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Validation of the Accuracy of Both Right and Left Ventricular Outflow Volume Determinations and Semiautomated Calculation of Shunt Volumes Through Atrial Septal Defects by Digital Color Doppler Flow Mapping in a Chronic Animal Model

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OBJECTIVES The aim of the present study was to quantitate shunt flow volumes through atrial septal defects (ASDs) in a chronic animal model with surgically created ASDs using a new semiautomated color Doppler flow calculation method (ACM).

BACKGROUND Because pulsed Doppler is cumbersome and often inappropriate for color flow computation, new methods such as ACM are of interest.

METHODS In this study, 13 to 25 weeks after ASDs were surgically created in eight sheep, a total of 24 hemodynamic states were studied at a separate open chest experimental session. Electromagnetic (EM) flow probes and meters were used to provide reference flow volumes as the pulmonary and aortic flow volumes (Q_p and Q_s) and shunt flow volumes (Q_p minus Q_s). Epicardial echocardiographic studies were performed to image the left and right ventricular outflow tract (LVOT and RVOT) forward flow signals. The ACM method digitally integrated spatial and temporal color flow velocity data to provide stroke volumes.

RESULTS Left ventricular outflow tract and RVOT flow volumes obtained by the ACM method agreed well with those obtained by the EM method ($r = 0.96$, mean difference $= 0.78 \pm 1.7$ ml for LVOT and $r = 0.97$, mean difference $= -0.35 \pm 3.6$ ml for RVOT). As a result, shunt flow volumes and Q_p/Q_s by the ACM method agreed well with those obtained by the EM method ($r = 0.96$, mean difference $= -1.1 \pm 3.6$ ml/beat for shunt volumes and $r = 0.95$, mean difference $= -0.11 \pm 0.22$ for Q_p/Q_s).

CONCLUSIONS This animal study, using strictly quantified shunt flow volumes, demonstrated that the ACM method can provide Q_p/Q_s and shunt measurements semiautomatically and noninvasively. (J Am Coll Cardiol 1999;34:587–93) © 1999 by the American College of Cardiology

Ultrasound methods such as M-mode recordings of interventricular septal motion and the size and shape of the right ventricle have been reported to be useful for evaluating right ventricular volume overload in patients with atrial septal defects (ASDs) (1–5). These M-mode and two-dimensional imaging methods are useful for qualitatively judging the existence and degree of right-sided volume overload. However, they do not quantitate ASD shunt flows or pulmonary/systemic flow (Q_p/Q_s) ratios, which may contribute to surgical decision making, especially for older adult patients and in following those having ASDs closed with transcatheter devices. In the 1980s, pulsed Doppler methods which multiply the cross-sectional area of the left and right ventricular outflow tract (LVOT, RVOT) by the velocity–time integral at the center of the outflow tract were introduced to provide Q_s and Q_p and to yield ASD shunt flow estimates as the difference between them (6,7). However, these pulsed Doppler methods assume a flat velocity profile during the entire duration of forward flow and a

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Abbreviations and Acronyms

ACM = automated computation method
ASD = atrial septal defect
LVOT = left ventricular outflow tract
Q_p/Q_s = pulmonary/systemic flow
RVOT = right ventricular outflow tract

constant flow area for both LVOT and RVOT (6–8). These assumptions may not hold true (8–11). In addition, pulsed Doppler methods require cumbersome calculations (6–10). In contrast, a newly developed semiautomatic digital color Doppler method which avoids having to rely on assumptions of a flat velocity profile and a constant flow area has been reported to be accurate for calculating stroke volume and cardiac output (12–14). Because this new method can semiautomatically integrate temporal and spatial velocity assignments across both the LVOT and the RVOT from Doppler echocardiographic flow maps, it should provide shunt flow volumes and Q_p/Q_s less laboriously and more accurately than pulsed Doppler methods.

The aim of the present study was to evaluate the new color Doppler semiautomated calculation method (automated calculation method, ACM) for determining ASD shunt volumes and Q_p/Q_s ratios using a chronic animal model with strictly quantified aortic and pulmonary artery flow volumes.

