ASSESSMENT OF PULMONARY/SYSTEMIC BLOOD FLOW RATIO AFTER FIRST-STAGE PALLIATION FOR HYPOPLASTIC LEFT HEART SYNDROME: DEVELOPMENT OF A NEW INDEX WITH THE USE OF DOPPLER ECHOCARDIOGRAPHY

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Objective: Circulatory maldistribution is believed to be a major cause of early death after first-stage palliation for hypoplastic left heart syndrome. Flow reversal in the reconstructed aorta may reflect the pulmonary/systemic blood flow ratio. The purpose of our study was to investigate the utility of arterial Po_2, arterial oxygen saturation, and a newly developed Doppler-derived flow index in predicting the pulmonary/systemic flow ratio after first-stage palliation for hypoplastic left heart syndrome.

Methods: Twenty-four infants who underwent first-stage palliation for hypoplastic left heart syndrome or a variant were studied. Superior vena cava blood samples were drawn to estimate the mixed venous saturation and permit calculation of the pulmonary/systemic blood flow ratio. Fifty-four samples were evaluated within the first 24 hours after surgery. Simultaneous blood draw and Doppler echocardiography were performed with interrogation in the distal aspect of the arch reconstruction. The ratio of the Doppler velocity-time integral of retrograde flow to the velocity-time integral of forward flow was calculated and compared with the pulmonary/systemic blood flow ratio.

Results: The median mixed venous saturation for the 54 samples was low (38.5%; range, 18%-64%). The median calculated pulmonary/systemic blood flow ratio was 1.4:1 (range, 0.3:1 to 4.2:1). Pulse pressure, mixed venous saturation, and arterial Po_2 were not statistically significant predictors of the measured pulmonary/systemic blood flow ratio. Although both aortic oxygen saturation ($R^2 = 0.84$, $P < .01$) and Doppler flow reversal ratio ($R^2 = 0.94$, $P < .001$) were significantly associated with the measured pulmonary/systemic blood flow ratio, the model coefficient of determination was greatest for Doppler flow reversal ratio.

Conclusion: Measures of arterial oxygen saturation and arterial Po_2 may be misleading in assessing the circulatory status of infants after first-stage palliation for hypoplastic left heart syndrome. Doppler echocardiography, through use of the Doppler flow reversal ratio, provides a more useful measure of pulmonary/systemic blood flow ratio. Low mixed venous saturation after surgery may be due to factors other than pulmonary overcirculation, such as ventricular dysfunction and low cardiac output. (J Thorac Cardiovasc Surg 2000;120:81-7)

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Maldistribution of cardiac output between the pulmonary and systemic circulations has been proposed as a major cause of hemodynamic instability after the first stage of palliation for hypoplastic left heart syndrome (HLHS).[1] After first-stage surgery, both the pulmonary and systemic circulations are perfused in parallel by the right ventricle. Ideally, the goal is to achieve an equitable distribution of blood flow between the two circulations, resulting in maximum oxygen delivery to the tissues.[2,3] However, sudden shifts in the resistance ratio between the two vascular beds can have a deleterious effect on the distribution of flow. A decrease in pulmonary vascular resistance, an increase in systemic vascular resistance, or both may result in pulmonary overcirculation and systemic hypoperfusion. This phenomenon has been implicated as a major cause for early death in these infants.[4] To avoid excessive maldistribution of flow, strategies that preserve a high pulmonary vascular tone and combat the predilection toward early pulmonary overcirculation are commonly used.[5] Postoperative management traditionally consists of frequent estimates of the pulmonary/systemic blood flow ratio (Qp/Qs) on the basis of the systemic arterial P_{O_2} or arterial oxygen saturation levels. These measures, however, may be misleading without knowledge of the mixed venous and pulmonary venous saturations.[6,7]

We have observed, by means of Doppler echocardiography, that the degree of flow reversal retrograde in the descending aorta is much greater in infants with pulmonary overcirculation and systemic hypoperfusion than in infants with well-balanced circulations after stage I palliation for HLHS. We hypothesize that in the absence of significant semilunar valve insufficiency, the degree of retrograde flow reversal in the descending aorta is reflective of flow through the shunt, and hence the ratio of retrograde flow in diastole to anterograde flow in systole may reflect the Qp/Qs ratio. The purpose of our study was to determine (1) the utility of arterial P_{O_2} and arterial oxygen saturation in reflecting Qp/Qs and (2) whether flow estimates obtained by Doppler echocardiography can provide a useful measure of Qp/Qs.

