EXPERIMENTAL STUDIES


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Objectives. The aim of the present study was to validate a digital color Doppler–based centerline velocity/distance acceleration profile method for evaluating the severity of aortic regurgitation.

Background. Clinical and in vivo experimental applications of the flow convergence axial centerline velocity/distance profile method have recently been used to estimate regurgitant flow rates and regurgitant volumes in the presence of mitral regurgitation.

Methods. In six sheep, a total of 19 hemodynamic states were obtained pharmacologically 14 weeks after the original operation in which a portion of the aortic noncoronary (n = 3) or right coronary (n = 3) leaflet was excised to produce aortic regurgitation. Echocardiographic studies were performed to obtain complete proximal axial flow acceleration velocity/distance profiles during the time of peak regurgitant flow (usually early in diastole) for each hemodynamic state. For each steady state, the severity of aortic regurgitation was assessed by measurement of the magnitude of the regurgitant flow volume/beat, regurgitant fraction and instantaneous regurgitant flow rates determined by using both aortic and pulmonary artery electromagnetic flow probes.

Results. Grade I regurgitation (regurgitant volume/beat <15 ml, six conditions), grade II regurgitation (regurgitant volume/beat between 16 ml and 30 ml, five conditions) and grade III-IV regurgitation (regurgitant volume/beat >30 ml, eight conditions) were clearly separated by using the color Doppler centerline velocity/distance profile domain technique. Additionally, an equation for correlating “a” (the coefficient from the multiplicative curve fit for the velocity/distance relation) with the peak regurgitant flow rates (Q [liters/rain]) was derived showing a high correlation between calculated peak flow rates by the color Doppler method and the actual peak flow rates (Q = 13a + 1.0, r = 0.95, p < 0.0001, SEE = 0.76 liters/min).

Conclusions. This study, using quantified aortic regurgitation, demonstrates that the flow convergence axial centerline velocity/distance acceleration profile method can be used to evaluate the severity of aortic regurgitation.

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pulmonary bypass. During this procedure the free edge of the right coronary cusp (three sheep) or the noncoronary cusp (three sheep) of the aortic valve was excised under direct vision. 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 (17). Postoperatively during recovery the sheep received maintenance dosages of digoxin and furosemide.

At the time of experimental study when the sheep were returned to the laboratory, anesthesia was induced with intravenous sodium pentobarbital (25 mg/kg body weight) and maintained with 1% to 2% isoflurane with oxygen; the animals were ventilated by means of an endotracheal tube using a volume-cycle ventilator. Repeat thoracotomy was performed.

Cardiac catheterization and electromagnetic flow meters. A Swan-Ganz catheter was positioned in the main pulmonary artery from the femoral vein. Another catheter was positioned in the right common femoral artery for monitoring systemic arterial pressure and arterial blood gases. These catheters were interfaced with a physiologic recorder (ES 2000, Gould Inc.) using fluid-filled pressure transducers (model PD23 ID, Gould Statham). Arterial blood gases and pH were maintained within physiologic ranges. A bilateral transverse thoracotomy was performed. After dissection two electromagnetic flow probes (model EP455, Carolina Medical Electronics, Inc.) were placed, one around the pulmonary artery just above the pulmonary valve sinuses and one fitting snugly around the skeletonized ascending aorta distal to the coronary ostia and proximal to the brachiocephalic trunk. Both flow probes were connected to flow meters (model FM501, Carolina Medical Electronics, Inc.) that were connected to the same physiologic recorders (ES 2000) used for hemodynamic pressure recordings. Aortic and left ventricular pressures were obtained from intracavitary manometer-tipped catheters (model SPC-350, Millar Instruments, Inc.) positioned transmurally. 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 before each hemodynamic state for measured hematocrit according to the manufacturer’s specification. The problem of the zero baseline drift was managed as follows. The pulmonary artery flow zero-level baseline was adjusted according to the contour of its electromagnetic flow probe signal; this baseline was reconfirmed by occlusive zeros. No sheep had physiologically important pulmonary regurgitation. Then the baseline for the aortic flow recording was adjusted until the forward minus the backward aortic flow volumes equaled the pulmonary forward flow volume. This method ignores coronary artery flow runoff. Coronary artery blood flow during ventricular diastole was measured in three sheep in a preliminary study. The coronary flow rate was small (0.13 to 0.23 liters/min). These values were similar to those reported by others (8) in studies of aortic regurgitation and thus were considered to be negligible compared to the regurgitant volumes delineated in this study. The correlation coefficient for the regression of pulmonary forward flow versus aortic forward minus aortic regurgitant flow was 0.98 (SEE = 0.03 liters/min). Regurgitant fraction was calculated as backward aortic flow volume/min divided by forward aortic flow volume/min. Once the curves for pulmonary and aortic flow were properly adjusted instantaneous regurgitant flow rates could be obtained. Regurgitant volume/beat, the integral of the instantaneous regurgitant flow rates during diastole, was obtained by planimetry of the regurgitant flow signal recordings.