METHODS

Chronic Animal Study

Eight juvenile sheep weighing 32 to 64 kg (mean 44 ± 14 kg) were studied. Thirteen to 25 weeks (mean 17 weeks) before the hemodynamic and ultrasonic studies that constitute the experimental setting for the present study, an ASD was created by excising under direct vision a portion of the septum 0.5 to 1.5 cm in diameter at the fossa ovale. All operative and animal management procedures were approved by the Animal Care and Use Committee of the National Heart, Lung, and Blood Institute. Preoperative, intraoperative and postoperative animal management and husbandry methods are described in detail elsewhere (15,16).

Electromagnetic flow probe and meter method. An electromagnetic flow probe (model EP455, Carolina Medical Electronics, King, North Carolina) was placed around the pulmonary artery just above the pulmonary valve sinuses. Another electromagnetic flow probe (model EP455, Carolina Medical Electronics) was placed snugly around the skeletonized ascending aorta distal to the coronary ostia and proximal to the brachiocephalic trunk. Both flow probes were connected to flowmeters (model FM501, Carolina Medical Electronics) and these were connected to the same physiologic recorders (ES 2000, Gould, Cleveland, Ohio) used for hemodynamic pressure recordings. All hemodynamic data were recorded at paper speeds of 250 mm/s. Four consecutive cardiac cycles were analyzed for each hemodynamic determination.

Calibration factors for the flow probes were corrected for the animals' hematocrits before each hemodynamic state according to the manufacturer's specification. The integrals of instantaneous flows over time were determined by planimetry of the flow signal recordings. Shunt flow volumes through the ASDs were calculated as the difference between pulmonary and aortic flow volume (Q_p minus Q_s) and the ratio of Q_p/Q_s for each steady state.

After baseline measurements, varying levels of atrial shunting were produced by altering preload or afterload using blood transfusion or angiotensin infusion. The calibrations of the flow probes were readjusted before each individual hemodynamic steady state, compensating for any change in hematocrit produced by insensible fluid loss, blood loss or the alteration of preload by blood transfusion. Insensible fluid loss and associated electrolyte disturbances exacerbated by the open thoracotomy were monitored by frequent (before each individual hemodynamic study) determinations of serum electrolytes and hematocrit; aberrations were avoided by continuous infusion of lactated Ringer's solution and 5% dextrose in water supplemented with potassium and calcium, as necessary. A total of 24 hemodynamic states (2 to 4 per animal) were obtained.

Color Doppler echocardiography. A Toshiba (Tokyo, Japan) Power Vision SSA-380A was used to image the LVOT and RVOT blood flows with a 3.75- or 5-MHZ sector probe. The ultrasound probe was placed directly on the heart near the apex and LVOT images were obtained using apical long-axis views (Fig. 1). The RVOT was imaged in an oblique short-axis view with the transducer placed lightly on the free wall of the right ventricle (Fig. 1). Color gain was adjusted to eliminate random color in areas without flow. The color Doppler filter was selected to deemphasize velocities less than 0.05 to 0.10 m/s. Imaging of both outflow tract flows was performed at aliasing velocities of 0.54 to 0.92 m/s and baseline shifts were used when the automated calculation was performed so as to avoid aliasing (Fig. 1). A narrow color sector was chosen to allow frame rates as high as 32/s so as to maximize the frame rate and image quality.

Automated calculation of flow volumes. For obtaining both LVOT and RVOT flow volumes, a region of interest was positioned in the LVOT and RVOT just distal to the semilunar valves for each flow state as shown in Figure 1.

As shown in Figure 2, within the region of interest for each frame, there existed five sequential velocity profile rows of sample volumes in the depth domain. From each still color Doppler frame, the instantaneous flow rate from each one of the five velocity profiles was calculated by integrating the Doppler interrogated velocity across the flow diameter in digital cine memory, assuming a half-circular symmetrical

