A new approach to noninvasive evaluation of aortic regurgitant fraction by two-dimensional Doppler echocardiography

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ABSTRACT The aortic regurgitant fraction was estimated noninvasively in 20 patients with aortic regurgitation from systolic aortic and pulmonary volume flow determined by duplex Doppler echocardiography. By assuming that an excess of the aortic volume flow (AF) compared with the pulmonary volume flow (PF) is due to aortic regurgitant flow, the aortic regurgitant fraction (RF) was calculated as follows: RF(%) = (AF - PF)/AF × 100. The aortic and pulmonary volume flows were determined as products of systolic integrals of ejection flow velocities and cross-sectional areas of the left and right ventricular outflow tracts, respectively. The Doppler estimate of the regurgitant fraction was compared by semiquantitative grading (1+ to 4+) by cineaortography and with the measurement of regurgitant fraction by catheter technique. The mean Doppler-determined aortic regurgitant fraction was 2.4% for normal subjects, 28.0% for the patients with 1+, 32.6% for the patients with 2+, 53.3% for the patients with 3+, and 62.4% for the patients with 4+. A fair correlation was found between Doppler estimates of regurgitant fraction and semiquantitative cineaortographic grades (r = .80, p < .01). In the patients without associated mitral regurgitation, a close correlation was observed between Doppler and catheter estimates of regurgitant fraction (r = .96, p < .01; y = 1.0x - 0.08). In the patients with associated mild mitral regurgitation, however, Doppler estimates of regurgitant fraction substantially underestimated those determined by the conventional catheter technique, which cannot separately quantify the aortic regurgitant fraction in the presence of mitral regurgitation. These observations indicate that the proposed Doppler technique provides a useful method to evaluate the aortic regurgitant fraction specifically regardless of the presence of associated mitral lesions.


A PULSED DOPPLER technique has been used to evaluate semiquantitatively the severity of aortic regurgitation based on the extent of the distribution of the flow disturbances in the left ventricle.1-5 Although this method is simple in clinical use, some problems have been identified in its use in the assessment of severity in the presence of other pathologic lesions. On the other hand, previous studies have demonstrated the clinical utility of the Doppler technique in investigating aortic flow velocity patterns for the quantitative evaluation of the severity of aortic regurgitation.6-8

However, these investigations were based only on the planimetric analysis of the aortic flow velocity traces, not on the actual measurement of the regurgitant flow volume, so that their results would suffer from several practical problems such as the differences in cross-sectional area between systole and diastole and loss of blood flow to the brain, upper extremities, and coronary arteries.7

Recent studies have demonstrated the accuracy and reliability of two-dimensional Doppler echocardiography in measuring aortic and pulmonary flow under normal circulatory conditions9-11 and even in the presence of intracardiac or extracardiac shunt.12-15 Because the Doppler technique provides net forward flow volume through the valves, Doppler measurement of the systolic aortic flow in the presence of aortic regurgitation is thought to be the sum of effective forward and
regurgitant flow, whereas that of the systolic pulmonary flow equals only the effective forward flow.

This study was designed to estimate the aortic regurgitant fraction from the Doppler measurements of systolic aortic and pulmonary flows by assuming that an excess of the aortic flow compared with the pulmonary flow is caused by aortic regurgitant flow. The accuracy and clinical utility of Doppler estimates of regurgitant fraction were examined by comparing them with catheter measurements and cineangiographic grades of regurgitation.

Material and methods

Study population. The study population comprised 20 patients with chronic aortic regurgitation either isolated or in association with other valvular abnormalities (13 male and seven female patients, ages 14 to 75 years, mean 42) who underwent diagnostic cardiac catheterization. Ten normal subjects (eight men and two women, ages 37 to 59 years, mean 49) served as control subjects. All patients met the following criteria: (1) the presence of aortic regurgitation of any origin confirmed by a cineangiogram, (2) left ventriculograms of good quality (the difference in heart rate during cineangiography and Doppler examination was within 10 beats/min), (3) the absence of intracardiac or extracardiac shunt lesions and absence of significant mitral regurgitation (more than 1+ by Sellers classification) and pulmonary regurgitation (regurgitant signal detected more than 1 cm from the pulmonary valve in the right ventricular outflow tract by the Doppler examination), and (4) absence of aortic stenosis (all patients had transvalvular gradients less than 10 mm Hg).