A hydrostatic standard was used for calibration of all pressure recordings. Left ventricular and aortic pressures were recorded simultaneously. All hemodynamic recordings were performed simultaneously with the echocardiographic studies. After baseline measurements were obtained, various degrees of severity of aortic regurgitation were produced by altering preload or afterload, or both, using blood transfusion or angiotensin infusion alone or in combination. 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 electrolyte and hematocrit; aberrations were avoided by continuous infusions of lactated Ringer solution and 5% dextrose in water supplemented with potassium and calcium, as necessary. A total of 22 stable hemodynamic states (3 to 4/sheep) were obtained.

Color Doppler echocardiography. Color Doppler flow mapping was performed with a Vingmed 775 system (Vingmed Sound, AS, Horten, Norway) by using a 5-MHz transducer placed directly near the apex of the heart. Scanning was accomplished at a pulse repetition frequency of 4.0 to 6.0 kHz. Color gain was adjusted to eliminate random color in areas without flow. The MTI filter was selected with a rolloff to deemphasize velocities less than 0.08 to 0.16 m/s. Aliasing velocities of 0.44 to 0.94 m/s were selected for the initial imaging of the flow convergence. Two-dimensional and M-mode color flow images from this system could be directly transferred into a Macintosh IICi computer (Apple Computer, Inc.) because the Vingmed 775 system is equipped with a digital output port allowing transfer of color Doppler data in their original digital format without conversion into analog format. The initial aliasing velocity could be changed by postprocessing software (EchoDisp, Vingmed Sound) in the computer system after the raw digital velocity data were transferred into the microcomputer.

The aortic regurgitant orifice was determined as the connection of the flow convergence and the turbulent regurgitant jet zones as identified by using two-dimensional color Doppler imaging, i.e., the vena contracta (Fig. 1). In positioning the M-mode cursor, care was taken to locate the orifice precisely by using magnification of the image. Because the epicardial
Figure 1. Example of two-dimensional flow convergence imaging in chronic aortic regurgitation. The connection of the flow convergence to the turbulent regurgitant jet (vena contracta) was defined as the position of the aortic regurgitant orifice. AO = aorta; LV = left ventricle.

Figure 2. Top, Color M-mode recording showing temporal changes in the aortic regurgitant flow convergence. Bottom, Centerline velocity/distance acceleration profile from the region of interest (white rectangle in M-mode recording). Digital output of velocity/distance data at three consecutive time periods (0.005 s apart in time) were postprocessed, and the complete axial centerline profile was developed. The velocity/distance acceleration curve toward the aortic regurgitant orifice from bottom to top on the color image (from red through a blue alias) showed organized acceleration fields with highly significant correlations using multiplicative regression fits: \( y = 0.37 \times x^{(-1.59)} \), \( R = 0.99365 \). ECG = electrocardiogram; other abbreviations as in Figure 1.

Hydraulic theoretic background of the centerline velocity/distance relation and use of multiplicative fit model. For nonviscid flow toward a pinpoint regurgitant orifice, according to the continuity principle, flow rate \( Q \) through the orifice is equal to the flow rate through any of the proximal isovelocity surfaces. This flow may be calculated from the product of the isovelocity surface area, which for an idealized hemisphere = \( 2\pi r^2 \) and its corresponding velocity \( V \). Thus,

\[
Q = 2\pi r^2 \cdot V, \tag{1}
\]

where \( Q \) is in ml/s, \( r \) in cm and \( V \) in cm/s. Then, the velocity at any proximal point \( r \) may be obtained by solving equation 1 for \( V \) to yield equation 2:

\[
V = \frac{Q}{2\pi \cdot r^2}, \tag{2}
\]

Substituting the coefficient "a" for \( Q/2\pi \) and "b" for the exponent 2 yields equation 3:

\[
V = a \cdot r^{-b}. \tag{3}
\]
Thus, “a” will increase with Q. For nonidealized hydrodynamic conditions such as occur in vivo, other factors including surrounding geometry of the orifice and fluid viscosity may modify this relation (13,15). This model is not able to describe the velocity/distance relation accurately in the very near proximity to (<2 mm) or within the orifice itself. Otherwise, velocity/distance profiles appear to fit closely to this multiplicative model in previously published in vitro and in vivo studies (13–16).