Methods

A convenience sample of 24 infants less than 7 days of age who underwent first-stage palliation for HLHS or a variant between May 1996 and January 1998 were chosen for the study (Table I). First-stage palliation consisted of anastomosis of the main pulmonary artery with the native aorta, aortic arch reconstruction with pulmonary homograft, atrial septectomy when necessary, and placement of a 3.5-mm tube graft between the takeoff of the innominate artery and the right pulmonary artery. Patients with greater than trace aortic or neoaortic (pulmonary valve) insufficiency were excluded.

At the end of the operation, a catheter (placed either through the umbilical vein or directly through the right atrium) was placed in the upper portion of the superior vena cava, and position was confirmed with radiography in the cardiac intensive care unit. Points of evaluation were chosen for convenience within the first 24 hours after the operation, at which time samples for arterial blood gas, arterial saturation, and superior vena cava saturation were obtained. Arterial blood was drawn from an umbilical arterial catheter positioned low in the descending aorta or from a catheter in the radial artery. Blood was also drawn from a catheter positioned in the upper portion of the superior vena cava to estimate the mixed venous saturation. Sampling for the study occurred at the time of routine blood gas assessments or when clinically indicated. Doppler echocardiography was performed by one observer (J.R.) simultaneous with drawing of the blood samples. Blood pressure and heart rate were recorded. The Qp/Qs ratio was calculated by the modified Fick equation, where Qp/Qs is equal to the following:

$$\frac{\text{Aortic saturation} - \text{Mixed venous saturation}}{\text{Pulmonary vein saturation} - \text{Pulmonary artery saturation}}$$

Calculation of the Qp/Qs is simplified in single-ventricle physiology. After first-stage palliation, pulmonary blood flow is solely dependent on shunt flow through the aorta, and hence pulmonary artery saturation equals aorta saturation. Pulmonary vein saturation in this study was not measured. If the inspired oxygen fraction was 30% or greater, then pulmonary vein saturation was assumed to be 100%; if the inspired oxygen fraction was less than 30%, then pulmonary vein saturation was assumed to be 95%.

Doppler echocardiography was performed with the transducer positioned in the suprasternal notch. A sagittal view of the reconstructed arch was obtained, and a pulse-wave sample was placed at the junction of the distal aspect of the arch reconstruction with the native descending aorta (Fig 1). A spectral time-velocity display of 3 to 5 beats was obtained and recorded on VHS videotape. Offline, the time-velocity integrals of retrograde (reverse) flow and antegrade (forward) flow in the descending aorta were measured by tracing the curves above and below the spectral baseline, respectively (Fig 2). The mean time-velocity integral of retrograde flow was divided by the mean time-velocity integral of antegrade flow for calculation of the Doppler flow reversal ratio (DFR ratio).

Exploratory data analysis included using scatter plots, as well as box and whisker plots, to assess the distribution of the variables and search for outliers. Tests of skewness and kurtosis[8] were performed to verify normality of the study variables. When appropriate, a Box-Cox transformation[9] was performed to identify a useful transformation to create a normally distributed variable. Associations between the study variables and calculated Qp/Qs measurements were assessed by using analysis of covariance, accounting for repeated mea-

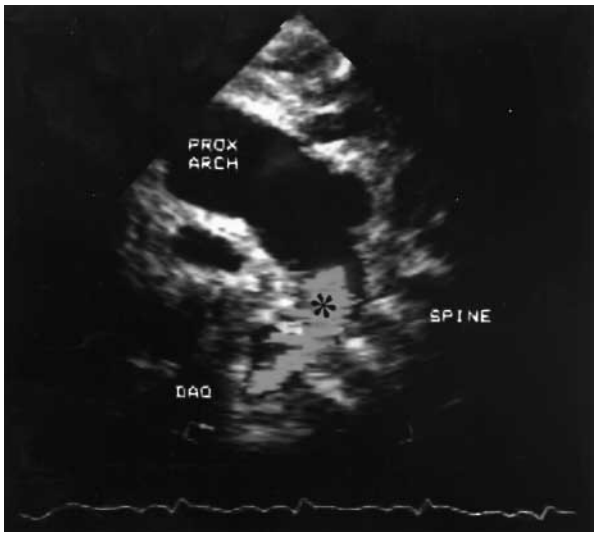

Fig 1. Echocardiographic image of arch reconstruction after first-stage palliation for HLHS. *Asterisk* marks the position in the descending aorta for Doppler interrogation and calculation of the DFR ratio. *DAO,* Descending aorta; *PROX ARCH,* proximal arch reconstruction.

