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AORTIC REGURGITATION

Studies on noninvasive quantitation of aortic regurgitation and the influence of vascular parameters

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AORTIC REGURGITATION- STUDIES ON NONINVASIVE QUANTITATION OF AORTIC REGURGITATION AND THE INFLUENCE OF VASCULAR PARAMETERS



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I am debtor both to the Greeks, and to the Barbarians; both to the wise and to the unwise.

Romans 1:14

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LIST OF PAPERS

The papers will later be referred to by their Roman numbers.

 I. Slørdahl SA, Piene H, Skjaerpe T. Pressure half-time in aortic regurgitation: evaluation with Doppler in a cardiovascular hydromechanical simulator and in a computer model.

J Am Soc Echocardiogr 1990;3:46-53.

- II. Slørdahl SA, Piene H, Solbakken JE, Rossvoll O, Samstad SO, Angelsen BAJ. Estimation of arterial compliance in aortic regurgitation: three methods evaluated in pigs. Med & Biol Eng & Comput 1990;28:293-299.
- III. Slørdahl SA, Piene H. Haemodynamic effects of arterial compliance, total peripheral resistance and glyceryl trinitrate on regurgitant volume in aortic regurgitation. Cardiovascular Research 1991;25:869-874.

IV. Slørdahl SA, Solbakken JE, Piene H, Angelsen BAJ, Rossvoll O, Samstad

SO. Quantification of aortic regurgitation by Doppler echocardiography: a new method evaluated in pigs. Med & Biol Eng & Comput 1990;28:300-305.

- V. Slørdahl SA, Kuecherer HF, Solbakken JE, Piene H, Angelsen BAJ, Schiller NB. Regurgitant volume in aortic regurgitation from a parameter estimation procedure. (submitted 1991)
- VI. Slørdahl SA, Myrheim J, Kværness J, Piene H. Left and right ventricular volumes by magnetic resonance imaging from a new biplane method. (submitted 1991)

INTRODUCTION

The danger of the disease is in proportion to the quantity of blood that regurgitates, and the quantity of blood that regurgitates will be large in proportion to the degree of inadequacy of the valve, and to the length of pause between contractions of the ventricle during which blood can be pouring back.

D.J. Corrigan, 1832

Aortic regurgitation means that blood flows from the aorta back into the left ventricle during diastole due to incompetence of the aortic valves. D.J. Corrigan's paper 'On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves' in 1832 was the first work that was devoted to aortic regurgitation: 'The pathological essence of the disease consists in inefficiency of the valvular apparatus at the mouth of the aorta, in consequence of which the blood sent into the aorta regurgitates into the ventricle'(Corrigan, 1832).

The diastolic flow of blood across the incompetent aortic valve increases the filling of the left ventricle and imposes a volume overload on the myocardium. In <u>chronic</u> aortic regurgitation left ventricular end-diastolic volume gradually increases due to the compensatory dilatation of the ventricular chamber (Osbakken et al., 1981), but the compensatory left ventricular hypertrophy tends to normalize systolic wall stress. Left ventricular stroke volume increases to maintain a normal cardiac output, but in the late stage of the condition the contractile state can be depressed and this will produce an increase in end-systolic volume with a decrease in ejection fraction (Henry et al., 1980). Left ventricular end-diastolic pressure will also increase as the elastic properties of the left ventricle diminish. At one stage in this process systolic wall thickness fails to accompany further dilatation of the left ventricle and wall stress increases.

The hemodynamic changes in <u>acute</u> aortic regurgitation is somewhat different. The ventricle is unable to compensate adequately to the increased filling when diastolic regurgitant flow suddenly imposes a volume overload on a normal left ventricle (Goldschlager et al., 1973; Wise et al., 1971). Left ventricular wall stress increases

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due to the sudden volume overload without compensatory hypertrophy. Left ventricular end diastolic pressure increases and an acute severe aortic regurgitation may rapidly lead to left ventricular pump failure. Acute severe aortic regurgitation is often associated with dissection of the ascending aorta or infective endocarditis which is generally an indication for surgery (Crosby et al., 1972; Wilson et al., 1978; Richardson et al., 1978; Lewis et al., 1982).

Chronic aortic regurgitation, however, is often well tolerated for several years before evidence of symptoms and left ventricular dysfunction (Segal et al., 1956; Bland and Wheeler, 1957; Spagnuolo et al., 1971; Goldschlager et al., 1973; Rapaport, 1975; Turina et al., 1987). Since aortic valve replacement has its complications such as hospital mortality, infective endocarditis, valve thrombosis and embolism, paraprosthetic leak, and AV dissociation (Kloster, 1975; Scott et al., 1985), surgery should not be performed before it is absolutely necessary (Rahimtoola, 1977). On the other hand, irreversable left ventricular dysfunction may develop in abscence of any symptoms or in mildly symtomatic patients (Bonow et al., 1982). Hence, a serious challenge to the evaluation of aortic regurgitation is the timing of valve replacement surgery in patients with chronic aortic regurgitation.

The mechanical performance of the heart is determined by mechanical factors such as preload and afterload and by the contractile state of the myocardium. Preload is the load that stretches the muscle to its initial length prior to contraction while afterload is the resistance encountered by the contractile ventricle when the aortic valve opens during systole. Both arterial compliance, which is defined as the increment in volume produced by an increment of pressure, and total peripheral resistance, which is defined as mean arterial pressure minus mean right atrial pressure divided by cardiac output, are important peripheral vascular parameters that influence afterload. It is therefore reasonable to believe that these vascular parameters will also influence regurgitant flow through the regurgitant orifice in diastole. It is of great interest to disclose the importance of these vascular parameters during aortic regurgitation.

In order to evaluate patients with aortic regurgitation properly, it is important to estimate the severity of regurgitation. Doppler echocardiography is a noninvasive technique that measures blood velocities with ultrasound, either by continuous wave

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or by pulsed wave Doppler. The advantage with pulsed wave Doppler is that one can measure the velocity in a defined distance (by range resolution) along the ultrasonic beam, but a disadvantage is that the maximum velocity that can be measured is limited. Continuous wave Doppler has no limit on maximum velocity, but has at the same time no range resolution. Color flow mapping is a pulsed wave ultrasound technique that color encodes the velocities in multiple sample volumes.

The velocity of the blood from the aorta back into the left ventricle during diastole in aortic regurgitation can be measured by continuous wave Doppler. The velocity of the jet is determined by the pressure gradient between the aorta and the left ventricle. Earlier studies have shown that pressure gradients can be calculated from a blood flow jet by the simplified Bernoulli equation $\Delta P = 4 \cdot v_{max}^2$ (velocity in m/s and pressure in mmHg)(Yock and Popp, 1985). In valvular stenosis the pressure gradient ΔP calculated from the jet velocity expresses the severity of the lesion (Currie et al., 1985), but in aortic regurgitation the maximum velocity of the regurgitant jet has no direct relationship to the severity of the lesion. If one could obtain, however, the regurgitant orifice area, the regurgitant volume could be estimated from the measured regurgitant velocity and the calculated regurgitant orifice area.

The Doppler recording of the regurgitant jet reflects the pressure equalization across the regurgitant orifice during diastole, i.e., how fast the pressure difference over the valve subsides. Several studies have reported that the severity of aortic regurgitation can be quantitated from a continuous wave Doppler recording by evaluating the rate of pressure equalization by means of the simplified Bernoulli equation (Masuyama et al., 1986; Teague et al., 1986; Labovitz et al., 1986; Grayburn et al., 1987; Beyer et al., 1987; Masuyama et al., 1989). The rate of pressure equalization is normally expressed as the pressure half-time, i.e, the time required for the maximum velocity to fall from peak velocity to peak velocity divided by $\sqrt{2}$ (Hatle et al., 1979), since pressure is related to velocity squared according to the Bernoulli equation. The basis for this approach is earlier studies in which the diastolic pressure drop in the aorta was used to estimate the amount of aortic regurgitation (Libanoff, 1973; Judge and Kennedy, 1970). Calculation of the pressure half-time from the deceleration slope of the regurgitant jet is a simple and attractive method, but one

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important uncertainty of the method is the probable influence of other factors, such as total peripheral resistance, arterial compliance, and left ventricular compliance.

A totally different method is to use continuous wave Doppler to evaluate the amplitude (power) of the Doppler spectrum. The regurgitant fraction is then calculated from the ratio of forward flow through the aortic and through the pulmonary valves when flow is measured by the systolic time integrals of the amplitude-weighted mean velocity from continuous wave Doppler spectra, i.e., the difference in the power of the Doppler signals represents the regurgitation (Hoppeler et al., 1990). The possibility to achieve acceptable results from this method is theoretically suprising since the measurements are dependant on the gain setting of the ultrasound machine, on the depth of the valves, on no range resolution, and on the width of the ultrasonic beam among other things.

The regurgitant velocity has also been evaluated with pulsed wave Doppler techniques, i.e., conventional pulsed wave Doppler and color flow mapping. With conventional pulsed wave Doppler the severity of regurgitation has been assessed by evaluating the extent of the jet into the left ventricle (Ciobanu et al., 1982; Veyrat et al., 1984; Switzer et al., 1987; Vigna et al., 1988; Masuyama et al., 1989) or by measurement of the regurgitant orifice area from a parasternal short-axis image where the entire orifice was checked along its vertical and horizontal axes for diastolic flow (Veyrat et al., 1983). Similarly the extent of the jet into the left ventricle as well as the the area of the jet and thickness at its origin relative to the size of the outflow tract have been evaluated with color flow mapping (Perry et al., 1987; Bouchard et al., 1989; Dall'Aglio et al., 1989; Galassi et al., 1990; Tribouilloy et al., 1991). The regurgitant fraction has also been calculated from the ratio of forward flow through the aortic and pulmonary (or mitral) valve with pulsed wave Doppler. Flow values have been obtained from one sample volume assuming an uniform velocity field for each valve and a orifice valve area estimate from two-dimensional echocardiography (Kitabatake et al., 1985; Rokey et al., 1986; Takenaka et al., 1986; Zhang et al., 1986). In addition, pulsed wave Doppler has been applied to evaluate flow reversal in the aorta due to aortic valve incompetence. The amount of flow reversal has been used as an

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expression of the severity of regurgitation (Boughner, 1975; Quinones et al., 1980; Touche et al., 1985; Tribouilloy et al., 1991).