The distribution of valvular diseases was as follows: 10 patients with isolated aortic regurgitation, seven with associated mild mitral regurgitation, one with associated mild mitral and pulmonary regurgitation, one with associated mitral stenosis-insufficiency and pulmonary regurgitation, and one with associated pulmonary and tricuspid regurgitation. The interval between the cardiac catheterization and Doppler examination was within 24 hr in 12 patients, within 1 week in four, within 1 month in two, and within 6 months in two. The clinical status of these patients did not change during the interval.

Apparatus. We used a duplex Doppler echocardiograph (either Hitachi EUB-10B or Toshiba SDS-21A with SSH-40A). Two-dimensional echocardiographic images, M mode echocardiographic tracings, and Doppler-determined flow velocity data were obtained with the same transducer array (2.5 MHz for EUB-10B and 2.4 MHz for SDS-21A). Any cursor line could be interrogated for Doppler recording and simultaneous M mode echocardiography. The Doppler sample volume could be positioned at any depth along the cursor line, which permitted the precise location of the sample volume on the two-dimensional echocardiographic image. The sample volume was a cylinder with a diameter of 3 mm and a length of 2 mm at a depth of 7.5 cm for the EUB-10B and with a diameter of 5 mm and a length of 2 mm at a depth of 10 cm for SDS-21A. In Doppler mode, for the former, the pulse repetition rate was 5.4 kHz for sampling at a depth within 12 cm; for the latter, the pulse repetition rate was 6 kHz for sampling at a depth within 12 cm and 4 kHz for a depth between 12 and 18 cm. In measuring blood flow parallel to the Doppler beam, the maximum detectable velocity within the Nyquist limit is 81 cm/sec for the former, 96 cm/sec within a depth of less than 12 cm, and 64 cm/sec for a depth between 12 and 18 cm for the latter. Doppler signals derived from the structures were minimized by a high-pass filter of 200 Hz. All sampled signals were analyzed in real time by the chirp-Z transform for the EUB-10B and by the fast-Fourier transform for the SDS-21A and were simultaneously displayed at a paper speed of 100 cm/sec on a strip chart recorder along with lead II of the electrocardiogram and phonocardiogram.

A continuous-wave Doppler device was also used in five patients (Sonocolor CD, Carolina Medical Electronics Inc.). Doppler sampling was performed with a 2.5 MHz interrogation frequency. The device allowed the detection of a maximum velocity of 6.0 m/sec. The quadrature Doppler signals were processed by the fast-Fourier transform; a 200 Hz filter was used to minimize the contamination of lower velocities from the cardiac structures. Doppler frequency outputs and simultaneous lead II electrocardiogram were recorded on a video recorder.

Doppler protocol

Measurements in the right ventricular outflow tract. Each patient rested in a supine position and breathed in a relaxed manner during Doppler examination. The transducer was placed in the third intercostal space on the right sternal border and was aimed to depict the long-axis view of the right ventricular outflow tract (figure 1, A). When a suitable image was achieved, the Doppler sample volume was positioned at the center of the pulmonary orifice and the ejection flow velocity was recorded. The Doppler incident angle and the orifice diameter were measured from a two-dimensional echocardiographic image gated in midsystole. The Doppler incident angle was measured as an angle of Doppler beam against the long axis of the structure of the outflow tract. In the measurement of the orifice diameter, we asked the patient to rest in a left decubitus position so as to obtain the echocardiogram on which the pulmonary orifice was depicted as parallel to the ultrasound beam as possible (figure 1, A) and the orifice diameter was measured as a distance between inner borders.

