A Doppler–two-dimensional echocardiographic method for quantitation of mitral regurgitation


ABSTRACT A noninvasive method to accurately quantitate the severity of mitral insufficiency would be of major clinical value. In theory, in the absence of confounding variables, regurgitant mitral flow should represent the difference between forward mitral blood flow and aortic blood flow. Since Doppler–two-dimensional echocardiographic (D2DE) methods for measuring transvalvular mitral and aortic flow have been validated, it should be possible to use mitral and aortic flows derived by this method to calculate regurgitant mitral flow. To assess the validity and accuracy of this combined approach for quantitation of regurgitant flow, we developed an open-chest canine preparation in which we could simulate, vary, and accurately measure degrees of mitral regurgitation. Seven animals were anesthetized and prepared to allow controlled right heart output. Mitral regurgitation was then simulated by placing a flexible conduit incorporating a one-way valve and electromagnetic flowmeter between the left ventricular apex and left atrium. Flow through the tube (effective mitral regurgitation) was varied between 0.2 and 1.8 liters/min and forward cardiac output ranged between 0.5 and 4 liters/min. Transmitral and transaortic flows were calculated by previously reported Doppler methods. Doppler-derived estimates of forward flow through the aortic valve correlated well with the flow measured by flowmeter (r = .92), and regurgitant flow and regurgitant fraction calculated by the D2DE approach also compared well with those measured by flowmeter (r = .84 and .83, respectively). This study demonstrates that mitral regurgitant flow and regurgitant fraction calculated by the D2DE method provide an acceptable measure of both absolute regurgitant flow and the regurgitant fraction in the experimental setting.


AN ASSESSMENT of the severity of mitral regurgitation is often important in the management of patients with mitral valvular disease. The degree of mitral regurgitation may be gauged angiographically with the use of the degree of left atrial opacification, as suggested by Sellers et al. Unfortunately, this approach is subject to considerable interobserver variability and the inherent qualitative nature of the data makes it difficult to assess changes in the degree of mitral regurgitation over time. The more rigorous Sandler-Dodge method, in which the regurgitant volume is calculated as the difference between the angiographic left ventricular output and forward cardiac output by the thermodilution, Fick, or dye-dilution technique is thus usually used to provide quantitative information. The accuracy of this approach, however, is limited by the nonsimultaneous acquisition of the angiographic and forward cardiac outputs, the errors inherent in each of the cardiac output measurements, and the presence of associated regurgitant lesions and arrhythmias. Finally, both the Sandler-Dodge and Sellers methods may provide somewhat misleading information in that changes in loading conditions and contractility induced by the catheterization procedure may lead to underestimation or overestimation of the basal severity of the lesion.

Several noninvasive techniques for assessing mitral regurgitation have also been reported. With M mode and cross-sectional echocardiography, the presence of regurgitation may be inferred from a large left ventricle and atrium, in association with abnormalities of mitral valve structure and/or function. An increased left-to-right ventricular stroke volume ratio on the radionuclide angiogram is suggestive of left-sided valvular
insufficiency. More recently, Doppler echocardiographic assessment of the spatial extent of systolic frequency dispersion within the left atrium has been shown to provide a semiquantitative measure of the severity of mitral regurgitation. Although use of these methods has the advantages of being noninvasive and providing information about function in the basal state, none provide truly quantitative data. Thus, to date, there is no completely satisfactory means, invasive or noninvasive, of quantitating mitral insufficiency.

Combined Doppler–two-dimensional echocardiographic (D2DE) techniques for measuring flows at specific points within the heart have recently been validated and the relationship of Doppler-derived systemic and pulmonic flows has been successfully used to quantitate intracardiac shunting. Since regurgitant flow through the mitral valve theoretically equals the difference between forward mitral and aortic flows, it should, likewise, be possible to calculate regurgitant volume as the difference between the Doppler–two-dimensional echocardiographically calculated flows through these valves.

The purpose of this study was to test the validity of this combined D2DE approach to the quantitation of mitral regurgitation with use of an open-chest canine preparation of mitral insufficiency in which both forward cardiac output and mitral regurgitant flow could be precisely controlled.

**Methods**

**Experimental preparation.** To create a preparation of effective mitral regurgitation, a preparation of controlled right heart cardiac output previously employed in our laboratory was modified by the addition of a valved conduit between the left ventricle and left atrium.