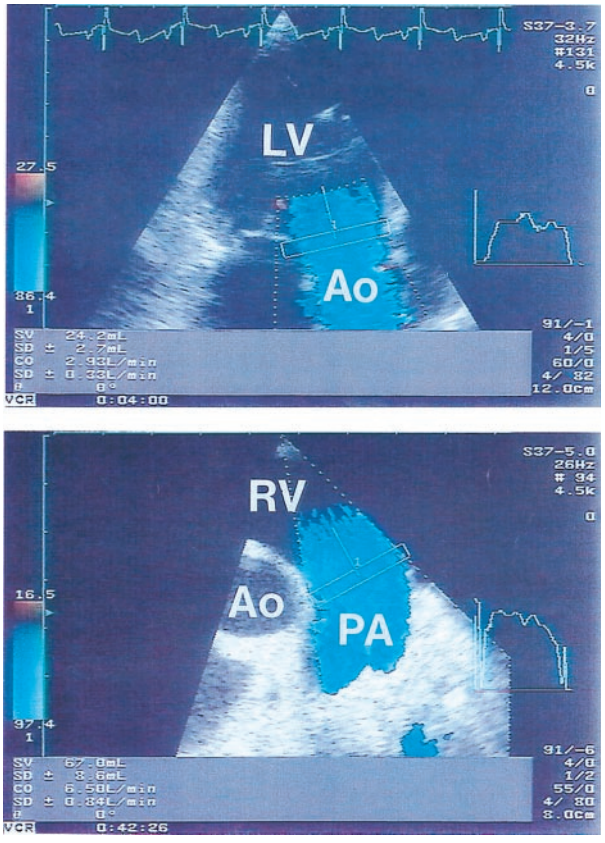

Figure 1. Examples of selected two-dimensional color Doppler images for measurements of forward flow volume in the left ventricular outflow tract (LVOT) **(top)** and right ventricular outflow tract (RVOT) **(bottom)**. Note that the sampling volume is at a depth of 3.5 cm for the RVOT, but it is almost 8 cm from the apex in the LVOT view. Ao = aorta; LV = left ventricle; PA = pulmonary artery; RV = right ventricle.

flow distribution for each radius from the center of the flow. As seen in Figure 2, the actual flow rate (Q) is equal to the product of the velocity of the flow (V), which is parallel to the direction of the vessel, times the area (S) which is the area of flow perpendicular to the vessel. This flow rate is also equal to the product of color Doppler–determined velocity ($V_{Doppler}$ = Vcosø) and the corresponding area of flow ($S_{Doppler}$ = S/cosø) perpendicular to the Doppler-determined velocity; flow rate calculated by using Doppler-determined velocities = Vcosø S/cosø = V S = Q. Note from Figure 2 that any obliquity to the flow direction increases flow cross-sectional area in proportion to the decrease in computed velocity. However, the system used only one axial dimension (r), assuming a circular flow area (actually a half circle for each radius from the center of the flow), whereas the actual area of flow imaged with this degree of obliquity is oval shaped. Thus, the flow measurement would still need to be corrected for the angle between the flow direction and the Doppler interrogation when the angle is >20° to 30°. In this particular study, however, angle correction was not necessary because of the optimal alignment of the Doppler imaging of both LVOT and RVOT (Fig. 1). The five different flow rates from the five sequential velocity profile rows in the depth domain within the region of interest of each frame were then averaged to determine the representative flow rate for that still frame.

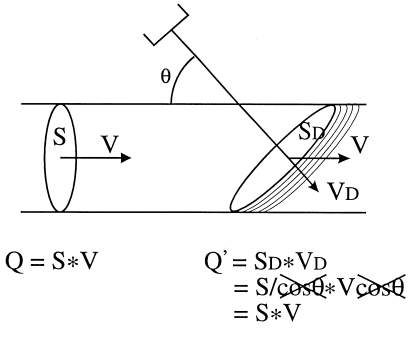

Figure 2. Schema of the principle for calculating actual flow rate (Q = V × S) using Doppler-imaged flow velocity in a region of interest. Note that obliquity decreases velocities by a cosine function but increases areas by the same function. Five parallel velocity interrogations in a region of interest were averaged by the ultrasound system (see text). S = area, S_D = Doppler area, V = velocity, V_D = Doppler velocity.

This computer-assisted method also accounts for temporal changes in flow area during the period of flow. The calculation of the flow rate described above was performed consecutively for each frame during the systolic time of flow. These flow rates during the selected systole were then added together and multiplied by the time interval of each frame to obtain the ejection volume during that particular systole (12).