Measurements in the left ventricular outflow tract. The transducer was placed on the cardiac apex and was aimed medially and superiorly to depict the left ventricular outflow tract on the left anterior oblique equivalent view (figure 1, B). The sample volume was positioned at the center of the aortic orifice and ejection flow velocity was recorded. When we encountered frequency aliasing, in which Doppler shift was greater than a half of pulse repetition frequency, we tried to record total Doppler shifts within a pulse repetition frequency by increasing the Doppler incident angle against the flow direction; therefore, the part of waveform exhibiting aliasing was successfully depicted without overlapping with the part of waveform under the baseline (figure 2, A). The Doppler incident angle was determined as an angle of Doppler beam against the long axis of the outflow tract on the midsystolic gated frozen image. The aortic orifice was measured as an inner diameter on the midsystolic gated frozen image of the parasternal long-axis view of the left ventricle.

In five patients, left ventricular ejection flow velocity was also measured with a continuous-wave Doppler technique and was compared with that obtained by the pulsed Doppler technique for examining the reliability of measuring the high flow velocity from the ambiguous waveform. The transducer was placed on the cardiac apex and was angulated medially and superiorly until maximum velocity was identified by listening to the audio outputs and by observing the Doppler outputs on the color monitor. The maximum velocity was identified by the highest and most uniform pitch of audio signals.

Analysis of Doppler recordings

Reconstruction of total Doppler waveform from ambiguous spectrum. Although all Doppler shifts of the right ventricular ejection flow were always within the Nyquist frequency, those of the left ventricular ejection flow exceeded the Nyquist fre-
frequency in 18 of 20 patients. In these patients, the flow deflection began with directional character, extending inferiorly as a tapering waveform, being cut off at the negative Nyquist frequency with the top of the waveform exhibiting aliasing, and appearing from the positive Nyquist frequency, as if in the opposite direction (figure 2). We obtained the total waveform of the Doppler shifts by taking the higher part and putting it on the flat top of the lower spectrum. The feasibility of this procedure has been theoretically confirmed by Hale et al.\textsuperscript{16} and Stevenson et al.\textsuperscript{17}

The reliability and accuracy of this procedure was examined by comparing the reconstructed waveform with the paired recording of the unambiguous waveform by the continuous-wave technique in five patients (figures 2 and 3). The shapes of these two waveforms were similar. Figure 3 shows the comparison of peak flow velocities (A) and systolic velocity integrals (B) between these two waveforms. Good coincidence was observed both in peak velocities and in systolic velocity integrals between the two. These results indicate that we can reliably obtain the total waveform of the Doppler shifts even from the ambiguous waveform by summing positive and negative velocity components. We then applied this procedure in the remaining 13 patients who underwent only pulsed Doppler examination.

Doppler estimation of regurgitant fraction. Right and left ventricular stroke volumes (RSV and LSV) were obtained as products of semilunar orifice areas and systolic integrals of angle-corrected flow velocity according to the following equations:

\[
R(L)SV = \pi (D/2)^2 \times \int_{Ee}^{Es} Vmax(t) dt
\]

\[
Vmax(t) = fd \times c/(2 \times fo \times \cos0)
\]

where \(Es \) = start of ejection, \(Ee \) = end of ejection, \(D \) = diameter of the pulmonary or aortic orifice, \(fd \) = Doppler shift frequency, \(fo \) = carrier frequency, \(c \) = sound velocity in biological material (1500 m/sec), \(0 \) = Doppler incident angle against the flow direction, and \(Vmax(t) \) = instantaneous maximum blood flow velocity.

Systolic velocity integral was obtained as an area under the envelope of the native or reconstructed Doppler spectrum with a digitizer (Cardio 80, Kontron Co., Ltd.). Correction for the Doppler incident angle was performed when the angle was greater than 20 degrees. Both right and left ventricular stroke volumes were obtained as averages of five to seven consecutive cardiac cycles. By regarding the right ventricular stroke volume as an effective forward output and the left as a total forward output, the regurgitant fraction was determined as the ratio of the difference between the left and right ventricular stroke volumes against the left ventricular stroke volume:

\[
\text{regurgitant fraction (\%)} = \frac{(LSV - RSV)}{LSV} \times 100.
\]

To test the reliability of this method, we randomly selected 10 patients from the 20 and calculated the regurgitant fraction by one observer on two occasions (intraobserver variability). Another observer independently performed the determination for the same 10 patients (interobserver variability). The observers were blinded to each other’s results as well as to the results of cardiac catheterization. Mean absolute differences between observations (expressed as a percentage of the first observer’s first observation) were 4.5% (intraobserver) and 7.6% (interobserver).