Seven mongrel dogs weighing 16 to 23 kg were studied. The dogs were anesthetized with sodium pentobarbital (35 mg/kg) and mechanically ventilated with a pressure-cycled respirator (Bird Corporation, Palm Springs, CA). The chest was opened through a midline sternotomy, and the heart suspended in a pericardial cradle. The superior and inferior vena cavae were cannulated to collect systemic venous return, and then severed proximal to the site of the cannula. A third cannula was inserted through the inferior vena cava stump into the coronary sinus and sutured in place to collect coronary sinus return. All three venous cannulae emptied into a bubble oxygenator and roller pump, which had been calibrated with use of a stopwatch and graduated cylinder. The output of the roller pump was returned to the right atrium through the stump of the superior vena cava (figure 1). Total forward cardiac output could thus be precisely controlled by the roller pump by regulating the amount of oxygenated blood infused into right atrium. Respiration was then suspended for the remainder of the experiment. To maintain a constant heart rate, the sinus node was crushed and atrial pacing was established with right atrial epicardial electrodes. An electromagnetically flow probe was placed snugly around the ascending aorta and calibrated to the roller pump. The femoral arteries were cannulated and the cannulae were attached to a second roller pump that permitted blood to be infused into or withdrawn from the aorta. This permitted maintenance of a constant aortic pressure (mean 75 mm Hg) at low flows, as well as variation of aortic impedance and therefore shunt flow during the experimental studies (see below). Left ventricular and central aortic pressure were continuously monitored with fluid-filled polyethylene catheters connected to Statham P-23 PD pressure transducers positioned at the mid-thoracic level.

To simulate regurgitant flow, a flexible polyethylene conduit (½ inch diameter) into which a one-way valve and electromagnetic flow probe were incorporated was inserted through stab wounds in the left ventricular lateral wall near the apex and the posterior left atrial wall and sutured in place (figure 1). The conduit valve permitted flow only from the left ventricle to the left atrium. The shunt flowmeter was calibrated before insertion against timed volumes measured by graduated cylinder. Flow through the shunt was regulated by variable occlusion of the tubing with an adjustable clamp as well as by varying aortic impedance throughout the infusion or withdrawal of blood from the aorta through the roller pump attached to the femoral arteries. A fluid-filled catheter was positioned in the left atrium through the shunt to monitor left atrial pressure. Aortic, left atrial, and left ventricular pressures, a monitoring (modified chest lead) electrocardiogram, and aortic and shunt electromagnetically measured flows were recorded on a multichannel recorder.

**Echocardiographic imaging and acquisition of Doppler data.** All D2DE studies were performed with a combined two-dimensional echocardiographic/range-gated Doppler instrument, ATL MK600 (Advanced Technology Laboratories, Bellevue, Washington), equipped with a mechanical transducer using a 3.0 MHz carrier frequency. Doppler velocity spectra, echocardiographic images, and simultaneous single-lead electrocardiograms were recorded on ½ inch videotape with VHS.
format on a Panasonic NV8200 Omnivision II recording system.

A saline bath was suspended over the heart to optimize the interface between the transducer and the heart. Care was taken throughout the study not to apply direct pressure to the heart or to distort cardiac anatomy. Complete exposure of the anterior surface of the heart allowed the transducer to be positioned appropriately so as to allow optimal structural imaging and Doppler velocity recordings.

**Echocardiographic image acquisition.** Calculation of cardiac output by the Doppler technique requires knowledge of the cross-sectional area of the vessel or valve through which blood is flowing and the linear velocity of flow. In this study, the aortic cross-sectional area was calculated from the vessel diameter, assuming a circular configuration. This diameter was measured from a long-axis recording of the aorta in which the scan plane was aligned to include the aortic valve and proximal ascending aorta (figure 2).

Calculation of the effective mitral valve flow area was more complex due to the normal variation in size of the mitral orifice during diastole. A mean diastolic mitral valve area was therefore computed, as illustrated in figure 3, following the method of Fisher et al.10

**Doppler velocity recordings.** Aortic flow velocities were recorded with the transducer placed directly over the cardiac apex. The scan plane was directed toward the base of the heart and rotated to include the left ventricular outflow tract and ascending aorta. The Doppler cursor was positioned as nearly parallel to flow in the left ventricular outflow tract as possible and the sample volume was placed superior to the aortic valve. From this starting point, the system was switched to the Doppler mode and the beam scanned in a tight radial pattern with slight changes in the axial depth of sampling until the velocity profiles with the largest Doppler shifts were recorded (see figure 2).