The great number of echocardiographic methods that are introduced for quantitating aortic regurgitation show the problems with the existing methods. A great challenge is to develop more reliable methods to assess the severity of aortic regurgitation by Doppler echocardiography using simple models of the cardiovascular system and advanced engineering mathematics. In addition, a great challenge is to evaluate the accuracy in quantitating aortic regurgitation from the regurgitant jet by Doppler echocardiography and to assess the influence of the arterial tree on the regurgitant jet and the regurgitant volume.

A problem in cardiovascular physiology is that the amount of parameters that can be measured is limited. A way of avoiding this problem is to use a model of the cardiovascular system that include both parameters that can be measured and parameters that cannot be measured. From such a model it is easier to develop methods for estimating the unknown parameters. Parameter estimation is a mathematical approach for determining unknown or uncertain parameters in a model. In this way we might obtain hidden information about the cardiovascular system and get values on parameters that cannot be directly measured.

Another challenge is to establish a reference method to echocardiography for noninvasive grading of aortic regurgitation. A promising new noninvasive technique is magnetic resonance imaging which was introduced in Trondheim in 1986. Several studies have already demonstrated the accuracy in calculating ventricular volumes (Sechtem et al., 1987; Underwood et al., 1988; Cranney et al., 1990; Semelka et al., 1990) and the possibility to calculate the regurgitant volume from the difference in left and right ventricular stroke volumes when no other lesion producing regurgitation or shunting is present (Underwood et al., 1986; Sechtem et al., 1988). It was therefore of great interest to establish such a method in Trondheim.

THE AIMS OF THE STUDY

The aims of the study were:

- To assess the applicability of continuous wave Doppler recordings of the regurgitant jet in aortic regurgitation to quantitate the degree of regurgitation by evaluating the rate of pressure equalization across the regurgitant orifice, i.e., the pressure half-time method.
- To develop noninvasive Doppler echocardiographic methods based on parameter estimation techniques to assess the severity of aortic regurgitation and to determine important vascular parameters like arterial compliance and total peripheral resistance.
- 3. To evaluate the influence of such vascular parameters, i.e., arterial compliance and total peripheral resistance, on the regurgitant volume.
- To develop a method of calculating ventricular volumes from magnetic resonance imaging in order to establish an independent noninvasive method to quantitate aortic regurgitation.

SUMMARY OF RESULTS

The influence of vascular parameters on the regurgitant jet obtained by continuous wave Doppler was studied in a cardiovascular hydromechanical model in order to determine if the deceleration slope of the jet was of any value for quantitation of aortic regurgitation. Aortic regurgitation was simulated in the cardiovascular model by prosthetic mechanical valves with defined holes in the discs which were placed between the 'ventricle' and the 'aorta'. The measured pressure half-time changed considerably, at constant regurgitant orifice areas, when total peripheral resistance increased or decreased (I). The difference in measured pressure half-time between two widely different orifice areas at a given total peripheral resistance was small compared with the variation induced by physiologically possible changes in total peripheral resistance the pressure half-time decreased by 75 milliseconds which was a significant influence in this case.

In a computer model of aortic regurgitation, based on an electrical analog model of the cardiovascular system, the pressure-half time was defined as the pressure gradient half-time between the aortic and left ventricular pressures. Such simulation demonstrated in a similar way that both peripheral resistance and arterial compliance had significant influence on the pressure half-times (I). The influence of left ventricular compliance on the pressure half-time was also investigated in the computer model, but had minimal influence on the measured pressure half-times.

In the computer model total peripheral resistance had a strong direct influence on the regurgitant volume. The correlation between decreased total peripheral resistance and decreased regurgitant volume was very strong (III). At a constant regurgitant orifice of 30 mm² and a constant value of arterial compliance of 1 ml/mmHg, the regurgitant volume fell from about 50 to 17 ml when total peripheral resistance was reduced from 3.0 to 0.5 mmHg·s/ml. As opposed to the influence of peripheral resistance, arterial compliance was hardly of any importance for the regurgitant volume. There was therefore a basic difference between the influence of arterial compliance on the pressure half-time and the regurgitant volume, since arterial compliance had a significant influence on the pressure half-time.

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An experimental model of aortic regurgitation in pigs was established. Acute aortic regurgitation was produced by opening a cage basket catheter inserted into the aortic valve, and the amount of aortic regurgitation could be altered by opening and closing the basket. Regurgitant aortic volume was measured as the difference between systolic and pulmonary stroke volumes obtained by electromagnetic flow probes. Arterial compliance was estimated from three different methods based on windkessel models (II). The three methods gave quantitatively similar estimates except during interventions that severely reduced mean aortic pressure. Discrepancies were small at mean aortic pressure above 60 mmHg, and aortic regurgitation did not seem to alter the arterial compliance was calculated from systole only and was therefore independent of the regurgitant volume.

The importance of total peripheral resistance on the regurgitant volume was found to be similar in the experimental pig model as in the computer simulation (III). In one group of assumed similar regurgitant orifice areas, 83% of the variance in the regurgitant volumes could be explained by variations in total peripheral resistance while arterial compliance seemed to be of small if any importance. A bolus of nitroglycerin reduced significantly regurgitant volumes and regurgitant fractions.

We developed two methods for quantitating the aortic regurgitant orifice area and volume, based on measurements of the velocity of the regurgitant jet, the aortic systolic flow, the systolic and diastolic pressures. In these methods we employed a Windkessel arterial model and parameter estimation techniques (IV,V). One of the methods was based on a two-element aortic Windkessel model (R-C) and a parameter estimation procedure that included assumptions about left ventricular pressure in diastole. This method was evaluated in 6 pigs. A strong correlation was found between the estimated regurgitant orifice areas and the regurgitant orifice areas as calculated from invasive data (IV). The same held true for the estimated regurgitant volume compared to the regurgitant volume measured with electromagnetic flow probes. A sensitivity analysis showed that inaccuracies in tracing the contour of a regurgitant Doppler velocity recording influenced the result less than inaccuracies in the blood pressure values. The most influential input to the parameter estimation procedure was mean aortic pressure.

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The other parameter estimation procedure was based on a three-element Windkessel model (r-C-R) and the method was evaluated in a cardiovascular hydromechanical simulator and in 10 patients (V). There was an excellent relationship between the regurgitant orifice area of 24 mm² in the mechanical aortic valve of the cardiovascular simulator and the estimated regurgitant orifice areas. In the patient study the estimated regurgitant fractions were compared to the semiquantitative grading of the severity of aortic regurgitation by echocardiography. This grading was based on an overall impression from the echocardiographic examination, and there was a fair relationship between the estimated regurgitant fractions and the semiquantitative gradings. In some patients it was difficult to get stable estimates of arterial compliance indicating that the input measurements to the estimation procedure were not accurate enough. The estimated mean values of total peripheral resistance and arterial compliance were 1.67 \pm 0.55 mmHg·s/ml and 1.30 \pm 0.42 ml/mmHg, respectively.

In order to obtain an accurate method to calculate the regurgitant volume in aortic regurgitation, we developed a biplane method for calculating ventricular volumes from magnetic resonance imaging. In order to calculate the ventricular volumes we used long axis images in end diastole and end systole and found the deviation from a circular cross section of the ventricles by using one to five short axis images in end diastole and end systole. The deviation was expressed by a shape factor defined as $4 \cdot \operatorname{area}/\pi \cdot (\operatorname{diameter})^2$ where the diameters were measured in the long axis image.

The mean difference between measured left and right ventricular stroke volumes according to this new method was 0.4 ± 2.0 ml (SE) in 16 healthy volunteers. The shape factor of the left ventricle was not significantly different from 1, hence circular geometry was a good approximation. The shape factor of the right ventricle was approximately 2. There was reasonably good correlation between the regurgitant fraction obtained by the new magnetic resonance imaging method and the semiquantitative evaluation by echocardiography in 4 patients with chronic aortic regurgitation.

GENERAL DISCUSSION

The present work shows the complexities and difficulties in assessing the severity of aortic regurgitation from Doppler echocardiography, the importance of vascular parameters like arterial compliance and total peripheral resistance, and the estimation of these. Still, the present work demonstrates the possibility to estimate the regurgitant orifice area and arterial compliance when aortic regurgitation is present. It also demonstrates the possibility to calculate the regurgitant volume from magnetic resonance imaging.

The simplest method for grading the severity by Doppler echocardiography in aortic regurgitation is to evaluate the rate of pressure equalization across the regurgitant orifice, expressed as the pressure half-time, from a continuous wave Doppler recording. We found as expected an inverse relationship between the regurgitant orifice area and pressure half-time in both the hydromechanical flow model and in the computer model, but changes in arterial compliance and total peripheral resistance significantly altered the pressure half-times (I). The great importance of total peripheral resistance for the pressure half-time was in accordance with a clinical study of Samstad et al. (Samstad et al., 1989), but their study did not assess the influence of arterial compliance. The low specificity of the technique has also been demonstrated by others (Pye et al., 1990).

These findings emphasize the need to be careful in evaluating aortic regurgitation from the rate of pressure equalization across the regurgitant valve, although the regurgitant orifice area remains as the main determinant of the pressure half-time in very large regurgitations. The same influence of arterial compliance and total peripheral resistance would be expected in all Doppler methods assessing the severity of regurgitation from the regurgitant jet or the amount of flow reversal in the aorta. Examples are methods assessing the severity of regurgitation from the extension of the regurgitant jet into the left ventricle either by conventional pulsed wave Doppler or by color flow mapping. An interesting thought would be to combine the observation of pressure half-time and flow reversal in the descending aorta into one method in order to include both the influence of the regurgitant orifice area, the arterial compliance and the total peripheral resistance. Unfortunately, however, a clinical

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observation is that a dilated ascending aorta will also influence flow reversal (Terje Skjærpe, personal communication), i.e., a dilated compliant ascending aorta in a severe regurgitation might give hardly any flow reversal in the descending aorta.