Results of the calculations of flow volumes/beat and volumes/minute with standard deviations were automatically displayed by the system, as was the velocity profile (Fig. 1). An average of 7.8 frames (range from 6 to 13 frames) per systole for the LVOT and 8.6 frames (range from 7 to 14 frames) for the RVOT were available based on a mean heart rate of 97 per minute. All the measurements in animals were performed at end expiration. Four determinations for both LVOT and RVOT flow volumes at each hemodynamic state were obtained and averaged. Atrial septal defect shunt flow volumes/beat were calculated by subtracting LVOT flow volumes/beat from RVOT flow volumes/beat and Q_p/Q_s as a ratio of RVOT to LVOT flows. These were compared with the four electromagnetic flows for the aorta and pulmonary artery obtained during ultrasound imaging of these same beats.

Both shunt flow volumes/beat and Q_p/Q_s determined by ACM were compared with corresponding reference data obtained by the electromagnetic flowmeter method.

Initial Clinical Study

For eight patients undergoing surgical repair of isolated secundum ASDs (age 5.6 ± 8.1 years, weight 16.7 ± 12 kg) intraoperative transesophageal echocardiography was performed using multiplane and/or biplane 5-MHz transduc-

ers. Before ASD closure, color flows through the RVOT and the LVOT were imaged and Q_p and Q_s were measured using the same technique as for the animal study. Flow through the ASD was also imaged and directly measured using ACM. The flow volumes through the ASDs and Q_p minus Q_s obtained by ACM were compared with each other.

Interobserver variability. To evaluate the effect of variability on the measurement of shunt flow volumes and Q_p/Q_s, 10 randomly selected flow conditions were scanned and then analyzed with the same ultrasound system by two independent observers who set up the system and performed the scan, each without knowledge of images selected by the other observer or the results obtained by the other observer or the flowmeter data.

Statistical analysis. Data are presented as mean values ± SD. Because multiple points were used from the same animal, multiple regression analyses were used to examine relationships within sheep between the electromagnetically determined shunt flow volumes and Q_p/Q_s and those calculated by the new echocardiographic method. Statistical significance was defined as a value of $p < 0.05$. To do this, we created the data matrix in the spread sheet of a statistical computer program (Stat View 1988, Abacus Concepts Berkeley, California) using dummy variables as columns to encode the different sheep and used the multiple regression function of Stat View (17). The agreement between the electromagnetically determined shunt flow volumes and Q_p/Q_s and those calculated by echocardiography were tested according to the method of Bland and Altman (18).

RESULTS

Chronic Animal Study

Shunt flow volumes and Q_p/Q_s. Electromagnetic flowmeter–based LVOT and RVOT systolic ejection flow volumes ranged from 8 to 34 ml/beat and from 18 to 75 ml/beat, respectively. Two out of the eight sheep had little or no ASD shunt flow (0.0 to 5.0 ml/beat) determined by the electromagnetic flowmeter method due to tissue contracture or atrial compliance alterations. In the remaining six sheep, ASD shunt flow volumes obtained by the electromagnetic flowmeters were clinically relevant for simple ASDs ranging from 13 ml/beat to 48 ml/beat (average 21 ± 14 ml/beat). Pulmonary/systemic flow ratios ranged from 1.5 to 3.3 (average 2.3 ± 0.72). Heart rates ranged from 84 to 125/min (average 97 ± 23/min).

Estimation of shunt flow volumes and Q_p/Q_s. Left ventricular outflow tract and RVOT flow volumes obtained by ACM agreed well with those obtained by the electromagnetic flowmeter method ($r = 0.96$, mean difference = 0.78 ± 1.7 ml for LVOT and $r = 0.97$, mean difference = −0.35 ± 3.6 ml for RVOT, Fig. 3). As a result, both shunt flow volumes and Q_p/Q_s by ACM agreed well with those