**FIGURE 2.** Aortic valve calculation of cardiac output with Doppler echocardiography. Top left, Measurement of the aortic diameter at the aortic valve anulus. Top right, Formula used to calculate area of the aortic valve. Bottom left, Positioning of sample volume for recording of aortic velocity integral. Bottom, Formula for calculation of cardiac output through the aortic valve.

Mitral inflow velocity recordings were obtained from the equivalent of the standard apical four-chamber or apical two-chamber view. The Doppler cursor was initially aligned parallel to the apparent direction of flow and the sample volume was positioned at the depth of the mitral anulus in diastole. In Doppler mode, the flow profile with the highest apparent velocities was searched for in a manner analogous to that described for the aortic valve (see figure 3). At the end of each flow recording, a careful search was made to exclude native mitral and aortic valvular insufficiency.

**Echocardiographic/Doppler analysis.** All measurements were made with an off-line computer graphics system (Easy View II, Microsonics, Indianapolis). Each echocardiographic and Doppler measurement was obtained in nine different cardiac cycles, and the average was used in subsequent analysis.

The systolic diameter of the aortic valve was measured at the point of insertion of the valve leaflets, in the field immediately following valve opening, from inner edge to inner edge. The mitral valve area was measured in short axis from the frame showing maximal diastolic opening by tracing the midpoint of the leaflet echoes. The e-c' distance, the d-c interval, and the total area between the anterior and posterior leaflets during diastole were measured from the M mode echocardiogram. The mean leaflet separation (area between the leaflets divided by the d-c interval) was divided by the maximal leaflet separation (e-c') to give the “mean-to-max” ratio. To determine a mean diastolic area of valve orifice, the maximal valve area derived from the two-dimensional study was then multiplied by this ratio.

Doppler measurements were made directly from the velocity spectra with the computer graphics system. The Doppler spectra chosen for analysis were those that demonstrated the greatest velocities and that had profiles with a narrow frequency bandwidth (representative of undisturbed “laminar” flow). The area

![Figure 3](image-url)
under the systolic (aortic) or diastolic (mitral) velocity profile was traced through the modal components of the frequency spectrum. The modal velocity, which is determined visually as the brightest component of the spectral display (highest amplitude), represents the velocity at which the greatest number of red cell scatterers are traveling. The enclosed area (velocity integral), in units of distance (cm), is the integral of the instantaneous velocities over time and is proportional to stroke volume. The cardiac cycle length (RR interval) was measured directly from the video tracing of the simultaneous electrocardiogram.

Quantitative flow calculations. Forward flow through each valve was then calculated from the product of the effective cross-sectional area and mean linear velocity. Mean linear velocity was determined by dividing the velocity integral by the RR interval. Aortic flow was calculated with the formula

\[
\text{Flow} = \pi \left( \frac{D}{2} \right)^2 \times \frac{SVI}{RR}
\]

where \( D \) = the diameter of the valve anulus; \( SVI \) = the systolic velocity integral; \( RR \) = the RR interval. Mitral valve flow was calculated from the formula

\[
\text{Flow} = MVO_{\text{max}} \times \frac{D_{\text{mean}}}{D_{\text{max}}} \times DVI
\]

where \( MVO_{\text{max}} \) = the maximal area of the mitral valve orifice; \( D_{\text{mean}}/D_{\text{max}} \) = ratio of mean to maximal M mode valve diameter. Since the flows resulting from these calculations were in cubic centimeters per second they were converted to liters per minute by multiplying 60 sec/min \times 1 liter/1000 cc.

In all velocity recordings, the angle between the Doppler cursor and the apparent direction of flow on the two-dimensional echocardiographic image was negligible, and no correction was made for the effect of angle on the recorded flow velocity.

Doppler-determined regurgitant volume was calculated as the difference between mitral (DMF) and aortic flow (DAF) as follows:

\[
\text{DRV} = \text{DMF} - \text{DAF}
\]

The Doppler-determined regurgitation fraction (DRF) was calculated as

\[
\text{DRF} = (\text{DMF} - \text{DAF})/\text{DMF} \times 100\%
\]

In cases in which the aortic blood flow was calculated to be greater than the mitral flow by the D2DE method (\( n = 7 \)), the regurgitant volume and regurgitant fraction were set to zero, since this situation is not physiologically possible.