Table I. *Cardiac anatomy of the 24 patients who underwent first-stage palliation*

Anatomy	*No. of patients*
HLHS {S,D,S}, MS, AS	8
HLHS {S,D,S}, MA, AA	7
HLHS {S,D,S}, MS, AA	2
CAVC {S,D,S}, misaligned to the RV	2
DORV {S,D,D}, LV hypoplasia, AS	2
TGA {S,L,L}, DILV, arch hypoplasia	2
TGA {S,D,D}, tricuspid atresia, arch hypoplasia	1

MS, Mitral stenosis; *AS,* aortic stenosis; *MA,* mitral atresia; *AA,* aortic atresia; *CAVC,* complete common atrioventricular canal defect; *RL,* right ventricle; *DORV,* double-outlet right ventricle; *RV,* right ventricle; *DILV,* double-inlet left ventricle; *TGA,* transposition of the great arteries.

sures.[10] Statistical significance of the associations was assessed by use of an F test of the partial sum of squares. The coefficient of determination (R^2) was used to assess the amount of variation in Qp/Qs measurements explained by each of the study variables and tested by use of an F test for the model. Influence of individual data points was sought through serial modeling. Trends in study variables over time were assessed by means of nonparametric methods (Mann-Whitney rank sum test) after dichotomizing the data (0-4 hours vs 24 hours).

Results

Fifty-seven samples were drawn in 24 patients; 10 patients had 3 or more samples drawn. Three (5%)

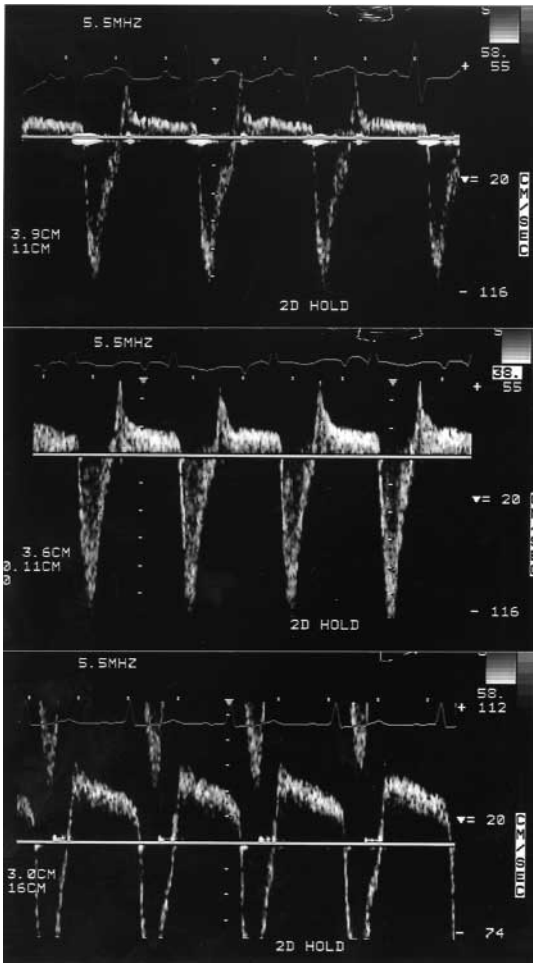

Fig 2. Doppler spectral display of the waveforms generated when sampling in the descending aorta after first-stage palliation for HLHS. Flow below the baseline represents antegrade flow in systole; flow above the baseline represents retrograde flow in diastole. The DFR ratio is calculated by measuring the velocity-time integral of retrograde and antegrade flow done by using planimetrics for the area under each curve and dividing the former by the latter. Three patients are exhibited. The *top panel* demonstrates a small amount of flow reversal, indicating low Qp/Qs; the *middle panel* demonstrates a moderate amount of flow reversal; and the *lower panel* demonstrates a large degree of reversal, indicating high Qp/Qs.

samples were eliminated from the study because of difficulty drawing back from the superior vena cava catheter, resulting in sample clotting. Adequate Doppler echocardiographic images were obtained in the descending aorta in all remaining 54 samples. Complete Doppler echocardiographic spectral data were obtained within 2 minutes of commencing imaging. No patient had coarctation of the reconstructed