Interobserver variability. To evaluate the effect of observer variability on the axial centerline velocity/distance profiles of aortic regurgitant flow convergence, 10 randomly selected hemodynamic conditions were analyzed at different times with the same computer by two independent observers, each without knowledge of the results obtained by others or the electromagnetic flow data. Both the grading of regurgitant severity determined by the centerline profiles and the calculated peak flow rates using the coefficient “a” derived from the multiplicative curve fit determined by these observers were compared.

Statistical analysis. Data are presented as mean value ± SD. The correlation between continuous variable data was determined by linear regression analysis. Simple regression analysis was used to examine the relation between the peak regurgitant flow rate and the coefficient “a” derived from the centerline profile multiplicative curve fit. Quantified peak flow rates were compared with those obtained by the electromagnetic flow meters by using correlation and simple regression analysis; agreement between the two measurements was tested according to the method of Bland and Altman (18). In addition, because multiple points were obtained in the same animals, a multivariate regression analysis was used to examine the relation of data between sheep. We created the design matrix in a spreadsheet of a statistical computer program (Stat View 1988, Abacus Concepts, Inc.) by using dummy variables as columns to encode the different sheep (19) and used the multiple regression function of Stat View. A value of p < 0.05 was considered statistically significant.

Results

In three studies of individual hemodynamic states (one with grade I and two with grade III-IV regurgitation), color Doppler images were not of adequate quality to obtain precise flow convergence centerline velocity/distance profiles. Therefore, these three hemodynamic states were excluded from analysis.

Severity of aortic regurgitation. Aortic regurgitant volumes and regurgitant fractions were within a clinically relevant range from 7.0 to 48 ml/beat (average 25 ± 12) and from 23% to 78% (average 53 ± 17%), respectively. Peak and mean regurgitant flow rates were also within a clinically relevant range from 1.8 to 9.8 liters/min (average 5.2 ± 2.5) and from 0.7 to 4.1 liters/min (average 2.4 ± 1.2), respectively.

Grading of severity of aortic regurgitation determined by the electromagnetic flow meters. Severity of aortic regurgitation was classified as grade I when regurgitant volume/beat was <15 ml (the peak regurgitant flow rate was <2.5 liters/min [six conditions, two sheep]), as grade II when regurgitant volume/beat was between 16 ml and 30 ml (the peak regurgitant flow rate was 2.5 to 6.0 liters/min [five conditions, four sheep]) and grade III-IV when regurgitant volume/beat was >30 ml (the peak regurgitant flow rate was >6.0 liters/min [eight conditions, four sheep]).

Relation between the centerline velocity/distance profile and severity of aortic regurgitation. The individual acceleration fields were described by velocity (ordinate, m/s) plotted against distance from the regurgitant orifice (abscissa, cm). All of the velocity/distance curves had highly significant correlations using multiplicative regression fits; y = ax−b, where y = centerline velocity and x = distance from the regurgitant orifice; r = 0.94 to 0.99; all p < 0.01, SEE = 0.012 to 0.041 m/s. The coefficients “a” ranged from 0.037 to 0.54 and the exponent “b” ranged from 0.31 to 1.90.

The coefficient “a” correlated well with regurgitant volumes/beat and peak regurgitant flow rates (r = 0.87 and r = 0.95, both p < 0.0001). The equation for correlating “a” (a coefficient of multiplicative curve fit) with the peak regurgitant flow rates (Q [liters/min]) as derived from simple regression analysis (Q = 13a + 1.0) provided calculated peak flow rates that were closely related to the actual peak flow rates as shown in Figure 3 (r = 0.95, p < 0.0001, SEE = 0.76 liters/min). The regression model to yield peak flow rates also allowed us to calculate regurgitant volume/beat by multiplying this number by a factor derived from the mean to peak continuous wave velocity ratios and diastolic flow time, which correlated well when compared with electromagnetic reference values in this series (r = 0.91, p = 0.0001, SEE = 4.6 ml/beat). Even when multiple regression analysis was used to account for multiple points within the same sheep, a significant relation still existed between the calculated and actual peak flow rates (r = 0.80, p < 0.0001, SEE = 0.96 liters/min).

All of the centerline velocity/distance profiles for grade III-IV regurgitation traversed a domain encompassed by velocities >0.6 m/s at distances from the orifices >0.70 cm and the profiles for grade I regurgitation resided in a domain encompassed by velocities <0.4 m/s at distances from the orifices <0.5 cm. The profiles for grade II regurgitation resided in a domain between these other two zones (Fig. 4).