Analysis of hemodynamic data. Forward flow through the aortic valve and shunt flow were also determined directly with the aortic and shunt electromagnetic flowmeters. Total mitral valve flow, \( MF_{\text{out}} \), was taken as the sum of the shunt flow (\( SF_{\text{end}} \)) and aortic flow (\( AF_{\text{end}} \)). Regurgitant fraction was calculated as \( RF_{\text{end}} = (SF_{\text{end}} + AF_{\text{end}}) \times 100\% \).

Experimental protocol. To test the ability of the Doppler method to record consistently accurate control flows through the mitral and aortic valves in this preparation, as well as to assess the ability of this method to quantitate varying levels of shunt flow, aortic and mitral flows were determined by Doppler echocardiography according to the following general protocol: (1) Control flows were recorded in all animals at roller pump flows of 1.5 to 2 liters/min, with aortic pressure maintained constant and the shunt closed. (2) With forward flow maintained constant, the shunt was opened. (3) With forward flow constant and the shunt opened, flow into the aorta was increased by the femoral artery roller pump to increase aortic impedance. The rate of aortic inflow was increased until an obvious increase in shunt flow was noted on the electromagnetic shunt flow recorders. (4) The shunt was then closed, aortic inflow was reduced to return aortic pressure to the control level, and roller pump output was increased to from 2.5 to 4.0 liters/min; and a second series of control values was then recorded at the higher forward flow. (5) At an increased forward flow (between 2.5 and 3.5 liters/min, depending on the size of the animal), the shunt was reopened to permit the highest flow the animal could tolerate without developing left ventricular failure (visibly apparent left ventricular dilatation with increasing left ventricular end-diastolic pressure). Fine adjustments in both forward and shunt flows were then made to stabilize the preparation. (6) When possible, aortic pressure was again increased to increase shunt flow. (7) Finally, to create the highest possible regurgitant fraction, forward output was reduced to 0.75 to 1 liter/min, the shunt was fully opened, and aortic impedance was increased. The experiment was then terminated and the animal was killed with an overdose of pentobarbital. In applying this protocol, it was necessary to adjust actual forward and shunt flows according to size of the animal and the ability of the left ventricle to tolerate the resulting volume load. This resulted in a wide range of forward and shunt flows across animals.

Reproducibility of measurements. Interobserver and intraobserver variations in measurements of mitral and aortic flows by Doppler echocardiography for our laboratory have been previously examined and reported. The relative correlations for two observers with a roller pump were \( r = .99 \) and \( .94 \) (\( n = 10 \)) for the aortic valve and \( r = .97 \) and \( .96 \) (\( n = 10 \)) for the mitral valve. The experimental design precludes meaningful assessment of observer variation for the regurgitant volume and regurgitant fraction.

Statistical analysis. Correlations between Doppler-derived flows and those recorded by electromagnetic flow probe were made by the least squares method of linear regression. The expected error for the derived mitral regurgitant volume was calculated as \( V_c = V_m + V_s \), where \( V_c \) is the expected variance, and \( V_m \) and \( V_s \) are the variance of the mitral and aortic flows, respectively. A first-order approximation was used to calculate the anticipated mitral regurgitant fraction error.

Results

Forward flows. Aortic and mitral flows were measured by the Doppler method and with the electromagnetic flow probe at 35 experimental stages with and without the shunt open. As illustrated in figure 4, an excellent correlation was observed between the two flow measurements over a range of forward outputs from 0.5 to 4 liters/min (\( r = .92, y = 1.06x + 0.16 \)). Doppler-determined mitral valve flow recorded with the shunt closed at 10 experimental stages showed an equally good correlation with forward cardiac output determined by electromagnetic flowmeter (\( r = .92, y = 1.05x + 0.08 \); figure 5). In each case, the slope of regression was close to unity. The correlation between Doppler-determined and electromagnetic mitral flow (aortic plus shunt flow by electromagnetic flow probe) was similar with the shunt open and closed (\( y = 0.58x + 0.59 \)) vs \( y = 1.05x + 0.08 \), respectively, \( p = NS \).