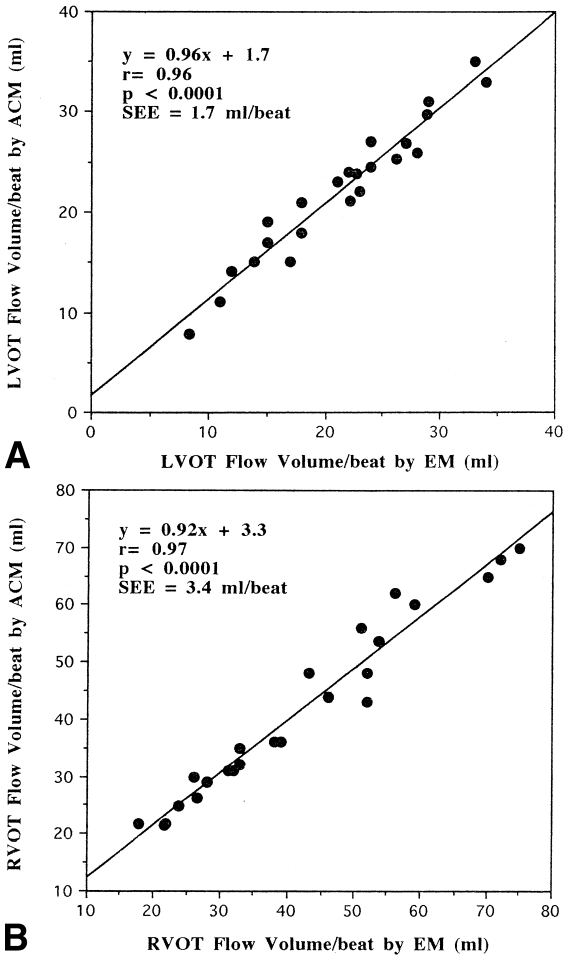

Figure 3. (A) Linear regression analyses between forward flow volumes through the left ventricular outflow tract (LVOT) obtained by the electromagnetic flowmeters (EM) and those obtained by the new digital method (ACM). **(B)** Linear regression analyses between forward flow volumes through the right ventricular outflow tract (RVOT) obtained by EM and those obtained by ACM. SEE = standard error of estimate.

obtained by the electromagnetic flowmeters ($r = 0.96$, mean difference = −1.1 ± 3.6 ml/beat for shunt volume and $r = 0.95$, mean difference = −0.11 ± 0.22 for Q_p/Q_s, Fig. 4).

For the two sheep with no shunt, the LVOT flow by ACM ranged from 15.6 ml to 36.9 ml/beat (mean = 25.2 ± 7.4 ml/beat) and the RVOT flow by ACM from 16.0 to 39.2 ml/beat (mean = 26.4 ± 8.1 ml/beat). There was an excellent correlation and agreement between them ($r = 0.94$, mean difference = −0.4 ± 2.9 ml/beat).

Initial Clinical Study

In eight patients with ASDs, before closure Q_p and Q_s ranged from 14.5 to 65 ml/beat and from 8 to 25 ml/beat, respectively. There was a good correlation ($r = 0.96$; $p < 0.0001$) and agreement (mean difference = 0.1 ± 4.5 ml/beat) between the directly measured shunt flow volumes through the ASDs and Q_p minus Q_s as shown in Figure 5, demonstrating the clinical applicability of this new