Both arterial compliance and total peripheral resistance constitute important parts of the load on the heart. Decreasing arterial compliance and increasing total peripheral resistance are known to increase the mechanical load of the left ventricle, although arterial resistance probably plays a dominant role (Urschel et al., 1968; Piene and Sund, 1979). Afterload reduction by arterial vasodilator therapy is a well recognized treatment of heart failure (Massie et al., 1981). In aortic regurgitation afterload reduction is known to have a favorable effect on regurgitant flow (Greenberg et al., 1980; Wilson et al., 1980; Klepzig et al., 1989; Scognamiglio et al., 1990), although conflicting results have been obtained about the value of chronic vasodilatation therapy in chronic severe aortic regurgitation (Kleaveland et al., 1986; Greenberg et al., 1988). The present work also demonstrates the potential in reducing total peripheral resistance in patients with aortic regurgitation; arterial compliance was, however, of small if of any importance for the regurgitant volume (III).

Calculation of total peripheral resistance is straightforward and estimates are easily obtained by measurements of cardiac output, aortic pressure and central venous pressure. Estimation of arterial compliance, which is the increment in volume produced by an increment of pressure, is on the other hand very difficult. Direct measurement of overall arterial compliance is only possible if one has accurate information about total arterial blood volume, and therefore arterial compliance is normally estimated only indirectly. Estimates can be made by assuming that the aortic diastolic pressure decays exponentially and by calculating the time constant of this decay. The time constant is considered as the product of arterial compliance and total peripheral resistance (Deswysen et al., 1980; Ventura et al., 1984; Randall et al., 1984; Simon et al., 1985; Levy et al., 1985; Messerli et al., 1985). In order to avoid pressure wave reflections or other perturbations that often distort diastolic aortic pressure, arterial compliance is best estimated by using the area under the diastolic pressure wave for calculating the time constant (Yin et al., 1987).

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In aortic regurgitation the diastolic aortic pressure decay is also dependent on the regurgitant orifice, but the present work shows that it is possible to estimate arterial compliance when the aortic valve is incompetent (II). The three employed methods gave quantitatively similar estimates of arterial compliance as long as the mean aortic pressure was above 60 mmHg, indicating that the estimate is indifferent to the use of two- or three-component windkessel models. The great advantage with one of the methods was that arterial compliance was calculated from systole only and no information about regurgitant flow was necessary.

The present work, as well as many earlier studies (Deswysen et al., 1980), demonstrates that the windkessel model of the arterial system, despite its simplicity continues to be extremely useful for understanding vascular physiology. The similarity in study III in the results from experimental data obtained in pigs and the results from the computer model of the cardiovascular system illustrates this point. The advantage of simple models consists in the finite number of parameters, and the possibility to estimate these parameters from flow and pressure mesurements. The quality of the estimated parameters will always depend on the accuracy of the measurements of the input variables, but the influence of each of the input variables will always depend on the model, the parameter estimation procedure and the number of input variables.

Study IV and V introduced the idea of estimating the regurgitant orifice area and the regurgitant volume from noninvasive measurements using different parameter estimation procedures. The estimated regurgitant orifice area from these methods gave an estimate of the effective area of flow and not an estimate of the anatomical regurgitant orifice area. In this way we in fact avoided the problem that the aortic valve morphology influences the regurgitant volume (Grayburn et al., 1991).

In the pig study some of the invasive data was used in the estimation procedure, but the main reason for this study was to investigate the possibilities of the approach in assessing the severity of aortic regurgitation. Pigs are known to have a vascular physiology similar to humans (Douglas, 1972; Dodds, 1982), and in this study we had control over all the main variables. The results show that the regurgitant orifice area can be expressed and estimated from a simple windkessel model. The next

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problem was to evaluate the feasibility of this approach in patients from only noninvasive measurements. Study IV disclosed that the accuracy in using the extended Kalman filter in the estimation procedure was very dependent on some of the input variables. We chose a somewhat different approach in the patient study (V) to avoid a model that needed information about left ventricular pressure.

The patient study (V) showed that it was possible to obtain the same data from a completly noninvasive setting, but it was more difficult to evaluate these results. The quality of the input variables could presumably be enhanced by using the oscillometric method for blood pressure measurements (Borow and Newburger, 1982) or to obtain the end systolic pressure from a carotid artery pulse tracing.

A problem in our studies of new methods to assess the severity of aortic regurgitation was to choose a reliable control method. Aortography has long been regarded as the most useful investigation for the grading of aortic regurgitation, but angiographic assessment of the severity is often at variance with the measured regurgitant volume index (Mennel et al., 1972; Hunt et al., 1973; Croft et al., 1984). At the Moffitt Hospital in San Francisco and at the Regional Hospital in Trondheim almost all investigations in suspected aortic regurgitation are done by echocardiography. This was the reason that the estimated values in study V were compared to the semiquantitative grading done by echocardiography.We believe that a combination of two-dimensional, M-mode, and Doppler echocardiography can provide as much information as angiography in assessing and detecting aortic regurgitation

However, we realized the need for other noninvasive methods as alternatives to echocardiography or as control methods for possible new echocardiographic methods as proposed in the present work. Gated blood pool scanning enables right and left ventricular stroke volumes to be compared if no other lesion producing regurgitation or shunting is present. By this method an expression for the regurgitant volume is obtained (Baxter et al., 1980; Sorensen et al., 1980; Bough et al., 1980; Lam et al., 1981; Kress et al., 1981). Magnetic resonance imaging is probably an even more promising approach due to the provision of tomographic images of the right and left ventricles with good contrast between the flowing blood and the

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myocardium, and to the inherent three-dimensional capabilities provided by this technique. Magnetic resonance imaging was chosen as a control method in the present work after the promising reports on the accuracy and quality of the technique, and the excellent working facilities that were established at the Magnetic Resonance Center in Trondheim.

We demonstrated that both left and right ventricular volumes can be calculated from magnetic resonance images using a shape factor in the formula for volume calculation (VI). The use of a shape factor makes the volume formula independent of any preconceived left and right ventricular shapes. Paper VI thus introduced a new approach for volume calculation and the method should be applicable for volume calculation in all kinds of cardiac disorders. The principle of using a shape factor should also be applicable for other imaging techniques like echocardiography. A complete assessment of the capabilities of the method was, however, beyond the scope of the present study.

CONCLUSIONS

The present study demonstrates the complex nature of factors that influence the regurgitant jet and volume, and their measurement, in aortic regurgitation. The arterial tree, represented by arterial compliance and total peripheral resistance, had significant influence on the rate of pressure equalization across the regurgitant orifice obtained from a continuous wave Doppler recording. Total peripheral resistance had a significant influence on the regurgitant volume. Three different methods were used to calculate arterial compliance and one of them can in principle be obtained noninvasively.

Parameter estimation procedures built on simple models of the cardiovascular system demonstrated that the regurgitant orifice area can be estimated both in an experimental models (pigs and a cardiovascular simulator) and from a complete noninvasive setting in patients, but further development should be done to increase the reliability of the estimated parameters.

Magnetic resonance imaging proved to be an accurate technique to calculate ventricular volumes in order to obtain the regurgitant volume in aortic regurgitation, and a new approach for volume calculation was introduced.

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Pressure Half-Time in Aortic Regurgitation: Evaluation with Doppler in a Cardiovascular Hydromechanical Simulator and in a Computer Model

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Doppler echocardiographic determination of pressure half-time has been proposed as a method of assessing the severity of aortic regurgitation. To evaluate this method, we assessed the relation between pressure half-time and simulated aortic regurgitant flow under various conditions in two models of the cardiovascular system. In a hydromechanical model we assessed the influence of total peripheral resistance and arterial compliance on the pressure half-time as measured by continuous wave Doppler echocardiography. In a computer model that used the half-time of the pressure gradient between the aorta and the left ventricle as an expression of pressure half-time, we assessed the influence of total peripheral resistance and arterial compliance and also the influence of left ventricular compliance on pressure half-time. In both models, although we found an inverse relation between regurgitant orifice area and pressure half-time, changing total peripheral resistance and arterial compliance (but not left ventricular compliance) within the physiologic range significantly altered the pressure half-times. We concluded that the influence of total peripheral resistance and arterial compliance limits the usefulness of Doppler echocardiographic determination of pressure half-time as a method of assessing the severity of aortic regurgitation. (Ј Ам Soc Есно 1990;3:46-53.)

Doppler echocardiographic determination of pressure half-time has been proposed as a method of assessment of the severity of aortic regurgitation. Several recent studies have reported that continuous wave Doppler recording of regurgitant flow velocity may be useful in quantitation of the degree of aortic regurgitation by evaluating the rate of pressure equalization across the regurgitant orifice by means of the simplified Bernoulli equation.¹⁻³ The basis for this approach is earlier studies in which the diastolic pressure drop in the aorta was used to estimate the amount of aortic regurgitation.⁴⁵ Libanoff⁴ found that the time needed for aortic pressure to drop to half its initial value, that is, pressure half-time, varied with the severity of aortic regurgitation.

However, none of these studies evaluated the influence of other factors, such as total peripheral resistance, arterial compliance, and left ventricular compliance, on pressure half-time. In a recent study, Samstad et al.⁶ found a positive correlation between total peripheral resistance and pressure half-time, raising questions about the uniqueness of the relationship between pressure half-time and aortic regurgitant flow. The purpose of this study was to evaluate Doppler echocardiographic determination of pressure half-time as a method of assessing the severity of aortic regurgitation. For this evaluation, we determined the influence of total peripheral resistance, arterial compliance, and left ventricular compliance on pressure half-time in hydromechanical and computer models of the cardiovascular system.

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Figure 1 Hydromechanical model of cardiovascular system: 1, atrium; 2, ventricle; 3, aorta; 4, compliant chamber ("windkessel"); 5, peripheral resistance; 6, venous system. All parts of simulator are made of silicone rubber except the atrium and the venous system.