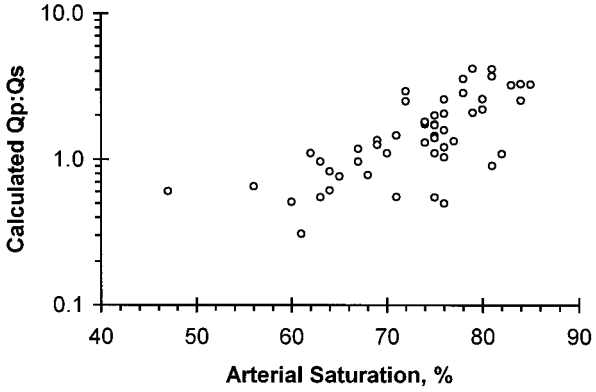

Fig 3. Scatter plot of arterial saturation versus calculated Qp/Qs. The Y axis is shown by using a logarithmic scale.

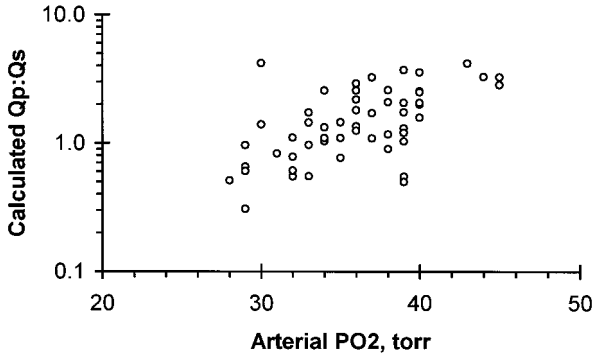

Fig 4. Scatter plot of arterial P_{O_2} versus calculated Qp/Qs ratio. The Y axis is shown by using a logarithmic scale.

Table II. *Medication infusions during the study*

Medication	*No. of samples*	*%*
Dopamine	54	100
Fentanyl	49	91
Vecuronium	36	67
Nitroprusside	16	30
Milrinone	2	4
Dobutamine	1	2

Table III. *Mean values for the 54 samples*

	Mean ± SD	*Range*
Heart rate (beats/min)	147 ± 16	119-184
Systolic blood pressure (mm Hg)	78 ± 11	61-109
Diastolic blood pressure (mm Hg)	37 ± 7	24-56
Arterial P_{O_2} (mm Hg)	36 ± 4	28-45
SVC saturation (%)	39 ± 10	18-64
Arterial saturation (%)	73 ± 8	47-85
Arteriovenous D_{O_2}	35 ± 12	11-52
Qp/Qs	1.7 ± 1	0.3-4.2
Systolic VTI	12.8 ± 5.1	4-25
Diastolic VTI	5.9 ± 2.4	1.6-16
DFR ratio	0.51 ± 0.21	0.19-1.11

SVC, Superior vena cava; *D_{O_2}*, oxygen difference; *VTI*, velocity-time integral.

arch or evidence of turbulent flow. At the time of sampling, all patients were supported by mechanical ventilation and were receiving at least one inotropic medication (Table II). Inspired oxygen ranged from 21% to 100%; more than one half of the samples (28/54) were drawn while patients were receiving 30% or greater inspired oxygen. Six (11%) samples were obtained while patients were receiving 14 mm Hg or more of supplemental inspired carbon dioxide.

The mean values for arterial P_{O_2}, mean superior vena cava saturation, mean arterial saturation, and mean Qp/Qs for all 54 samples are listed in Table III. Because of skewed nonnormal distributions, the calculated Qp/Qs ratio, pulse pressure, superior vena cava saturation, arterial saturation, and DFR ratios were transformed. Although the arterial saturation (Fig 3) was directly related to the calculated Qp/Qs ratio ($P < .01$, $R^2 = 0.84$), the pulse pressure measurements (Fig 4), arterial P_{O_2} (Fig 5), and superior vena cava saturation (Fig 6) were not significantly associated with the systemic flow ratio ($P = .55$, $R^2 = 0.78$; $P = .84$, $R^2 = 0.78$; and $P = .08$, $R^2 = 0.80$, respectively). The DFR ratio explained the most variation in the observed Qp/Qs measurements (Fig 7; $P < .001$, $R^2 = 0.94$).