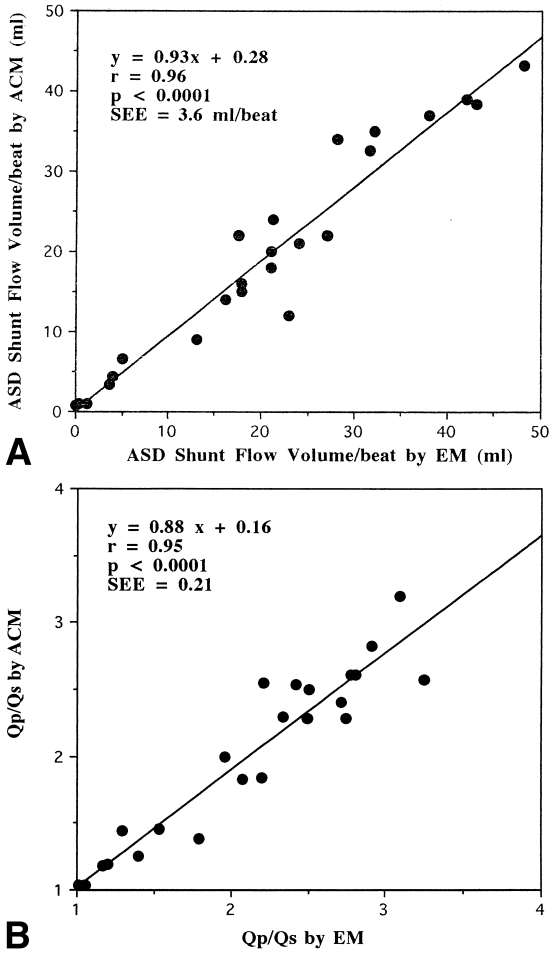

Figure 4. Linear regression analyses of shunt flow volumes through atrial septal defects (ASDs) **(A)** and pulmonary/systemic flow (Q_p/Q_s) ratios **(B),** comparing the electromagnetic flowmeter method (EM) to the new digital semiautomatic method (ACM). SEE = standard error of estimate.

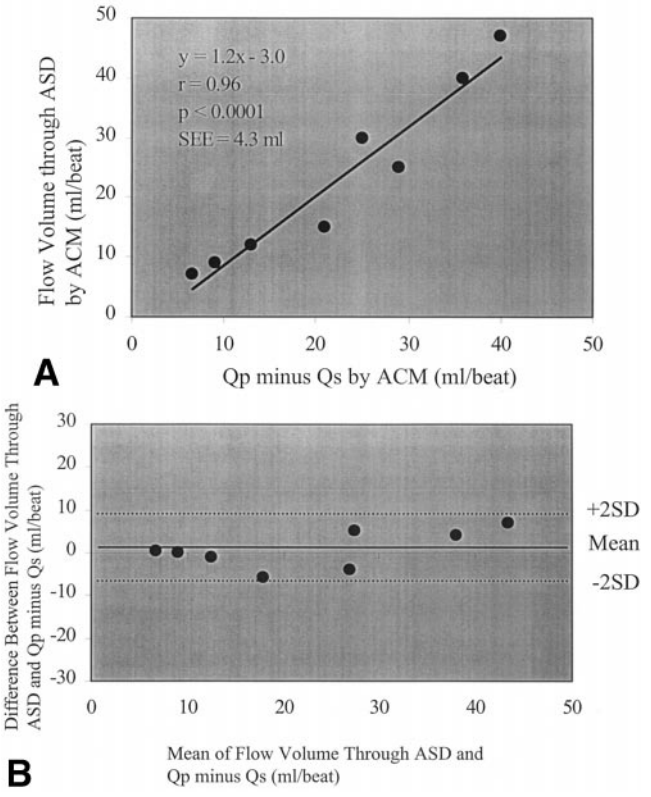

Figure 5. (A) Linear regression analyses of shunt flow volumes through atrial septal defects (ASDs) and pulmonary minus systemic flow (Q_p minus Q_s) in patients obtained by the new digital semiautomatic method (ACM). **(B)** Agreements for flow volumes through ASDs and Q_p minus Q_s obtained by ACM examined according to the method of Bland and Altman (18). SEE = standard error of estimate.

computer-assisted method. Postoperatively for this group, Q_p/Q_s was a mean of 1.06 ± 0.32.

Observer variability. There was also excellent agreement between the two independent observers' measurements of shunt volumes and Q_p/Q_s using the new digital color Doppler method (r = 0.95, mean difference = 2.5 ± 3.4 ml and r = 0.91, mean difference = 0.13 ± 2.5, respectively).

DISCUSSION

In the present study, using strictly quantified ASD shunt flow volumes in a chronic animal model, the determination of both ASD shunt volumes and Q_p/Q_s by ACM appeared to be reliable. It also was shown to be clinically applicable.

Previous echo studies of ASDs. Several noninvasive methods have been reported to be useful for studying patients with ASDs (1–5). Pulsed Doppler methods were introduced in the 1980s to provide quantitative information about ASD shunt flow volumes. These pulsed Doppler methods for evaluating ASD shunt flows may be divided into two major categories: direct measurement of ASD shunt flow and indirect measurement by subtraction of systemic from pulmonic flow (Q_p minus Q_s). When biplane color Doppler transesophageal imaging became available, ASDs could be imaged even in adults and the area estimated using geometric assumptions about the shape of the defect (19,20). This ASD area was multiplied by the velocity time integral of the central velocity through the defect to obtain the shunt flow volume (19,20). Alternatively, subcostal or right parasternal approaches have been proposed for imaging ASDs for direct determination of ASD shunt flow volumes (21). On the other hand, Valdes-Cruz et al. and Kitabatake et al. reported success using the indirect subtraction (i.e., Q_p minus Q_s) method for evaluating ASD shunt flows and Q_p/Q_s (6,7). In both direct and indirect pulsed Doppler methods, however, the velocity is measured only at the center of the defect or the great arteries assuming both a flat velocity profile and a constant flow area during the period of flow. This may not hold true, especially for ASD shunt flows and RVOT flows (9,11). The earlier studies, except that of Valdes-Cruz et al., used cardiac catheterization reference standards for evaluating