Interobserver variability. Selection and processing of the original digital color M-mode tracings performed by two independent observers revealed very similar axial centerline velocity/distance profiles, resulting in the same grading of severity in all of the 10 randomly selected hemodynamic conditions (3 grade I, 3 grade II and 4 grade III-IV). As a result, there was excellent interobserver agreement regarding the calculated peak regurgitant flow rates with an equation using the coefficient “a” derived from simple regression analysis. (r = 0.98, SEE = 0.04 liters/min, mean percent difference = 4.8%).
This study demonstrates applicability of a color Doppler flow convergence based centerline velocity/distance acceleration profile method for determining severity of aortic regurgitation.

**Previous studies and the centerline method.** Several non-invasive methods have been reported (1–10) to be useful for judging the severity of aortic regurgitation. When patients with aortic regurgitation are examined by echocardiography, several observations including color Doppler jet area size, proximal jet width measurements (and its ratio to left ventricular outflow tract size), regurgitant flow velocity deceleration pattern and pressure half-time of continuous wave Doppler study, and diastolic reversal of flow in the descending aorta have been used to estimate the severity of aortic regurgitation (1–6,8–10). However, reliability of these methods has never been validated by using truly quantitative reference standards. Those involving color Doppler may be affected by hemodynamic and instrument settings. For example, jet eccentricity as well as color Doppler filter settings may affect the results of color jet area methods (19–22). Left ventricular diastolic function and compliance may affect the continuous wave deceleration patterns and pressure half-times; the geometry of the aortic regurgitant orifice may affect the size of the proximal jet width (5,23). Reversal flow in the descending aorta is at best an indirect observation related to the severity of aortic regurgitation (10).

Initially Giesler et al. (13,14), and later our laboratory (15,16), described flow convergence centerline velocity/distance methods for evaluating the severity of mitral regurgitation. These methods directly reflect the regurgitant flow rates quantitatively and are not affected by instrument factors such as gain and aliasing velocity settings. In one of our previous studies (16), we found this method effective and practical for judging the severity of mitral regurgitation by using a centerline velocity/distance domain map. In the present study on chronic aortic regurgitation, we found similar results by using the centerline domain map to evaluate the regurgitant severity although separation points were different. When compared with the centerline profiles for mitral regurgitation, those for aortic regurgitation showed a slight rightward and upward shift (toward higher velocities at shorter distances) at smaller regurgitant flow rates. This difference in the flow convergence centerline velocity/distance profile position between mitral and aortic regurgitation may be related to the differing geometry of surrounding valve structures adjacent to walls or other cardiac structures around the regurgitant orifice and the level and timing of pressure differences across the two valves during regurgitation. Constraint of convergent flow toward the aortic regurgitant orifice may be the more dominant determinant of this difference. Postmortem observations of the mitral and aortic regurgitant orifices in our studies suggested constraint by leaflet and aortic sinus tissues for the aortic accelerating convergence flow field. Also, in preliminary in vitro pulsatile flow studies, we observed rightward and upward shifts of the centerline profiles for a trileaflet aortic regurgitant valve model as compared with that for a mitral prolapsed orifice model at the same peak regurgitant flow rate. Three-dimensional reconstruction of the aortic and mitral leaflet geometry surrounding the regurgitant orifices and the spatial distribution of their corresponding acceleration flows should be helpful in clarifying this difference (24).

**Clinical importance of the centerline methods compared with other flow convergence methods.** Imaging of the proximal flow acceleration zone or convergence region toward a regurgitant orifice has been reported to be useful for identifying the site of regurgitation and for grading its severity by using simplified geometric assumptions of hemispherical isovelocity flow convergence surfaces (25–34). However, a serious problem of the quantitative flow convergence method using the simple hemispheric isovelocity surface assumption (or any other geometric assumption) is that the shapes of the flow
convergence surface imaged by Doppler color flow mapping are affected by the angle between the Doppler interrogation and the actual direction of accelerated blood flow. Because of this angle dependency, any geometric assumption of the isovelocity surface may cause problems with underestimation or overestimation of actual flow rates. Even when the isovelocity surface shape appears to be a hemisphere in a certain view, the entire three-dimensional contour of the actual surface may not be so. For larger but still restrictive orifices like those in mitral stenosis, we have encountered flattened hemiellipsoid shapes of the isovelocity surfaces. In a model of mitral stenosis, we (35) observed substantial underestimation of transmitral inflow rates and effective orifice areas even when we used the hemielliptic isovelocity surface model with orthogonal axial measurements. In contrast to the geometric isovelocity surface flow convergence methods, the centerline flow convergence method is free from Doppler angle problems because only axial velocity/distance data are used. The centerline method's use of a continuous set of data points instead of one spatial velocity data point results in increased accuracy for determining flow information. Therefore, aspects of the centerline velocity/distance method appear to be more reproducible than those of the previously described geometric methods. With further clarification of geometric boundary constraints on centerline acceleration profiles for the aortic valve, both the domain map application and quantitative estimation of regurgitant flow rates using the coefficient "a" derived from multiplicative curve fits could potentially provide information on grading of aortic regurgitation in clinical studies.