MATERIAL AND METHODS

Hydromechanical Simulator

A cardiovascular hydromechanical simulator driven by an electropneumatic unit was used (Figure 1). The simulator consisted of an "atrium," a "ventricle," two "valves" (aortic and mitral), elastic tubes representing the aorta, carotid, renal, and femoral arteries, and a delay tube ("veins"). The elastic parts of the simulator were made of silicone rubber. The delay tube and the atrium were made of plastic. Cardiac output was measured by a Pitot device positioned between the delay tube and the atrium and was accurate to ± 0.1 L/min between 2.0 and 7.0 L/min.

Before the experiment, we adjusted maximum ventricular pressure, the duration of systole, the rates of pressure increase and decrease, and the duration of diastole. For fluid, we filled the model with 5 L water and added Sephadex particles (20 to 50 μ m, Sephadex G-25/Superfine, Pharmacia Fine Chemicals, Uppsala, Sweden) to obtain an ultrasound signal. In a control experiment, the compliance of the elastic vessels ("arteries") was determined to be approximately 0.70 ml/mm Hg by direct measurements of absolute volume and pressure in the vessels.

For the experiments, aortic regurgitation was produced by two mechanical aortic valves with holes of 16 mm² or 24 mm² in the disc. The diastolic pressure gradient across the aortic valve was obtained by means of Statham P23ID (Gould Inc., Oxnard, Calif.) pressure transducers connected to fluid-filled catheters in the ventricle and the aortic root. To simulate changes in peripheral resistance, we placed various resistances at the outlets of the elastic tubes. Total peripheral resistance was determined as mean arterial pressure divided by cardiac output. To reduce arterial compliance, we clamped the "femoral artery" part of the model (constituting about 20% of arterial vessel volume). The effect of left ventricular compliance on pressure half-time could not be evaluated in the simulator because this variable could not be controlled independently.

The pressure drop across the aortic valve was calculated from the maximum velocity obtained with continuous wave Doppler by use of the simplified Bernoulli equation:

$$p_1(t) - p_2(t) = 4v^2$$

in which p is pressure in millimeters of mercury and v is velocity in meters per second. Pressure half-time was defined as the time required for the maximum velocity to fall from peak velocity to peak velocity divided by $\sqrt{2}$.⁷

To measure pressure half-time from a velocity recording, a line was drawn along the maximum velocity envelope, and a second line was drawn parallel to the baseline at the velocity corresponding to maximum velocity divided by $\sqrt{2}$. Pressure half-time was then measured along the baseline from the time of maximum velocity to the intersection of the two drawn lines.⁶ Continuous wave Doppler recordings were made on a CFM 700 (Vingmed, Oslo, Norway) by use of a 2 MHz transducer from a fixed position on the aortic arch. All measurements from the velocity curves were averaged over at least five consecutive cardiac cycles.



Figure 2 Computer (electric analog) model of the circulatory system. Capacitors with *diagonal* arrows represent time-dependent compliances (active elements). *RV*, Right ventricle; *RRA*, resistance right atrium; *RCPA*, resistance central pulmonary artery; *RPPA*, resistance peripheral pulmonary artery; *RLA*, resistance left atrium; *RCAO*, resistance central aorta; *RPAO*, resistance peripheral aorta; *CV*, compliance venous bed; *CPA*, compliance pulmonary artery; *RIV*, resistance insufficient valve; *CRA*, compliance right atrium; *CRV*, compliance right ventricle; *CLA*, compliance left ventricle; *CAO*, compliance aorta.

Table 1	Hemodynamic	variables	in the	cardiovascular	model wi	ith a i	regurgitant	orifice area	of 24	mm ²
							<i>(</i>) <i>(</i>)			

			Total		
Pressure half-time (msec)*	Cardiac output (L/min)	Regurgitant volume (L/min)	peripheral resistance (mm Hg · sec/ml)	Maximum aortic pressure (mm Hg)	Minimum aortic pressure (mm Hg)
123 ± 4	6.0	3.1	0.55	138	14
153 ± 9	5.5	3.5	0.65	138	20
193 ± 11	5.0	3.9	0.71	138	25
223 ± 19	4.4	4.0	0.96	140	35
263 ± 8	3.8	4.4	1.26	142	48
310 ± 26	3.0	4.7	1.77	145	60
323 ± 5	2.0	4.9	3.05	148	78

Heart rate was 92 beats per minute.

*Mean ± standard deviation.

Computer Model

The computer model (Figure 2) was based on the electrical analog model of the circulatory system proposed by Piene et al.⁸ Four active heart chambers, that is, the atria and ventricles (right atrium, left atrium, right ventricle, and left ventricle), were modeled by time-varying "compliances." The atria and ventricles were connected to each other by unidirectional valves and by small resistances. The right ventricle was connected to the left atrium by a lumped windkessel model of the pulmonary circulation, that

is, a network consisting of the pulmonary valves, two resistances, and a compliant element. The left ventricle was connected to the venous bed through a similar representation of the systemic arteries. The venous bed was represented by a large compliance and a small inflow resistance next to the right atrium. The valve between the left ventricle and the arterial bed was unidirectional during systole and was represented by a resistance during diastole to simulate aortic regurgitation.

To simulate different regurgitant flows, different



Figure 3 A, Relationship between pressure half-time (*PHT*) and total peripheral resistance (*TPR*) at two different regurgitant orifices: 16 mm² and 24 mm². B, Relationship between regurgitant volume (*REG VOL*) and total peripheral resistance in the same situations. Asterisk marks two pairs of connected data points.

regurgitant orifice areas were obtained by varying the regurgitant resistance between 0.5 and 4.0 mm Hg \cdot sec/ml. This gave regurgitant fractions from 0.1 to 0.6. Total peripheral resistance was varied from 0.5 to 3.0 mm Hg \cdot sec/ml, and arterial compliance was varied from 0.5 to 2.0 ml/mm Hg. Changes in left ventricular compliance were simulated in two different ways: (1) by increasing the stiffness of the left ventricle up to four times by changing the pressure-volume relationship during diastole and (2) by extending the model to contain an elastic pericardium whose pressure-volume characteristic was described by an exponential pressure-volume relation in which position along the volume axis could be changed by a volume offset.⁸ Thus different pericar-

dial offset volumes influenced left ventricular compliance. Pressure half-time in this model was defined as the pressure gradient half-time between the aortic and left ventricular pressures. Heart rate was constant at 60 beats per minute.

RESULTS

Hydromechanical Simulator

In the hydromechanical simulator the hemodynamic values varied widely during the experiments (Table 1). The values are not necessarily pertinent to the hemodynamic situation in humans because the model



Figure 4 Relationship between pressure half-time and total peripheral resistance at normal and reduced arterial compliance (C) in the cardiovascular hydromechanical simulator. To reduce arterial compliance, about 20% of elastic vessel volume was clamped. Regurgitant orifice area was 24 mm². Abbreviations are shown in the *legend* of Figure 3.



Figure 5 Relationship between pressure half-time and different sizes of the regurgitant orifice area represented by different resistances (Ri) in the computer model. Total peripheral resistance and arterial compliance were 2 mm Hg \cdot sec/ml and 1 ml/mm Hg, respectively. Abbreviations are shown in the *legend* of Figure 3.

did not incorporate any compensatory regulation; for example, it did not maintain a stable cardiac output irrespective of the regurgitant volume.

When total peripheral resistance was increased or decreased within the physiologic range pertinent to humans, the measured pressure half-time increased or decreased considerably (Figure 3, A). This was

true for both the 16 mm^2 and the 24 mm^2 regurgitant orifice areas. The difference in measured pressure half-time between the two orifice areas at a given total peripheral resistance was small compared with the variation induced by total peripheral resistance changes, as shown by comparison of the two connected data points in Figure 3, *A*. Increasing the



Figure 6 Relationship between pressure half-time and total peripheral resistance in the computer model. Different regurgitant orifice areas are represented by different resistances (Ri) from 0.5 to 4.0 mm Hg \cdot sec/ml. These resistances gave regurgitant fractions from 0.1 to 0.6. Abbreviations are shown in the *legend* of Figure 3.

regurgitant orifice area shortened pressure half-time, as expected. In addition, increasing the regurgitant orifice area increased the regurgitant volume (Figure 3, B). However, a change in regurgitant volume above 1 L/min changed the pressure half-time by only about 10% (see the two pairs of connected data points in Figure 3). Conversely, if pressure half-time was changed by about 10% (20 milliseconds), that could, according to Figure 3, represent a change in regurgitant volume of more than 1 L/min, but it could also result from a change in total peripheral resistance of about 0.25 mm Hg \cdot sec/ml.

Reduction of arterial compliance also influenced the measured pressure half-times (Figure 4). When arterial compliance was reduced by approximately 20% at a given peripheral resistance, pressure halftime decreased by about 75 milliseconds. These data indicate that, with different arterial compliance values, a range of different pressure half-times can be obtained with the same regurgitant orifice area.

Computer Model

In the computer model, when total peripheral resistance and arterial compliance were held constant at 2 mm Hg \cdot sec/ml and 1 ml/mm Hg, respectively, and different resistances in the regurgitant orifice simulated different degrees of regurgitation, there was a proportional relationship between pressure half-time and a regurgitant orifice resistance below 2 mm Hg \cdot sec/ml (which equals a regurgitant fraction of greater than 0.3). Above 2 mm Hg \cdot sec/ml the relationships leveled off (Figure 5).

However, when total peripheral resistance was changed, pressure half-time changed accordingly. The change in pressure half-time depended on the resistance in the regurgitant orifice. For example, increasing the resistance in the regurgitant orifice (and thus decreasing the regurgitant fraction) increased the influence of total peripheral resistance on pressure half-time (Figure 6). These results in the computer model were similar to the results in the hydrome-chanical simulator, but the deviation of curves at different regurgitant orifice resistances as total peripheral resistance increased was more obvious in the computer model (compare Figure 3, A).

Similarly, increasing arterial compliance increased the pressure half-time, and again the importance of arterial compliance increased as the regurgitant orifice resistance increased, that is, as the regurgitant orifice area decreased. The effect is again clearer in the computer model (compare Figure 4 and Figure 7). With regurgitant fractions of about 0.4 to 0.6, equal to a regurgitant orifice resistance of 0.5 to 1.0 mm Hg \cdot sec/ml, changes in arterial compliance had only a small influence on the measured pressure half-time.