shunt flows employing Fick-determined Q_p/Q_s, which may not always be reliable (7,20,21). These conventional pulsed Doppler methods are also time-consuming to apply clinically and therefore have not been used widely.

Advantages of the new semiautomated method. The ACM method we used for the animal study is an indirect subtraction (Q_p minus Q_s) method. On the basis of our clinical experience, this indirect method has an important advantage over direct ASD computation methods. Direct methods apply only for geometrically simple ASDs, being difficult to apply to sinus venous, primum or multiple defects, whereas the indirect method is capable of determining the magnitude of shunts for any type of ASD without requiring transesophageal imaging or assumptions about the defect's shape.

Compared with previously described indirect pulsed Doppler methods, the new color Doppler method has two major advantages. First, conventional pulsed Doppler methods use just the modal spectral velocity from a centrally placed sample volume, whereas the ACM method uses all of the velocity assignments across the flow diameter (115 points/line $\times$ 5 lines/region of interest = 575 points/frame). This computer-assisted method also accounts for temporal changes in flow area during the period of flow. Second, with the ACM method, cumbersome manual measurements of flow area and tracing of spectral velocity profiles are not necessary.

Our animal study provides separate validation of LVOT and RVOT flow calculations compared with electromagnetic flowmeter readings, a quality of validation for this method previously unavailable. In addition, RVOT flow computation requires different considerations regarding views, vessel expansion and flow profile from LVOT flow computation and has not been previously reported for this new method. For patients without shunts, these determinations can serve as internal validations of the application of the ACM method for noninvasive determinations of cardiac output.

Limitations of the study and of the method. In addition to the inherent limitations of experimental studies which we have discussed previously (22,23), ACM assumes axisymmetric flow, that is, velocity information from one diameter is assumed to be representative of the entire flow area velocity. In both the LVOT and the RVOT, skewed forward velocity profiles have been described (24–29). However, it is likely that averaging over the entire axial flow velocity field cancels out the overestimation from one radius and the underestimation from another radius for both LVOT and RVOT flows. In fact, we have on occasion used two orthogonal imaging planes for both LVOT and RVOT, obtaining very similar results with each of the two orthogonal views, as Sun et al. have reported for LVOT flows (14). The electromagnetic flow method assumes an axisymmetric flow profile. Although in vitro studies have shown that nonaxisymmetric flow may introduce errors up to 15% in instantaneous flow rates, eccentric flow does not necessarily render flow rates determined from electromagnetic flow devices unreliable (30).

Because this digital method requires nonaliased color flow signals, high velocity flows that alias multiple times and turbulent flows that alias cannot be measured by this method. Also, even with parallel processing, to allocate Doppler interrogation lines sufficient to maximize velocity accuracy, the frame rates available are limited. In addition, several technical factors affect the flow volume measurement by ACM, including color gain setting, wall filter, transmission frequency and depth of the region of interest (14,30). Although optimal settings and visual standards of "color fill" developed in these studies could be obtained in our animal model even at depths of 7 to 8 cm from the apex, similar quality images may not be obtainable in larger or adult patients. However, our intraoperative transesophageal echo study with this method has shown that the LVOT and RVOT flows can be measured in patients. Thus, both the experimental study and the initial clinical experiences with this ACM method are encouraging, showing promise for obtaining accurate noninvasive estimation of ASD shunt flow volumes and Q_p/Q_s in patients.

Conclusions. This study demonstrates that the ACM method, when compared with strictly quantified electromagnetic flow data, provides reliable quantitative information about ASD shunt volumes and Q_p/Q_s.

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