In the 10 patients for whom there were data on serial assessment, no difference was noted between arterial saturation at 0 to 4 hours and at 24 hours after the operation (77% ± 5% vs 75% ± 3%, $P = .29$). Superior vena cava saturation increased significantly (37% ± 9% vs 48% ± 10%, $P = .02$) and the arteriovenous oxygen difference decreased significantly (41% ± 9% vs 30% ± 10%, $P = .03$) at 24 hours. Although a trend toward a decrease in Qp/Qs was noted within the first 24 hours, this was not statistically significant (2 ± 0.9 vs 1.4 ± 0.5, $P = .07$).

Discussion

Survival after first-stage palliation for HLHS continues to improve; however, early mortality is still one of the highest for any form of congenital heart disease.[11] Death may occur despite a successful surgical reconstruction with a technically good result and is believed to be due in some infants to circulatory maldistribution

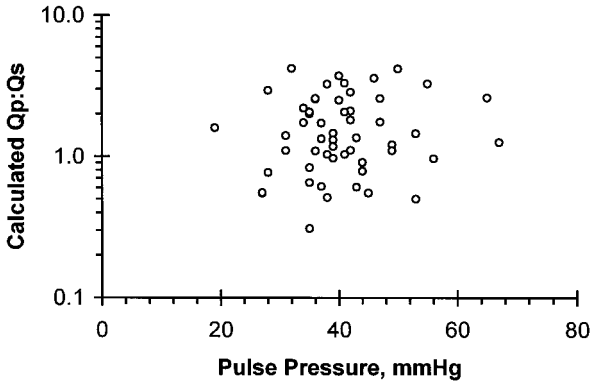

Fig 5. Scatter plot of the pulse pressure versus calculated Qp/Qs. The Y axis is shown by using a logarithmic scale.

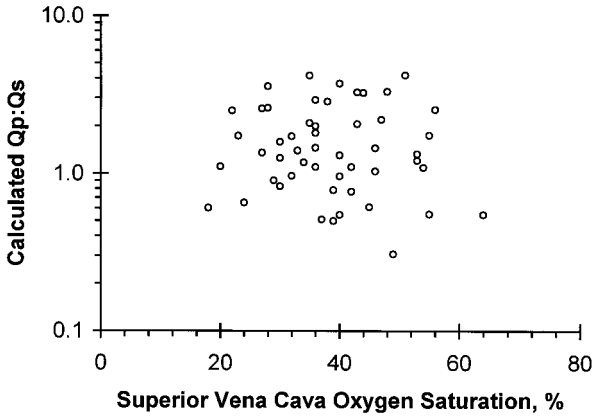

Fig 6. Scatter plot of the superior vena cava saturation versus calculated Qp/Qs ratio. The Y axis is shown by using a logarithmic scale.

