheterization. In one of these cases, the shunt was detected by contrast echocardiography before the onset of the typical systolic murmur of a ventricular septal defect. These studies were therefore a clue for planning the subsequent cardiac catheterization.

The detection of right-to-left interventricular shunting in the patients with tetralogy of Fallot is probably best performed by imaging the ventricular septum just below the level of the aortic override. Our previous cross-sectional contrast studies have suggested that shunting takes place most commonly at the top of the ventricular septum from the right ventricle directly into the aorta rather than more inferiorly in front of the mitral leaflets. Nonetheless, in this series, visualization of mitral leaflets themselves was an important clue in detecting associated right-to-left atrial shunts, some of which had not been suspected before catheterization.

The addition to these venous studies of the arterial contrast technique for the detection of left-to-right shunting of patent ductus arteriosus has been useful in the detection and management of patent ductus arteriosus in premature infants, especially when combined with dimensional echocardiographic data for shunt quantitation. We have likewise found the technique extremely helpful in following serially left-to-right ductal shunting in cyanotic term infants with cardiorespiratory disease as well. Most importantly, the technique has been useful in the patients with tetralogy of Fallot and pulmonary atresia who may be ductus-dependent. Echocardiographic findings of a small pulmonary outflow tract with or without aortic override along with a significant left-to-right ductal shunt in the cyanotic infant probably suggest ductal dependency and a need for hemodynamic investigation as an emergency procedure. Such an infant should probably not be placed in high oxygen, since this could induce ductal closure. Such infants may benefit from a temporary infusion of prostaglandin E₂ to maintain ductal patency until a shunt can be performed. An infant with this anatomy and an equivalent level of cyanosis who has little or no left-to-right ductal shunting may not be ductus-dependent and significant antegrade pulmonary flow can usually be demonstrated on an appropriate venous contrast study performed in the nursery.

Anatomical information from M-mode echocardiography for differentiating cardiac and respiratory disease in infants with congenital heart disease may now be supplemented by reliable, safely obtained physiologic flow information using our echo contrast methodology on arterial and venous studies. This serially obtained information can be important in the management of the ill newborn with respiratory disease as well as in the initial precatheterization evaluation of the patient with congenital heart disease. In such patients the study can indicate the urgent or nonurgent nature of the hemodynamic investigation and suggest additional and often unsuspected problems to be investigated during cardiac catheterization. In the postcatheterization period, after balloon atrial septostomy or after palliative surgery, these techniques can assist in serial postoperative management. The technique appears to be safe and compatible with the usual practices in the intensive care nursery where it provides important information about critically ill newborns.

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SUMMARY A ventricular parasystolic focus capable of generating manifest ectopic beats should not be totally insulated from the electrical events that accompany depolarization in the surrounding tissue; the intrinsic cycle length of the ectopic discharge may be modulated by electrotonic influences transmitted across the zone of "protection." To study the nature of the interaction, response patterns were examined in a mathematical model programmed to simulate an ectopic pacemaker protected, but not divorced from ventricular responses to the normal pacemaker. Computer runs covered a wide range of heart rates, and a wide range of magnitudes of the simulated electrotonic influence. Application of the results obtained in the model to published examples of complex arrhythmias revealed a remarkably close fit to many clinical examples. This finding suggests that many patterns attributed to a re-entrant "extrasystolic" rhythm may, in fact, represent the modulated activity of a parasystolic focus.

VENTRICULAR PARASYSTOLE occurs when an ectopic pacemaker, "protected" by entrance block, fires at a fixed frequency independent of the normal pacemaker. Manifest premature beats or fusion beats appear when the ectopic focus discharges at a time when the exit pathway and the surrounding ventricular tissue are excitable. Except when the two pacemakers beat at frequencies that are harmonically related as simple ratios, the coupling intervals of the manifest ectopic beats will wander through the basic cycle of the sinus rhythm, attesting to the independence of the two rhythms. When, by chance, simple ratios between the two rhythms occur, fixed coupling may appear.¹

The fixed cycle length assumed to characterize the parasystolic focus is only relatively fixed, and a "play" of ±100 msec or more is commonly allowed, on the assumption that no biological oscillator is likely to have a constant period.² When interectopic intervals do not appear to be simple multiples of an approximately constant period, either the diagnosis of parasystole is withheld, or alternative assumptions are added. A wide departure from the common denominator may be ascribed to "intermittence," i.e., temporary cessation of pacemaker activity in the ectopic site. Failure of ectopic activity to appear on schedule is ascribed to exit block that prevents access to the otherwise receptive ventricles.

Rigid constancy of a pacemaker might be expected if the entrance block were complete, but if there is an escape route available for the emergence of ectopic activity, then clearly there must be an effective ionic communication, not complete insulation, between the two tissues. If there is an electrical communication between the two, then the depolarization of the surrounding ventricle may influence the ectopic pacemaker. That influence will be electrotonic; depolarization of the surrounding field will induce a partial depolarization of the pacemaker cells.

Partial and temporary depolarization of a pacemaker can influence its cycle length. Occurring early during phase 4 depolarization, the electrotonic event will delay the next discharge;³ later in the cycle, as membrane resistance increases and the membrane potential approaches threshold, a slight additional depolarization should hasten the subsequent discharge, or "capture" the pacemaker.⁴ These interactions suggest that an ectopic focus, although protected by entrance block, cannot be totally independent of electrical events in the surrounding tissue. Its frequency cannot be fixed, but must be modulated to a degree dependent upon the amplitude of the electrotonic influence, and upon the ratio of the intrinsic cycle durations of the two oscillators.

Recently, we tested these assumptions in an experimental model consisting of a bundle of dog Purkinje fibers mounted in a 3-chamber perfusion apparatus.⁵ The central chamber, perfused with isotonic sucrose, provided an area of conduction block between the two ends of the fiber. Pacemaker ac-
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