Catheterization. All patients underwent diagnostic right and left heart catheterization, left ventriculography, and cineangiography. Effective forward cardiac output was measured by the thermodilution method before the administration of the contrast materials. Left ventricular volumes were determined from the right anterior oblique projection of the single-plane left ventriculogram by the area-length method. The regurgitant fraction was calculated as the ratio of the difference between angiographic left ventricular output and forward output against the angiographic output. Cineangiographic findings were graded on a 1+ to 4+ scale on the following findings: 1+ = slight

FIGURE 1. Measurements of flow velocity and diameter in the right (A) and left (B) ventricular outflow tracts in a patient with aortic regurgitation. The Doppler beam and the sample volume are shown as a white cursor line and a white dot on the line, respectively, on the midsystolic gated frozen images (upper left panels of A and B), from which the Doppler incident angle against the flow vector is determined. The diameter of the pulmonary orifice is axially measured as an interval between inner walls (solid white line in the upper right panel of A). The diameter of the aortic orifice is measured from a midsystolic gated frozen image of the parasternal view of the left ventricle. Bottom panels of A and B are Doppler recordings obtained. Ao = aorta; ECG = lead II electrocardiogram; LV = left ventricle; PA = pulmonary artery; PCG = phonocardiogram; RV = right ventricle; SV = Doppler sample volume.
opacification of the left ventricle clearing completely in one cycle, 2+ = moderate opacification of the left ventricle not completely clearing in one cycle but without progressive opacification, 3+ = progressive opacification of the left ventricle over three or more cycles, 4+ = total opacification of the left ventricle within one or two cycles.

Statistical analysis. All results were described as mean ± SD. The Doppler estimate of regurgitant fraction was compared with the cineangiographic grade in the patients with the aortic regurgitation. The significance of the differences found among mean values was assessed with an analysis of variance and Student’s t test. The estimates of regurgitant fraction by the Doppler and catheter techniques were compared by linear regression analysis.

Results

Doppler estimates of regurgitant fraction in normal subjects. In 10 normal subjects, the calculated value for the Doppler estimate of regurgitant fraction was 2.4 ± 5.0% and always less than 10%. These data demonstrate that the Doppler estimates of regurgitant fraction approximate zero in normal subjects and the upper limit of the normal range for these Doppler estimates is about 10%.

Comparison with semiquantitative angiography in patients with aortic regurgitation. In the patients with aortic regurgitation, Doppler estimates of regurgitant fraction were significantly greater than those for normal subjects (p < .01) and were greater than 10%. The relationship of the semiquantitative cineangiographic grades to the Doppler estimates of regurgitant fraction is shown in figure 4. The Doppler estimate of regurgitant fraction was 28.0 ± 9.2% in two patients with 1+, 32.6 ± 10.0% in four patients with 2+, 53.3 ± 8.6% in 10 patients with 3+, and 62.4 ± 5.5% in four patients with 4+ regurgitation. Even though there was significant overlap among different groups, the regurgitant fraction tended to increase with higher grade of severity (r = .80, p < .01). The regurgitant fraction for the patients with 3+ and 4+ regurgitation was significantly greater than that for patients with 2+ and 1+ regurgitation (p < .05).