Left ventricular compliance had a minimal influence on pressure half-time. When ventricular diastolic stiffness was increased up to a factor of 4, with regurgitant fractions varying from 0.1 to 0.6,



Figure 7 Relationship between pressure half-time and arterial compliance in the computer model with different degrees of regurgitation (resistance of 0.5 is equivalent to a regurgitant fraction of 0.6 and resistance of 2 to a regurgitant fraction of 0.2). Ri is a resistance representing the regurgitant orifice. Abbreviations are shown in the *legend* of Figure 3.

pressure half-time changed a maximum of 30 milliseconds. When pericardial offset volumes were changed, giving end-diastolic pressures from 10 to 20 mm Hg, pressure half-time changed by a maximum of 20 milliseconds.

DISCUSSION

The use of pressure half-time to assess the severity of aortic regurgitation was developed in the catheterization laboratory by Libanoff.⁴ Libanoff found an inverse correlation between aortic pressure halftime and the angiographic severity of aortic regurgitation. Other investigators have found a similar correlation between the rate of pressure equalization across the regurgitant orifice obtained with Doppler echocardiography and the severity of aortic regurgitation in patients.¹⁻³ Teague et al.² found that Doppler pressure half-times were inversely related to the regurgitant fraction and angiographic severity and that the pressure half-time was independent of pulse pressure, mean arterial pressure, ejection fraction, and left ventricular end-diastolic pressure. Masuvama et al.¹ found that the half-time index (the time to decline to half peak velocity) was significantly lower in patients with moderate aortic regurgitation than in patients with mild aortic regurgitation $(0.89 \pm 0.14 \text{ versus } 1.22 \pm 0.24 \text{ seconds})$ and was significantly lower in patients with severe aortic regurgitation $(0.52 \pm 0.08 \text{ seconds})$ than in patients

with moderate aortic regurgitation. Labovitz et al.³ found a high correlation (r = 0.93) between the grade of aortic insufficiency by angiography and the velocity deceleration slope as measured by continuous wave Doppler, whereas there was an inverse correlation between the pressure half-time and the severity of aortic regurgitation as graded by angiography (r = 0.73).

In contrast is a recent study of humans by Samstad et al.6 that suggested that other factors, such as total peripheral resistance, arterial compliance, and left ventricular compliance, probably influence pressure half-time enough to limit the usefulness of pressure half-time as a method of evaluating aortic regurgitation. However, this study did not assess the influence of arterial compliance and left ventricular compliance on pressure half-time because these variables could not be measured. In accordance with Samstad et al.6 we observed, in preliminary experiments in the hydromechanical flow model, that identical pressure half-times are obtained by manipulation of total peripheral resistance, even with a difference in regurgitant volume of almost 5 L/min.9 In pig experiments we have observed that similar pressure half-times are obtained after total peripheral resistance is altered by pharmacologic agents, even with a fivefold increase in regurgitant volume (Slørdahl SA, Piene H, Rossvoll, et al. June 1988. Unpublished data).

This study corroborates that pressure half-time obtained with Doppler echocardiography in aortic regurgitation is not only a function of the regurgitant

orifice area but is also influenced by total peripheral resistance and arterial compliance enough to limit its usefulness as a method of evaluating the severity of aortic regurgitation. Results in the hydromechanical simulator showed that over the physiologic range of total peripheral resistance pertinent to humans pressure half-time varied from about 100 to 250 milliseconds at both of the regurgitant orifice areas and that reducing arterial compliance by clamping about 20% of the elastic vessel volume reduced pressure half-time by about 75 milliseconds. The findings in the computer model were similar. With a regurgitant fraction of 0.2 to 0.3, the pressure half-time more than doubled when total peripheral resistance was reduced from a high to a low physiologic value (3.0 to 0.5 mm Hg \cdot sec/ml), and reductions in arterial compliance had an even greater proportional influence. At increasing regurgitant fractions, the influence of total peripheral resistance and arterial compliance on pressure half-time was reduced. For severe regurgitations the pressure half-time was mainly determined by the regurgitant orifice area (regurgitant fraction of 0.5 to 0.6). The computer model also showed that left ventricular pressure during diastole had little influence on the rate of pressure equalization across the regurgitant orifice, indicating that we can ignore left ventricular compliance as an important factor in determining pressure half-time.

In addition, according to our observations a lumped arterial ("resistance-compliance-resistance") model can explain the diastolic pressure decay that occurs in the aorta of pigs when mean aortic pressure is above 60 mm Hg (Piene H, Slørdahl SA, Samstad SO, et al. May 1989. Unpublished data). Considering the arterial bed as a reservoir with drains through the incompetent aortic valve and the arterioles, opening one drain or the other should have the same influence on aortic pressure decay. This is in essence what Samstad et al.⁶ found in patients. Other properties of the reservoir, such as compliance, would also influence the rate of pressure drop, as demonstrated here.

In conclusion, this study emphasizes the need to be careful in the evaluation of aortic regurgitation with pressure half-time methods, particularly at small to moderate regurgitations. Pressure half-time methods might become more reliable if total peripheral resistance and arterial compliance could be taken into account.

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Paper II



	Physiological measurement
anten de Secondo	Estimation of arterial compliance in
	aortic regurgitation: three methods
energi est. Constante	evaluated in pigs
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	Abstract—Three methods for measuring arterial compliance when aortic regurgita- tion is present are examined. The first two methods are based on a Windkessal model composed of two elements, compliance C and resistance R. Arterial compliance was estimated from diastolic pressure waveforms and diastolic regurgitant flow for one method, and from systolic aortic pressure waveforms and systolic flow for the other method. The third method was based on a three-element Windkessel model, com- posed of characteristic resistance r, compliance C and resistance R. In this method arterial compliance was calculated by adjusting the model to the modulus and phase of the first harmonic term of the aortic input impedance. The three methods were compared and validated in six anaesthetised pigs over a broad range of aortic pres- sures. The three methods were found to give quantitatively similar estimates of arterial compliance varied widely, probably because of poor validity of the Windkessel models in the low pressure range.
	Keywords—Aortic regurgitation, Arterial compliance, Fourier analysis, Impedance, Mean aortic pressure, Peripheral resistance, Windkessel model
an a	Med. & Biol. Eng. & Comput., 1990, 28, 293-299

1 Introduction

RELIABLE METHODS for measuring arterial compliance in patients with aortic regurgitation are important. One reason is that total arterial compliance, an important component of the load of the heart (ELZINGA and WESTERHOF, 1973), decreases with age (MOZERSKY *et al.*, 1972; RENEMAN *et al.*, 1986) and thus may contribute to the gradual haemodynamic deterioration observed in patients with chronic aortic regurgitation (PERLMUTTER *et al.*, 1988). Another reason is that methods for measuring arterial compliance may help to clarify how arterial compliance influences the regurgitant velocity measured by Doppler echocardiography, which is used in quantifying aortic regurgitation (MASUYAMA *et al.*, 1986).

Estimates of arterial compliance can be made indirectly by assuming that aortic diastolic pressure decays exponentially and calculating a time constant as the product of total arterial resistance and compliance (DESWYSEN *et al.*, 1980; VENTURA *et al.*, 1984; RANDALL *et al.*, 1984; SIMON *et al.*, 1985; LEVY *et al.*, 1985; MESSERLI *et al.*, 1985). A problem with this method is that reflections and other perturbations often distort diastolic aortic pressure. To avoid this problem, YIN *et al.* (1987) proposed an alternative method for estimating arterial compliance by using the

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area under the diastolic pressure wave rather than depending on a strictly exponential shape of the pressure decay and calculation of the time constant. However, Yin *et al.*'s method cannot be used without modifications when aortic regurgitation is present because diastolic aortic pressure decay in the presence of aortic regurgitation is also dependent on the regurgitant orifice (JUDGE and KENNEDY, 1970), thus further increasing the number of factors influencing the aortic pressure decay.

Three methods are proposed for estimating arterial compliance when aortic regurgitation is present. One method is similar to the method proposed by YIN et al. (1987), in which the area under the diastolic pressure wave is used to calculate the time constant of aortic pressure decay. YIN et al.'s method has been modified to take into account both the regurgitant flow and the peripheral flow that influence the pressure decay at a given arterial compliance. The second method is similar to the first method except that we used the area under the systolic pressure wave rather than the diastolic pressure wave to calculate arterial compliance. In the third method, the modulus and phase for the first harmonic term of the aortic input impedance were determined by Fourier analysis, and arterial compliance was calculated according to a three-element arterial analogue demanding identical impedance at the frequency of the first harmonic.

The three methods were compared and validated in pigs.

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2 Materials and methods

2.1 Pig experiments

Six pigs (age about 3 months, body weight $21 \cdot 3 \pm 2 \cdot 3$ (SD) kg) were anaesthetised with pentobarbital, 700– 1000 mg intraperitoneally initially and then 3–4 mg min⁻¹ by continuous intravenous infusion. The pigs were tracheotomised and ventilated with a volume-regulated respirator (Model No. 613, Harvard Apparatus, Massachusetts). Blood gases and pH were repeatedly measured on an IL 1306 pH/blood gas analyser (Instrumentation Laboratories, Massachusetts). Body temperature was recorded by a rectal thermometer and kept at normal levels by a heating pad and wrappings. The urinary bladder was drained through a cystostomy.

A thoracotomy was performed by splitting the sternum, and the heart was exposed by a pericardiotomy and suspended in a pericardial cradle. A saline-filled polyvinyl catheter (no. 7F) was introduced through the apex of the left ventricle for recording left ventricular pressure. Similar catheters (no. 7F) were introduced through the left carotid artery and internal jugular vein to record the pressures in the ascending aorta and in the right atrium. All catheters were stiff and short to obtain resonant frequencies (tap test) above 60 Hz after connection to Statham P231D transducers. The transducers were statically calibrated against a mercury manometer with zero pressure referred to the midlevel of the left ventricle.