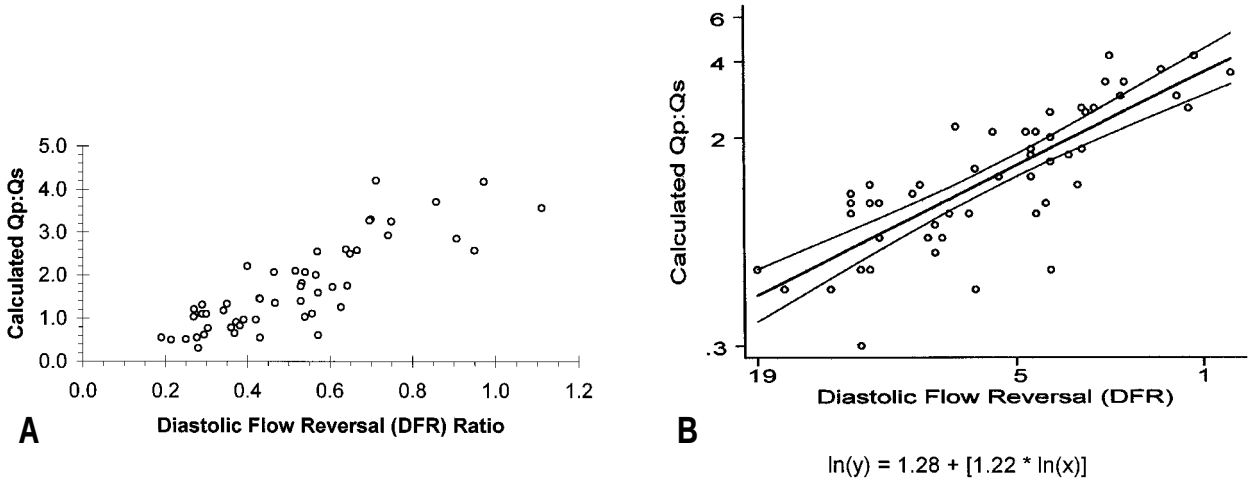

Fig 7. Scatter plots with raw nontransformed data of DFR ratio versus calculated Qp/Qs **(A)** and predicted regression line for natural logarithm of the transformed DFR ratio versus a similarly transformed calculated Qp/Qs **(B)**. Ninety-five percent confidence limits about the predicted line are shown. The natural logarithm scale is used on both the X and Y axes. Natural logarithm equation is provided. A DFR ratio of 0.35 predicts a calculated Qp/Qs of 1:1, and a DFR ratio of less than 0.5 suggests a Qp/Qs of less than 1.5:1.

early after the operation.[1-7] Mathematical analysis with computer-simulated models of blood flow in a circuit of a single ventricle with parallel circulations has shown that oxygen delivery to the tissues is at its maximum if Qp/Qs is less than 1.5:1.[3] Similarly, studies in experimental animal models of single ventricle with parallel circulations have demonstrated that reduction in Qp/Qs results in improved oxygen delivery.[12-14] In the human clinical setting, pharmacologic and ventilatory measures are typically initiated to achieve a target Qp/Qs of approximately 1:1, with the goal to improve systemic flow and maximize oxygen delivery during the early hours after surgery. To make the appropriate management decisions, which will achieve this goal and improve survival, it is necessary to have reliable clinical tools that will correctly assess the circulatory status.

In our study we looked at the utility of conventional laboratory measures in reflecting the Qp/Qs ratio in the clinical setting of infants after first-stage palliation. We found that arterial saturation and arterial Po_2 correlated weakly with the Qp/Qs ratio with a wide range of val-

ues noted in our patients. For example, an arterial saturation of 75%, a value likely to suggest a balanced degree of pulmonary-systemic flow, was present in patients with Qp/Qs ratios ranging from as low as 0.5:1 to as high as 3:1. Arterial P_{O_2} was similar, with a wide spectrum of Qp/Qs ratios noted for any one specific arterial P_{O_2}. We also speculated that the pulse pressure might reflect Qp/Qs, with a wide pulse pressure indicating a large amount of diastolic runoff into the shunt. There was no correlation found between pulse pressure and Qp/Qs, suggesting that other factors beside Qp/Qs influence the magnitude of difference between the systolic and diastolic blood pressures.

Although arterial oxygen saturation is the most commonly used laboratory variable for estimation of Qp/Qs, interpretation of this variable in the setting of a single ventricle with parallel circulations can be confusing. As pulmonary blood flow increases, so does arterial oxygen saturation. However, a rise in arterial oxygen saturation may be either related to a disproportionate degree of pulmonary blood flow relative to systemic flow (high Qp/Qs) with the deleterious consequence of systemic "steal," or it may be due to an increase in pulmonary blood flow with commensurate increase in systemic blood flow secondary to an improving total cardiac output. Conversely, a low arterial saturation may provide a false sense of security in suggesting a low distribution of pulmonary–systemic blood flow, yet the mixed venous saturation may be extremely low in the setting of poor cardiac output and the actual Qp/Qs may be high. Recently, investigators have advocated the monitoring of superior vena cava saturation as a useful adjunct in managing these infants.[6,7] Our data support the previously suggested notion that without knowledge of the mixed venous saturation, arterial oxygen saturation values alone can be deceptive and are not useful indicators of the circulatory status of these infants.

As an adjunct to conventional laboratory variables, we have developed a new clinical tool by using Doppler echocardiography to assess the circulatory status of infants after first-stage palliation for HLHS. The ratio of flow reversal in proportion to forward flow in the descending aorta correlated strongly with the Qp/Qs and was superior to arterial oxygen saturation or arterial P_{O_2} alone. In the absence of an extrinsic stimulus for flow reversal in the reconstructed descending aorta (ie, semilunar valve insufficiency), retrograde flow must obligatorily be due to flow into the aortopulmonary shunt. The degree of flow reversal, which occurs during diastole, is a factor of the resistance ratio between the systemic vascular resistance and the combined resistance of the shunt plus pulmonary vasculature. Hence the time-velocity integral of flow reversal divided by the time-velocity integral of forward flow is a measure of this resistance ratio indexed to forward systemic flow for each beat of the cardiac cycle.