Comparison of regurgitant fractions measured by Doppler and catheter techniques. Doppler estimates of regurgitant fraction were compared with those obtained by left ventriculography and the thermodilution method (figure 5). On the whole, a fair correlation was found
between these two variables with a correlation coefficient of .94 ($p < .01$; $y = 1.0x + 4.1$). If the patients with associated mitral regurgitation were excluded, a close correlation was demonstrated between these two measurements ($r = .96$, $p < .01$; $y = 1.0x - 0.08$) and a good coincidence was found between the two variables especially in the higher range. On the other hand, although the correlation was significant, catheter measurements of the regurgitant fraction in the patients with associated mild mitral regurgitation tended to substantially overestimate the Doppler estimates ($r = .93$, $p < .01$; $y = 0.84x + 15.5$). The differences between Doppler- and catheter-determined regurgitant fractions would reflect the contribution of the mitral regurgitant flow, which cannot be differentiated from aortic regurgitant flow by a conventional catheter method.

Discussion

The unique feature of this study was that the aortic regurgitant fraction was determined noninvasively from the Doppler measurements of the aortic and pulmonary flows by assuming that an excess of the aortic flow compared with pulmonary flow is caused by the regurgitant flow in the presence of aortic regurgitation. Our results indicate that this quantitative Doppler method provides a specific and accurate estimation of the aortic regurgitant fraction.

In measuring flow velocity by a pulsed Doppler

FIGURE 3. Comparison of peak flow velocity (left) and systolic velocity integrals (right) of the reconstructed and unambiguous Doppler waveforms. Good coincidence was observed both in peak velocities and in systolic velocity integrals between these two waveforms.

FIGURE 4. Comparison of Doppler estimates of regurgitant fraction (RF) with cineoartographic grades. In normal subjects, the Doppler-determined regurgitant fraction approximated zero, whereas the values for the patients with aortic regurgitation (AR) were significantly greater than those for normal subjects (N). Although there was variation in the values for the regurgitant fraction within each group, the regurgitant fraction increased with higher grade of the severity ($r = .80$, $p < .01$).

FIGURE 5. Doppler estimates of regurgitant fraction (RF) plotted against those obtained by catheter technique. A fair correlation was found between the two variables with a correlation coefficient of .94. A close correlation was found between the two variables in the patients without mitral regurgitation (MR) ($r = .96$, $p < .01$; $y = 1.0x - 0.08$). On the other hand, in the patients with associated mild mitral regurgitation, catheter measurements substantially overestimated the regurgitant fraction compared with Doppler estimates ($r = .93$, $p < .01$; $y = 0.84x + 15.5$). AR = aortic regurgitation.
technique, the frequency aliasing has been thought to be one of the factors that might obscure the accurate recognition of the total flow velocity pattern and it was recommended that the Doppler shifts be recorded within the Nyquist limit. In this study, however, we could not record the left ventricular ejection flow velocity within the Nyquist limit in 18 of 20 patients with aortic regurgitation. When the transmitted frequency is fixed, maximal detectable velocity within the Nyquist frequency is proportional to the pulse repetition frequency, which is inversely proportional to the sampling depth because of the finite transit time of the pulsed signal. In the patients with aortic regurgitation, Doppler recordings of the left ventricular ejection flow velocity often suffer from the frequency aliasing phenomenon because of the augmented flow velocity due to the increase in total forward output and because of the deep location of the sample volume due to the dilated left ventricle. Even when the frequency aliasing was observed, we could successfully obtain the total Doppler wave form by summing the positive and negative velocity components, as Hatle et al.\textsuperscript{16} and Stevenson et al.\textsuperscript{17} suggested. This procedure can be reliably performed only when the flow deflection is directional and the continuity of the envelope of the positive and negative waveform is easily recognizable. In this study, we examined the reliability of this reconstruction procedure by comparing the reconstructed total waveform of the left ventricular ejection flow velocity with the corresponding unambiguous waveform by the continuous-wave technique in five patients with aortic regurgitation. Good coincidence was found both in peak velocities and in systolic velocity integrals between these two waveforms. These results indicate that we can determine the total waveform of the Doppler shift even from the ambiguous waveform with high reliability. When a Doppler device with an electronic zero shifter is available, this reconstruction process is performed automatically.