Acute aortic valve regurgitation was produced by opening a cage basket catheter (Laboratorie Porges, Paris, France) inserted into the aortic valve. The catheter was advanced from the right carotid artery and the position was verified by echocardiography (CFM-700, Vingmed, Oslo, Norway). The amount of aortic regurgitation could be altered by opening or closing the basket. Through the left femoral artery a catheter with an inflatable balloon tip (Fogarty occlusion catheter, 22F) was placed in the descending aorta in four pigs. Aortic pressure was increased by inflating the balloon and decreased by deflating the balloon. In some samples aortic pressure was manipulated with pharmacological agents. We used the α -receptor stimulators metoamine (Vasoxine, 20 mg, n = 3samples) or metaraminol (Aramine, 0.5 mg, n = 2) to increase aortic pressure, and nitroglycerin (10 mg, n = 11)to decrease aortic pressure.

Two electromagnetic flow probes (12-16 mm ID, Skalar Instruments, Delft, The Netherlands) were placed snugly around the ascending aorta and the pulmonary artery close to the valves. Before regurgitation was induced, mean aortic and pulmonary flows were calibrated to give the same volume by calculation of a fixed calibration factor in the computer analysis program (see below). The physiological discrepancy between pulmonary and aortic flow due to coronary flow was disregarded. Regurgitant aortic volume was measured as the difference between systolic aortic and pulmonary stroke volumes. Cardiac output was measured as pulmonary flow, and the regurgitant fraction was measured as the ratio between aortic regurgitant volume and aortic systolic volume. Total peripheral resistance was determined as mean arterial pressure minus mean right atrial pressure divided by cardiac output.

All signals were continuously recorded on a Mark VII WR 3101 Graphtec Linearecorder at paper speeds of 1 or 50 mm s^{-1} . The signals were also stored by a digital computer (PDP-11/23 Plus with A/D convertor, Digital Equipment Corp., Massachusetts) connected to the recording systems. The analogue-to-digital conversion system worked at a sampling rate of 10 ms in each channel.

2.2 Calculations

Methods 1 and 2 are both based on a two-element Windkessel arterial model consisting of a resistance R and a compliance C in parallel. If the volume of the arterial system is denoted by V, the continuity equation is

$$\frac{dV}{dt} + q_{out} = q_{i\pi} \tag{1}$$

where q_{out} is flow out of the arterial system into the venous system and q_{in} is flow into the system from the ventricle. In regurgitation q_{in} has a negative value during diastole.

Total arterial compliance was defined as

$$C = \frac{dV}{dP_a} \tag{2}$$

where P_a is the arterial pressure.

Outflow of blood into the venous system was assumed to be proportional to the pressure difference

$$q_{out} = \frac{P_a - P_{ven}}{R} \tag{3}$$

where P_{ven} is the venous pressure.

By combining eqns. 1-3 we obtain

$$\frac{CdP}{dt} + \frac{P_a - P_{ven}}{R} = q_{in} \tag{4}$$

which we assumed to be valid at any time period during the heart cycle.

Method 1 Calculation of arterial compliance during diastole

For any time period during diastole, $q_{in} = 0$ in eqn. 4 as long as there is no diastolic backflow through the aortic valve. If we define $P_a = P_1$ at $t = t_1$ and assume that C is a constant, the solution to eqn. 4 during diastole is

$$P(t) - P_{ven} = (P_1 - P_{ven})e^{(t-t_1)/RC}$$
(5)

As $P_a \ge P_{ven}$, C can be calculated from resistance R and time constant RC according to

$$P = P_1 e^{(t-t_1)/RC}$$
(6)

which is the most widely used exponential equation of aortic pressure decay.

To obtain a more valid equation, YIN et al. (1987) proposed integrating eqn. 4, directly over a diastolic time period t_1 to t_2 , with $q_{in} = 0$ (zero diastolic aortic flow), because the pressure decay is not always an exact exponential. However, neither eqn. 6, nor this modification can be used when aortic regurgitation is present, because diastolic flow is assumed to be equal to zero. Therefore, in our first method we modified YIN et al.'s method to account for regurgitant diastolic flow back into the left ventricle during diastole. Specifically, we replaced q_{in} by $-q_{reg}$ in eqn. 4 and, after integration, obtained

$$C \int_{t_1}^{t_2} \frac{dP}{dt} dt + \frac{1}{R} \int_{t_1}^{t_2} (P - P_{ven}) dt + \int_{t_1}^{t_2} q_{reg} dt = 0$$
$$t_s < t_1 < t_2 < T \qquad (7)$$

where t_1 is the end of systole and T is the end of diastole. In our method we defined t_1 to be the time of the left ventricular pressure minimum and t_2 to be the time of the aortic pressure minimum minus 50 ms, to avoid pressure oscillations at the closure and opening of the aortic valves. If P_1 and P_2 denote the pressures corresponding to t_1 and t_2 , and A_d is the area under the pressure curve above the

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venous pressure P_{ven} , i.e., $P_a - P_{ven}$ integrated over the time interval t_1 to t_2 , eqn. 7 is transformed to

$$C(P_2 - P_1) + 1/RA_d + Q_{reg} = 0$$
(8)

where Q_{reg} is the total regurgitant blood volume from t_1 to t_2 . Rewritten to express arterial compliance explicitly, method 1 is

$$C = \frac{Q_{reg} + A_d/R}{P_2 - P_1} \tag{9}$$

Method 2 Calculation of arterial compliance during systole In method 2 we obtained an alternative expression for compliance by integrating eqn. 4 during systole:

$$C \int_{t_1}^{t_2} \frac{dP}{dt} dt + \frac{1}{R} \int_{t_1}^{t_2} (P - P_{ven}) dt = q_{in}$$
(10)

We defined t_1 and t_2 to be the start and end of systolic

ejection, respectively. The corresponding pressures at t_1 and t_2 were denoted P_d (diastolic pressure) and P_c (endsystolic pressure). If A_a is defined as the area under the pressure curve (above the venous pressure, P_{ven}) during systole, the expression for arterial compliance will be

$$C = \frac{Q_{in} - A_s/R}{P_c - P_d} \tag{11}$$

An advantage of this method is that the regurgitant volume is not needed because there is no regurgitation during systole, although increased total stroke volume will reflect the degree of aortic regurgitation and influence the calculated arterial compliance value.

Method 3 Calculation of arterial compliance from impedance analysis

Method 3 is based on a three-element Windkessel model, the r-C-R model (WESTERHOF, 1968). r represents characteristic resistance, which is the model's representa-

Fig. 1 20-50 consecutive arterial compliance values obtained by the three methods and the effect of interventions by either the occlusion catheter or pharmacological agents in each of the six pigs. All samples are listed in consecutive order for each pig. C: control sample(s), B: balloon inflation, D: balloon deflation, A: metaraminol (0.5 mg), N: nitroglycerin (10 mg), V: metoamine (20 mg) \Box method 1 \blacklozenge method 2 + method 3

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tion of the characteristic impedance of the aorta. r can be measured from the ratio between aortic pressure change and flow in early systole (DUJARDIN and STONE, 1981). We calculated r as the regression slope of aortic pressure against flow from the time of the aortic pressure minimum to the aortic flow maximum. R was determined by subtracting r from the total peripheral resistance. Arterial compliance was estimated by determining the modulus and phase for the first harmonic term of the aortic input impedance by Fourier analysis of recorded aortic pressure and flow over a complete heart cycle at stable haemodynamic conditions. The input impedance Z of the r-C-R model is given by the equation

$$Z = r + \frac{R}{j\omega CR + 1} \tag{12}$$

where $\omega = 2\pi f$ (f = frequency) and $j = \sqrt{-1}$. Rewritten with a real and an imaginary part, this equation transforms to

$$Z = r + \frac{R}{1 + \omega^2 R^2 C^2} - j \frac{\omega R^2 C}{1 + \omega^2 R^2 C^2}$$
(13)

Because the modulus |Z| and the phase β are determined from the first harmonic term of pressure and flow, total

arterial compliance is given by the equation:

$$C = \frac{-1 |Z| \sin \beta}{\omega R(|Z| \cos \beta - r)}$$
(14)

since $Z_{imaginary} = |Z| \sin \beta$ and $Z_{real} = |Z| \cos \beta$, $\omega = 2\pi \times \text{heart rate.}$

2.3 Statistics

All average values are given \pm the standard deviation (SD). To study the agreement between the three arterial compliance estimates, we used BLAND and ALTMAN's method (1986) to calculate how much methods 2 and 3 differed from method 1. For this calculation, we plotted the difference between two methods against the mean value of the same two methods. We were thereby better able to disclose systematic differences between the methods over the range of obtained values. The lack of agreement was summarised by calculating the bias, estimated by the mean difference (mean) and the standard deviation of the differences (SD). Most of the differences were expected to lie within two standard deviations (95 per cent confidence interval), as the differences are likely to follow a normal distribution.

Fig. 2 The relationship between mean aortic pressure (MAP) and arterial compliance in the six pigs for the three methods \Box method 1 \blacklozenge method 2 + method 3

3 Results

The three different methods of estimating arterial compliance gave quantitatively similar estimates except during the two interventions, balloon deflation and nitroglycerin infusion, that reduced mean aortic pressure (Fig. 1). Discrepancies between the three methods were largest at mean aortic pressures below 60 mm Hg (Fig. 2). In addition, arterial compliance tended to increase when mean aortic pressure was decreased (Fig. 2). This tendency was pronounced for mean aortic pressures below 60 mm Hg. In a few cases (n = 8) when mean aortic pressure was below 60 mm Hg, estimated arterial compliance values for one or two of the methods became negative; these estimates are not included in the results. In these cases the sample is represented only by the other method(s).