The DFR ratio is noninvasive and obviates the need for placement of an indwelling superior vena cava catheter. The DFR ratio can be useful in providing a clearer picture of the circulatory status of these infants when used in conjunction with the arterial oxygen saturation. For example, at relatively high arterial saturations, a low DFR ratio suggests a low Qp/Qs with good cardiac output, whereas a high DFR ratio would suggest a high Qp/Qs and pulmonary overcirculation. Most important, the DFR ratio can be helpful in clarifying the picture in the presence of a relatively low arterial oxygen saturation, whereby it may be falsely presumed that the circulations are in balance. A high DFR ratio in this scenario would indicate a high Qp/Qs and extremely poor cardiac output, with a very low mixed venous saturation. From our regression line (Fig 7, *B*), a DFR ratio equal to 0.35 predicts a Qp/Qs of 1:1, and a DFR ratio of less than 0.5 suggests a Qp/Qs of less than 1.5:1. These values may hence be used as targets to achieve balance in the Qp/Qs ratio through pharmacologic and ventilatory manipulations.

We observed strikingly low superior vena cava saturations and high arteriovenous oxygen difference values overall in our infants studied, suggesting a very high oxygen extraction rate, which is likely related to poor oxygen delivery. Although we expected to find that superior vena cava saturation would be lowest in the infants with the highest Qp/Qs, surprisingly this was not the case. This suggests that other factors beside circulatory maldistribution and high Qp/Qs are contributing to poor oxygen delivery. Low cardiac output caused by diminished ventricular function may be an important factor and is underestimated in these infants because of the lack of adequate noninvasive measures for assessment of right ventricular performance. Factors such as preoperative presentation and acidosis, preoperative volume load, myocardial protection during surgery, circulatory arrest times, and potential coronary vascular insufficiency may all contribute to poor right ventricular performance after surgery. As previously reported by Rossi and colleagues,[6] we found a significant improvement in superior vena cava saturation and a reduction in the arteriovenous oxygen difference within the first 24 hours after surgery; however,

unlike previous authors, Qp/Qs in our patients improved only slightly. We postulate that ventricular performance is impaired in the early hours after first-stage palliation for HLHS, which improves over the first 24 hours. Ventricular dysfunction and not circulatory maldistribution may therefore be the primary cause for hemodynamic instability in some of these infants. This notion is further supported by the fact that supplemental oxygen did not have a deleterious effect on the hemodynamics of our infants, a finding similar to that noted by Mosca and colleagues.[15] In addition, there was no relationship between the degree of pulmonary overcirculation and survival in our patients. Recently, the use of α antagonists to lower systemic vascular resistance has been advocated to balance the circulations and improve hemodynamics.[16] We suggest that because ventricular function may play an important role, agents that improve myocardial performance, as well as lower systemic vascular resistance, such as phosphodiesterase inhibitors (eg, milrinone), are the optimal drugs to use in these infants.

A number of limitations to our study should be mentioned. First, the DFR ratio is an index that only reflects Qp/Qs and is not a direct measurement of the quantities of pulmonary and systemic flow because systolic flow into the aortopulmonary shunt is not considered in this calculation. Second, the presence of other impetus for flow reversal in the descending aorta, such as aortopulmonary collaterals, coronary-cameral fistulas, or cerebral arteriovenous malformation, may affect the DFR ratio calculation and hence should not be used if these are present. Third, care should be taken in performing the Doppler interrogation at the site of distal anastomosis of the arch reconstruction, with the distal suture line beyond the take-off of the left subclavian artery as a landmark, because more proximal or distal sampling may affect the degree of flow reversal seen. Finally, assumptions have been made concerning the pulmonary venous saturation values. In addition, it is assumed that superior vena cava saturation reflects the true mixed venous saturation in the patients studied.

In summary, we have found that conventional measures of arterial saturation and arterial P_{O_2} may be misleading in assessing the circulatory status in infants after first-stage palliation for HLHS because they are poor predictors of Qp/Qs. Doppler echocardiography, through use of the Doppler flow reversal ratio, is a more useful measure of Qp/Qs and can aid in understanding the complex physiology of these infants.

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