With the flow convergence centerline method, in contrast to the geometric isovelocity surface assumption method, a wide variety of aliasing velocities may be used to obtain clear images of the flow convergence. In clinical settings, this ability may prove quite valuable because one usually selects lower aliasing velocities for mild regurgitation to obtain clear images of the flow convergence and higher aliasing velocities for severe regurgitation. Therefore, it is very likely that clinically useful aliasing velocities will result in points that will allow the centerline velocity/distance profiles to fit within a domain. Once one or two points of the centerline velocity profiles are obtained in a domain, the severity of aortic regurgitation (i.e., with a range of peak regurgitant flow rates or regurgitant volumes/beat) can be determined even if the entire centerline profiles cannot be obtained. In the absence of automated computation for acquiring the centerline velocity/distance profiles in clinical settings, this simple approach may provide rapid assessment of the severity of regurgitation. On follow-up evaluations, changes in the position of the centerline profiles may be helpful to identify changes in severity of the aortic regurgitation.

**Study limitations.** For determining the centerline velocity/distance profile it is critical to locate the precise position of the regurgitant orifice and sample a true radial line for flow toward the orifice. In our study because the epicardial position of the transducer minimized the effect of translational movement of the heart and provided images of very high resolution, we were able to locate and follow the orifice by using the center of the two-dimensional flow convergence and the aortic leaflet position, directing the color M-mode cursor accordingly. Under clinical conditions, such alignment may not be possible in some patients with aortic regurgitation. In our animal study, routine clinically used apical views rarely provided good flow convergence images. However, atypical or more basally located positions of the transducer usually did demonstrate good flow convergence images. With the flow convergence centerline method, in contrast to the geometric isovelocity surface assumption method, a wide variety of aliasing velocities may be used to obtain clear images of the flow convergence. In clinical settings, this ability may prove quite valuable because one usually selects lower aliasing velocities for mild regurgitation to obtain clear images of the flow convergence and higher aliasing velocities for severe regurgitation. Therefore, it is very likely that clinically useful aliasing velocities will result in points that will allow the centerline velocity/distance profiles to fit within a domain. Once one or two points of the centerline velocity profiles are obtained in a domain, the severity of aortic regurgitation (i.e., with a range of peak regurgitant flow rates or regurgitant volumes/beat) can be determined even if the entire centerline profiles cannot be obtained. In the absence of automated computation for acquiring the centerline velocity/distance profiles in clinical settings, this simple approach may provide rapid assessment of the severity of regurgitation. On follow-up evaluations, changes in the position of the centerline profiles may be helpful to identify changes in severity of the aortic regurgitation.

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which are associated with the axial centerline velocity/distance profiles as quantitative indicators of regurgitant severity, were separated without overlap when we chose this grading system. A primary purpose of our study was to demonstrate the applicability of a “domain” grading classification for evaluating the severity of aortic regurgitation independent of the hemispheric assumption. This purpose was achieved when we chose this grading system.

As a final limitation, the only etiology of aortic regurgitation that we investigated was that due to incised aortic valve leaflets with shortening at the free edge; however, this etiology is clinically relevant because one frequently encounters patients with a rolled and shortened leaflet edge. In our study, the regurgitant jet was directed from the central leaflet coaptation toward the anterior mitral leaflet or the interventricular septum, a condition similar to that commonly observed clinically. The centerline method does appear to be applicable to this geometrically complex form of regurgitant orifice. However, before the method is applied to lesions with other types of aortic regurgitant orifice geometry, including lesions due to bicuspid aortic valves and rheumatic aortic valve disease, the relation of the centerline velocity/distance profile to regurgitant flow rates may need to be modified.

Conclusions. This study, using quantified aortic regurgitation, demonstrates that the flow convergence axial centerline velocity/distance acceleration profile method can be used to evaluate the severity of aortic regurgitation.

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References