Similarly, when we compared our three arterial compliance estimates by plotting the difference between two methods against their mean, we found that the agreement between the three methods was far better when only the samples with mean aortic pressure above 60 mm Hg were included than when all samples were included (Fig. 3). The mean difference between methods 1 and 2 for all samples was $0.14 \text{ ml mm Hg}^{-1}$, and +2SD and -2SD were $1.40 \text{ ml mm Hg}^{-1}$ and $-1.12 \text{ ml mm Hg}^{-1}$, respectively. Thus, results obtained by method 2 were on average 1.1 ml mm Hg⁻¹ below or 1.4 ml mm Hg⁻¹ above method 1. However, for samples with mean aortic pressure above 60 mm Hg the mean difference was $-0.03 \text{ ml mm Hg}^{-1}$ and +2SD and -2SD were 0.13 ml mm Hg and $-0.19 \text{ ml mm Hg}^{-1}$, respectively, indicating acceptable agreement. Similarly, for methods 1 and 3, the mean difference between the methods for all samples was $0.12 \,\mathrm{ml}\,\mathrm{mm}\,\mathrm{Hg}^{-1}$, and +2SD and -2SD were $1.30 \text{ ml mm Hg}^{-1}$ and $-1.06 \text{ ml mm Hg}^{-1}$, respectively. For samples with mean aortic pressure above 60 mm Hg, the mean difference was $-0.03 \text{ ml mm Hg}^{-1}$, and +2SDand -2SD were $0.21 \text{ ml mm Hg}^{-1}$ and $-0.27 \text{ ml mm Hg}^{-1}$, respectively.

Aortic regurgitation at mean aortic pressures above 60 mm Hg did not alter arterial compliance estimates from control values (Table 1). The difference between a control sample and the first regurgitation sample at a similar mean aortic pressure was $0.03 \pm 0.02 \text{ mm Hg}^{-1}$; this differ-

Table 1 Arterial compliance for the three different methods before (B) and after (A) aortic regurgitation

Pig		n	Method 1	Method 2	Method 3
1	B	1	0.55	0.52	0.59
	Α	21	0.46 ± 0.05	0.52 ± 0.06	0.54 ± 0.08
2	В	5	0.57 ± 0.03	0.53 ± 0.01	0.66 ± 0.09
	Α	27	0.65 ± 0.08	0.69 ± 0.10	0·61 ± 0·09
3	в	9	0.56 ± 0.04	0.63 ± 0.05	0.75 ± 0.17
	Α	21	0.60 ± 0.15	0.66 ± 0.12	0.60 ± 0.07
4	В	7	0.50 ± 0.09	0.53 ± 0.16	0.55 ± 0.11
	Α	20	0.52 ± 0.05	0.52 ± 0.05	0.55 ± 0.08
5	в	4	0.42 ± 0.02	0.39 ± 0.03	0.48 ± 0.05
	Α	3	0.37 ± 0.02	0.39 ± 0.02	0.41 ± 0.01
6	в	4	0.36 ± 0.06	0·36 ± 0·06	0.41 ± 0.09
	Α	5	0.34 ± 0.06	0.32 ± 0.10	0.33 ± 0.11

n: number of samples. Data are mean \pm SD for 127 samples from six pigs whose mean aortic pressure was above 60 mm Hg.

ence was not significant. In addition, all three methods gave similar estimates both in presence and absence of aortic regurgitation (Table 1). Furthermore, all three methods gave similar estimates regardless of the degree of regurgitation. At a regurgitant fraction above 0.5 and mean aortic pressures above 60 mm Hg, there were no sig-

Fig. 3 Mean arterial compliance values plotted against mean difference for (a) methods 1 and 2 and (c) methods 1 and 3 for all samples, and mean aortic pressure (MAP) values above 60 mm Hg plotted against mean difference of arterial compliance values for (b) methods 1 and 2 and (d) methods 1 and 3

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nificant differences between estimates of arterial compliance (n = 7).

Cardiac output, mean aortic pressure and total peripheral resistance varied over broad ranges for all 190 samples from the six pigs (Table 2). Cardiac output varied from 1.7 ± 0.3 to 2.9 ± 0.4 litre min⁻¹, mean aortic pressure from 37 ± 6 to 100 ± 12 mm Hg, and total peripheral resistance from 1.2 ± 0.6 to 3.3 ± 0.8 mm Hg s ml⁻¹. The regurgitant fractions measured electromagnetically ranged from 0.1 to 0.6.

aortic pressures (Fig. 4).

In this study, we estimated total arterial compliance by using three Windkessel models. Another possible way to estimate total arterial compliance could be to calculate local arterial compliance at some defined areas, since several methods are available for calculating local arterial compliance from measurements of vessel diameters and arterial pressure (RENEMAN *et al.*, 1986; MILNOR, 1989). However, to be able to use local arterial compliance as a reliable estimate of total arterial compliance, one first has

Table 2 Range of haemodynamic variations induced in six pigs with aortic regurgitation

Pig	п	CO, litre min ⁻¹	RF	HR, beats min ⁻¹	MAP, mm Hg	TPR, mm Hg s ml ⁻¹
1	26	1.3-2.9	00-5	73-84	48-77	2.3-5.0
2	26	1.6-3.6	0-0-3	83-113	27-106	0.9-2.3
3	38	2.1-3.2	0-0-6	93-108	37-100	0.7-2.8
4	39	2.1-2.8	0-0-3	89-117	34-118	0.9-3.0
5	19	1.7-2.4	00-3	7 9 87	34-100	0.8-3.3
6	19	1.4-2.3	00-4	99-116	39-100	1.4-3.5

n: number of samples; CO: cardiac output; RF: regurgitant fraction; HR: heart rate; MAP: mean aortic pressure; TPR: total peripheral resistance.

4 Discussion

In the present study we propose three methods for estimating arterial compliance during aortic regurgitation. Methods 1 and 2 are based on a Windkessel model composed of two elements (C and R). Arterial compliance is estimated from diastolic aortic pressure waveforms and diastolic regurgitant flow for method 1, and from systolic aortic pressure waveforms and systolic flow for method 2. Method 3 is based on a three-element Windkessel model (r-C-R), and arterial compliance is calculated by adjusting this model to the modulus and phase of the first harmonic term of the aortic input impedance. Thus, the methods calculate arterial compliance from different parts of the heart cycle: methods 1 and 2 from the diastolic and the systolic periods, respectively, and method 3 from the whole heart cycle.

We found that the three methods gave quantitatively similar estimates with little variation as long as mean aortic pressure was above 60 mm Hg. This finding indicates that either of the two-element Windkessel models can be used for calculating arterial compliance for mean aortic pressures above 60 mm Hg in pigs, and that the r of the three-element model is of little practical consequence for the arterial compliance estimates because calculating arterial compliance from either systole or diastole by the two-element model gave similar estimates. The advantage of method 2, in which arterial compliance is estimated from systolic aortic pressure waveforms and systolic flow, is that it can be applied in a clinical situation to estimate arterial compliance noninvasively from Doppler measurement of aortic flow and blood pressure values obtained by cuff.

Below 60 mm Hg, in addition to the results of the three methods varying substantially, the arterial compliance estimates tended to increase abruptly. The dependency of arterial compliance on mean aortic pressure is in accordance with earlier findings (BERGEL, 1961), but the large variation in the arterial compliance estimates, and the sometimes negative arterial compliance, were probably the result of poor validity of the Windkessel models in the low pressure range. Both models are based on the implicit assumption that the aortic diastolic pressure decay is exponential. However, this assumption is poor at low to determine the relationship between local and total arterial compliance. Even our estimates of arterial compliance from the Windkessel models may not represent total arterial compliance, but only the part of this compliance that influences aortic pressure at the aortic root, i.e. the compliance which is pertinent to the load of the left ventricle.

Fig. 4 An aortic blood pressure recording when mean aortic pressure was below 60 mm Hg. The aortic diastolic pressure decay is far from being exponential

In conclusion, we have developed three methods to calculate arterial compliance in pigs with aortic regurgitation, to study how changes in total arterial compliance influence the load on the heart and to obtain better estimates of regurgitant volume. The variations between the methods are small and acceptable for mean aortic pressures above 60 mm Hg.

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HAEMODYNAMIC EFFECTS OF ARTERIAL COMPLIANCE, TOTAL PERIPHERAL RESISTANCE, AND GLYCERYL TRINITRATE ON REGURGITANT VOLUME IN AORTIC REGURGITATION

BY STIG A SLØRDAHL, HROAR PIENE

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Haemodynamic effects of arterial compliance, total peripheral resistance, and glyceryl trinitrate on regurgitant volume in aortic regurgitation

Stig A Slørdahl, Hroar Piene

Abstract

Study objective – Afterload reduction is known to reduce regurgitant flow in patients with aortic regurgitation. Both arterial compliance and total peripheral resistance are determinants of afterload. The aim of this study was to evaluate the influence of arterial compliance and total peripheral resistance on the regurgitant volume.

Design – The values of arterial compliance and total peripheral resistance were assessed during aortic regurgitation at different regurgitant orifice areas in eight pigs before and after a bolus of glyceryl trinitrate. In a computer model the importance of arterial compliance and total peripheral resistance on the regurgitant volume was assessed by keeping each of them constant while the other variable was changed.

Measurements and main results – In both the experimental and computer models a very strong correlation was found between decreased total peripheral resistance and decreased regurgitant volume. Arterial compliance was of hardly any importance. A bolus of glyceryl trinitrate reduced regurgitant volumes and regurgitant fractions significantly.

Conclusions – Total peripheral resistance is an important factor in influencing the regurgitant volumes at a given regurgitant orifice area in aortic regurgitation, while arterial compliance is of less importance. Glyceryl trinitrate effectively reduces the regurgitant volumes by its effect on peripheral resistance.

Afterload reduction is known to have a favourable effect on regurgitant flow and left ventricular

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Key words: aortic regurgitation; glyceryl trinitrate; regurgitant orifice; regurgitant volume; arterial compliance; total peripheral resistance

Submitted 19 February 1991 Accepted 30 April 1991 performance in aortic regurgitation.¹⁻⁴ Both total peripheral resistance and arterial compliance are important physical properties of the arterial system and determinants of afterload. Decreasing arterial compliance and increasing total peripheral resistance are known to increase the mechanical load of the left ventricle, although arterial resistance probably plays a dominant role.⁵⁶ Another important point about arterial compliance is that due to the non-linear elastic properties of artery walls, ie, arterial compliance changes as a function of mean arterial pressure, any drug that reduces mean aortic pressure will increase arterial compliance. The independent influence of arterial compliance on the regurgitant volume compared to that of peripheral resistance has not however been assessed. The purpose of this study was to investigate how changes in arterial compliance and total peripheral resistance influenced regurgitant volume before and after a bolus of intravenous glyceryl trinitrate in anaesthetised pigs, and by simulating aortic regurgitation in a computer model of the circulatory system.