Regurgitant flows. Effective mitral regurgitant flow measured by the shunt flowmeter ranged from 0.2 to 1.8 liters/min. The relationship between directly mea-
Doppler echocardiography is uniquely able to non-invasively measure volumetric flow at multiple locations within the heart and great vessels. In the normal flow state, this capability permits the determination of forward cardiac output from flow data derived from each of the four cardiac valves. When flow is disturbed as a result of shunt or valvular regurgitation, quantitation of the disturbance should theoretically also be possible by comparison with flow volumes at serial points along the path of normal blood flow through the heart.

The accuracy of the Doppler method in defining forward cardiac output,10,11 the effects of sampling site on these measurements,3 and its accuracy in assessing shunt flow14-16 have been extensively studied. Less attention, however, has been given to the use of this technique for quantifying regurgitant flow.20

We have recently presented preliminary clinical data suggesting that a significant correlation (p = .001) exists between the Doppler-derived regurgitant fraction and the hemodynamic/angiographic mitral regurgitant fraction calculated by the method of Sandler and Dodge.3 The clinical method of Sandler and Dodge, however, is based on the difference between forward cardiac output as measured by thermodilution, Fick, or dye-dilution techniques and the angiographic stroke volume. Each of these measurements contains significant inherent sources of error.21 Furthermore, although this method is theoretically attractive, it has not to our knowledge been independently validated. Therefore, we believed that to properly interpret and understand our clinical data, it was important to define the accuracy of the Doppler method of calculating re-

**FIGURE 4.** Comparison of Doppler-determined aortic cardiac output with that measured by electromagnetic flowmeter.

**FIGURE 5.** Comparison of Doppler-determined mitral cardiac output, in the absence of mitral regurgitation, with aortic cardiac output determined by electromagnetic flowmeter.

**FIGURE 6.** Regurgitant flow measured by the D2DE method vs that measured by electromagnetic flowmeter.

The clinical method of Sandler and Dodge, however, is based on the difference between forward cardiac output as measured by thermodilution, Fick, or dye-dilution techniques and the angiographic stroke volume. Each of these measurements contains significant inherent sources of error.21 Furthermore, although this method is theoretically attractive, it has not to our knowledge been independently validated. Therefore, we believed that to properly interpret and understand our clinical data, it was important to define the accuracy of the Doppler method of calculating re-

**FIGURE 6.** Regurgitant flow measured by the D2DE method vs that measured by electromagnetic flowmeter.
gurgitant fraction in a more rigidly controlled experimental preparation in which forward and regurgitant flows could be precisely measured.

Our preparation was a modification of one with controlled right heart output that we had previously used to study the accuracy and sources of variability in Doppler flow measurements through the mitral, aortic, and pulmonic valves. To simulate mitral regurgitation, the basic preparation was modified by placing a valved conduit between the left ventricular apex and left atrium. To exclude the possibility that the addition of the conduit would alter left ventricular or mitral valve geometry in a manner that would adversely affect flow measurements, we initially compared the Doppler-determined aortic flow and mitral (shunt closed) measurements to those obtained with the aortic electromagnetic flow probe. As noted, the correlation between the Doppler- and electromagnetically determined aortic flow was good and similar to that obtained in a previous study in which no valved conduit was used. Likewise, the baseline mitral flows with the shunt closed correlated well with simultaneous electromagnetically measured aortic flows. Finally, since flow through the conduit should alter the pattern, volume, and pressure of return to the left atrium, we compared electromagnetically calculated absolute mitral flow (conduit plus aortic) when the shunt was open with absolute Doppler-determined mitral flow. Again, the correlation was good \( r = .82 \), and the line of best fit did not differ significantly from that observed with the shunt closed.

Having validated the accuracy of the basic Doppler measurements in this preparation of modified flow, we then tested the accuracy of the D2DE quantitation of mitral regurgitant flow, which was calculated as the difference between total left ventricular inflow and forward cardiac output. In this study a good correlation \( r = .84 \) was obtained between D2DE and electromagnetic estimates of regurgitant flow and the slope of the line of best fit approximated unity \( (0.97) \). These data therefore suggest that this method can accurately measure regurgitant volume in the ideal experimental setting. The fact that the correlation coefficient between Doppler- and electromagnetically based calculations of regurgitant volume was weaker than that between the “raw” aortic and mitral valve flows determined by the two methods may simply reflect the relatively narrow range of regurgitant volumes (0 to 1.8 liters/min) obtainable in this experimental preparation as opposed to the broader range of forward cardiac outputs (0.5 to 4.0 liter/min). For example, if electromagnetic and D2DE estimates of aortic flow are compared over a range comparable to that in the regurgitant volume study (i.e., 2 to 4 liters/min), the \( r \) value falls between .92 and .78.