In the patients with isolated aortic regurgitation, a close correlation was found between Doppler- and catheter-determined regurgitant fractions. Especially in the higher range of regurgitant fraction, Doppler estimates agreed closely with catheter measurements. These results indicate that our proposed Doppler method allows the accurate quantitation of regurgitant fraction in the patients with mild-to-severe aortic regurgitation. However, in the patients with associated mild mitral regurgitation, catheter measurements of regurgitant fraction substantially overestimated those determined by Doppler method. Hunt et al.\textsuperscript{18} demonstrated that any conventional catheter procedure cannot separately quantify the amount of mitral regurgitant flow from that of aortic regurgitant flow, since both aortic and mitral regurgitation contributed to the regurgitant flow, which is obtained as the difference between angiographic output and that by the thermodilution method. In the present Doppler method, the aortic regurgitant flow was estimated as the difference between Doppler measurements of the aortic and pulmonary flows, so that it would not be affected by the presence of associated mitral regurgitation. Thus the proposed Doppler technique provides a novel and specific means of estimating the aortic regurgitant fraction regardless of the presence of associated mitral regurgitation. The differences between Doppler- and catheter-determined regurgitant fractions in the patients with associated mitral regurgitation would reflect the extent of the contribution of mitral regurgitation to the total regurgitant fraction by the catheter method.

The Doppler estimates of regurgitant fraction for normal subjects never exceeded 10%, which seemed to be the upper limit of the normal range, whereas those for the patients with aortic regurgitation were significantly greater than those for the normal subjects. In comparison with cineangiographic grades, although the Doppler estimates of regurgitant fraction increased progressively with increasing degrees of aortic regurgitation, some overlapping occurred in the range of those values in each cineaortographic grade of regurgitation. The Doppler estimates of regurgitant fraction for the patients with 3+ and 4+ regurgitation were significantly greater than those for the patients with 2+ and 1+, whereas no significant difference was found between those values for patients with 1+ and 2+ nor for patients with 3+ and 4+ regurgitation. The cineaortographic grading is semiquantitative and dependent on the visual inspection, so that it may be influenced not only by the amount of regurgitation but also by other factors, such as the size and the contractile function of the left ventricle and the presence or absence of mitral regurgitation.\textsuperscript{18-20} Even if the amount of regurgitation were the same, the low contractile state of the left ventricle and concomitant mitral regurgitation might lead to the long persistence of regurgitated contrast material in the chamber, which would lead to the overestimation in the severity of the cineaortographic grade.

Limitations. Outflow obstructions, intracardiac or extracardiac shunts, and pulmonary regurgitation limit the use of this pulsed Doppler method. Extreme high velocity and associated flow disturbances caused by stenotic lesion introduce difficulties in the recognition of true velocity deflection by a pulsed Doppler tech-
nique. A continuous-wave Doppler technique may have the potential to overcome this limitation. Pulmonary regurgitation is also thought to modify the Doppler estimates of regurgitant fraction according to the severity of regurgitation, since Doppler measurement of pulmonary flow is not effective but total forward flow through the pulmonary valve. The results of our previous study demonstrated that the mild pulmonary regurgitation, in which the regurgitant flow signals are detected within 1 cm from the pulmonary valve in the right ventricular outflow tract, did not cause a significant error in the quantitation of the pulmonary to systemic flow ratio in the patients with atrial septal defects.\(^{15}\) In this study, three of 20 patients had mild pulmonary regurgitation revealed by the additional Doppler examination, in whom significant discrepancy was not found between Doppler- and catheter-determined regurgitant fractions. Intracardiac or extracardiac shunts also limit the use of this technique, since a shunt lesion itself causes the unequal Doppler measurements of pulmonary and aortic flow. Thus the presence or absence of shunt lesions should be evaluated with additional and careful Doppler and echocardiographic examinations before the application of this proposed Doppler technique.

**Conclusion.** Our proposed Doppler method provides the accurate estimation of regurgitant fraction in patients with aortic regurgitation. This technique is noninvasive and can be performed repeatedly without deleterious effects, so that it may be promising in the initial screening examination, the assessment of serial changes in hemodynamics, and the evaluation of the response to drugs and surgical interventions.

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**References**

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