While one might expect that the errors in the raw data would be compounded in the regurgitant volume and fraction correlations, the variance for both these calculated variables is less than predicted from the errors in the directly measured variables (observed = .35, 11%; predicted = .50, 27%). Thus, it appears that some of the inherent error is canceled in the calculation of the regurgitant volume or fraction.

In seven instances, Doppler-derived aortic blood flow was greater than Doppler-calculated mitral blood flow by an average of 175 ml. This difference is within the error of the method. In all but one case, in which the shunt flow was 0.45 liter/min, the shunt was closed when this occurred.

“The application to disease states of data derived from acute canine experiments which simulate such states, is necessarily limited.” Despite this, when testing any new technology, it is important first to define its capabilities and limitations in an ideal setting where it can be tested against established standards of known accuracy. Experimental validation of a new technique is particularly important in areas in which the clinical “gold standard” has significant inherent sources of error. The information derived from the validation studies provides the framework that is necessary to interpret the results from clinical studies in which few physiologic parameters can be controlled. Thus, our preparation, while admittedly different from the human situation in which the mitral valve itself is responsible for the regurgitant flow, hemodynamically simulates mitral insufficiency while allowing regulation and precise measurement of both forward and effective regurgitant flow. In addition, in this preparation, all valves are intrinsically normal and the open-chest setting provides optimum conditions for Doppler recording and echocardiographic imaging. This ensures any that errors due to intrinsic valvular regurgitation or difficulty in measurement of valve orifices or velocity integrals are minimized. Thus, we were able to validate our method of calculating regurgitant flow and evaluate its accuracy in the absence of confounding variables.

When applying these results to the clinical environment, a number of problems can be expected. First, in patients with mitral regurgitation, the mitral and aortic valves are frequently deformed, making measurement of valve areas and velocity integrals more difficult. Second, coexisting aortic insufficiency may cause an overestimation of the true forward flow and may affect
the measurement of mitral valve area and velocity integral as a result of impingement of the regurgitant aortic jet on the mitral valve. Third, differences in heart rate may make measurement more complex. All of our studies were performed at a paced heart rate of 120 beats/min to maintain a constant cardiac output during acquisition of the D2DE data. Since our method for calculation of cardiac output does include the effects of heart rate, the results for individual measurements should not be significantly influenced by the rate. However, large variations in heart rate or changes in rhythm may affect both forward flow and regurgitant volume, and if there is an interval between the measurement of aortic and mitral flows it may affect the calculation of regurgitant volume.

Finally, there appear to be species-specific differences in the geometry of the mitral valve anulus that have produced conflicting opinions as to the appropriate method for measuring mitral flow. In the dog, the method of Fisher et al. has been extensively validated and its accuracy has been demonstrated. When applied to human studies, however, others have found this approach less accurate and several alternative methods for measuring the effective mitral orifice in the clinical setting have been suggested. Although this methodologic point is of major importance, it can be assumed that once the optimal clinical method for measuring mitral valve area is determined, the concepts and methods validated in this study can be easily adapted to the derived clinical formula.

In conclusion, we have described a method for the noninvasive measurement of regurgitant mitral flow. This method employs combined D2DE techniques to measure aortic outflow and mitral inflow and is based on the theory that the difference between total mitral inflow and forward flow through the aortic valve equals the regurgitant flow. We have demonstrated that this method can provide accurate quantification of regurgitant mitral flow in the experimental setting. This technique, being noninvasive, repeatable, and accurate has significant advantages over angiography and may prove to be the method of choice in the clinical assessment of mitral regurgitation.

We gratefully acknowledge the secretarial assistance of Kathleen Lundgren.

References
A Doppler-two-dimensional echocardiographic method for quantitation of mitral regurgitation.

doi: 10.1161/01.CIR.72.2.377

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/72/2/377