Methods

PIG EXPERIMENTS

This study was performed according to the guidelines of the American Physiological Society for the use of laboratory animals. Eight pigs (age about 3 months, body weight 20-25 kg) were anaesthetised with pentobarbitone, 700-1000 mg intraperitoneally initially, and 3-4 mg min⁻¹ by continuous intravenous infusion. The pigs were tracheotomised and ventilated with a volume regulated ventilator (Model No 613, Harvard Apparatus, MA, USA). Blood gases were repeatedly measured on an IL 1306 pH/blood gas analyser (Instrumentation Laboratories, MA, USA). Body temperature was recorded by a rectal thermometer and kept at normal levels by a heating pad and wrappings. The urinary bladder was drained through a cystostomy.

A thoracotomy was performed by splitting the sternum. The heart was exposed after pericardiotomy and suspended in a pericardial cradle. A saline filled polyvinyl catheter (No 7F) was introduced through the apex of the left ventricle for recording of left ventricular pressure. Similar catheters were introduced through the left carotid artery and internal

jugular vein to record the pressures in the ascending aorta approximately 2 cm above the valve and in the right atrium. All catheters were stiff and short to obtain resonant frequencies (tap test) above 60 Hz after connection to Statham P23ID transducers. The transducers were calibrated by a mercury manometer and zero pressure was referred to the mid left ventricular level.

A cage basket catheter (Laboratorie Porges, Paris, France) was inserted into the aortic valve and acute aortic valve regurgitation was produced by opening the cage. This type of catheter is known as the type used to remove kidney stones. The thin spiral wires were made to balloon out to impair valve closure in order to simulate valve incompetence in diastole, while creating hardly any stenosis during systole. The catheter was advanced from the right carotid artery and the position was verified by echocardiography (CFM-700, Vingmed, Oslo, Norway). The amount of aortic regurgitation was altered by opening or closing the wire basket. Glyceryl trinitrate was given as an intravenous bolus of 10 mg.

Two electromagnetic flow probes (12-16 mm internal diameter, Skalar Instruments, Delft, The Netherlands) were placed snugly around the ascending aorta and around the pulmonary artery close to the valves. Before regurgitation was induced, aortic and pulmonary mean flows were calibrated to give the same volume by calculation of a fixed calibration factor in the computer analysis program (see below). The physiological discrepancy between pulmonary and aortic flow due to coronary flow was disregarded. Cardiac output was measured as pulmonary flow and regurgitant aortic volume was measured as the difference between systolic aortic and pulmonary stroke volumes. The use of pulmonary flow as measurement of cardiac output avoided ambiguities concerning the zero baseline of aortic flow. The regurgitant fraction was measured as the ratio between regurgitant volume and systolic aortic stroke volume. Total peripheral resistance was determined as mean arterial pressure minus mean right atrial pressure divided by cardiac output. Pressure half time was defined as the pressure gradient half time between the aortic and left ventricular pressures.

All signals were continuously recorded on a Mark VII WR 3101 Graphtec Linearecorder at paper speeds of 1 or 50 mm \cdot s⁻¹. The signals were also stored by a digital computer (PDP-11/23 Plus with A/D converter, Digital Equipment Corporation, MA, USA) connected to the recording systems. The analogue to digital conversion system worked with a sampling rate of 10 ms in each channel.

COMPUTER MODEL

The computer model was based on the electrical analogue model of the circulatory system proposed by Piene *et al.*⁷ Four active heart chambers, ie, the left and

right atria and the left and right ventricles, were modelled by time varying "compliances". The atria and ventricles were connected to each other by unidirectional valves and small resistances. The right ventricle was connected to the left atrium by a lumped windkessel model of the pulmonary circulation, ie, a network consisting of the pulmonary valves, two resistances, and a compliant element. The left ventricle was connected to the venous bed through a similar representation of the systemic arteries. The venous bed was represented by a large compliance and a small inflow resistance next to the right atrium. The valve between the left ventricle and the arterial bed was unidirectional during systole and was represented by a resistance during diastole to simulate aortic regurgitation.8

To simulate different regurgitant flows the resistance that was introduced in parallel with the aortic unidirectional valve was varied between 0.5 and 4.0 mm Hg[.]s[.]ml⁻¹, thus simulating different regurgitant orifice areas. Due to the non-linear properties of the regurgitant orifice resistance the estimated orifice area (see below) could be different for the same input regurgitant resistance in the model. Regurgitant fractions ranged from 0.1 to 0.6. Total peripheral resistance was varied from 0.5 to 3.0 mm Hg·s·ml⁻¹, and arterial compliance was independently varied from 0.5 to 4.0 ml mm Hg⁻¹. Pressure half time was defined as the pressure gradient half time between the aortic and left ventricular pressures. Heart rate was constant at 60 beats min⁻¹. The computer model results were obtained in the same format as the experiments. Both sets of data were analysed in the same way in the calculations described below.

CALCULATIONS

Arterial compliance was calculated as described earlier.⁹ We chose to use a method that was independent of regurgitant volume. The method is based on a two element Windkessel arterial model consisting of a resistance R and a compliance C in parallel. The expression for arterial compliance during systole will be:

$$C = \frac{Q_{in} - A_s/R}{P_c - P_d}$$
(1)

where Q_{in} is systolic blood volume pumped into the arterial system from the ventricle, A_s is defined as the area under the pressure curve (above the venous pressure) during systole, and P_d and P_c are diastolic and end systolic valve closure pressures respectively.

Gorlin and Gorlin¹⁰ described a formula to calculate the relationships between pressure, area, and flow through stenotic valves. Ask *et al*¹¹ described a similar formula for flow through regurgitant valves:

$$q = C_d A_o \sqrt{\frac{2}{\rho}} (p_1 - p_2)$$
 (2)

Compliance, resistance, and glyceryl trinitrate in aortic regurgitation

Haemodynamic variables in the pigs with and without aortic regurgitation. Samples with four different calculated regurgitant orifices areas were used. Values are means(SD)

Regurgitant area (mm ²)	RF	Regurgitant volume (ml)	Aortic pre Mean	ssure (mm H Systolic	lg) Diastolic	Stroke volume (ml)	Compliance (ml·mm Hg ⁻¹)	TPR (mm Hg·s·m[⁻¹)	PHT (ms)	HR (beats min ⁻¹)
0			· · ·							
Control $(n = 16)$		0	82.1(8.3)	99.5(9.8)	63.4(7.7)	26.6(6.5)	0.57(0.13)	1.79(0.52)	665(165)	101.7(10.5)
GTN (n=6)		Õ	41.7(5.5)	68.2(9.9)	27.0(4.0)	26.4(3.0)	1.46(0.64)	0.82(0.09)	950(479)	96.2(5.3)
0-4										
Control $[2.4(1.7), n=24]$	0.07(0.05)	2.0(1.3)	84.2(6.5)	101.5(7.2)	65.3(6.6)	30.3(5.6)	0.68(0.13)	1.83(0.39)	455(61)	94.6(9.6)
5-9										
Control $[6,5(1,0), n=25]$	0.22(0.10)	5.3(1.4)	78.8(11.9	95.1(14.7)	59.0(11.4)	26.2(5.9)	0.57(0.10)	2.65(1.01)	388(78)	90.0(10.6)
GTN [6.7(1.6), n=6]	0.12(0.07)	2.8(1.3)	46.3(13.9	70.2(14.1)	32.1(13.1)	23.1(10.9)	1.65(0.86)	1.25(0.50)	538(344)	99.4(9.8)
15-19										
Control $[17,2(1,4), n=6]$	0.37(0.02)	8.8(0.9)	74.2(3.1)	99.4(3.0)	52.9(1.6)	23.8(1.3)	0.64(0.14)	2.20(0.30)	312(78)	98.7(1.1)
GTN [16.5(1.2), n=5]	0.25(0.03)	6.3(0.9)	43.3(3.6)	77.5(2.5)	23.9(11.9)	25.0(4.4)	1.61(0.43)	1.24(0.25)	630(57)	102.0(14.2)
28-32										
Control [30.6(1.3), n=6]	0.53(0.05)	16.7(3.2)	64.5(7.8)	88.2(4.8)	41.7(6.4)	31.2(3.8)	0.68(0.10)	2.34(0.24)	233(35)	98.2(5.8)

RF=regurgitant fraction; TPR=total peripheral resistance; PHT=pressure half time; HR=heart rate; GTN=glyceryl trinitrate

where q is regurgitant flow, C_d is a "discharge coefficient", A_o is the regurgitant orifice, ρ is the density of blood, and p_1 - p_2 is the pressure difference across the valve. Downstream from the orifice and close to the hole the jet is characterised by a contraction of the flow. The point along the jet where the jet area is minimal is termed the "vena contracta". The discharge coefficient of equation 2 is defined as: $C_d = C_v C_c$, where C_c is the coefficient of flow jet contraction, ie, the ratio of the area of the jet at the vena contracta, A_c , to the area of the orifice, A_0 . C_v is a velocity coefficient equal to the ratio of the actual velocity versus the velocity for frictionless flow. For the orifice type of hole C_v is essentially 1. For realistic pressure differences and a sharp edged orifice larger than 0.1 mm in diameter, the coefficient C_d has experimentally been found to be constant and equal to 0.61. The formula in equation 2 was therefore used to calculate the regurgitant orifice with a "discharge coefficient" of 0.61.

STATISTICS

All values are means(SD). To study the relationship between total peripheral resistance and the regurgitant volume, and between arterial compliance and the

Figure 1 Relationship between regurgitant area and regurgitant volume in the computer model for five different values of arterial compliance $(0.5, 1.0, 2.0, 3.0, 4.0 \text{ ml} \cdot \text{mm} \text{Hg}^{-1})$.

regurgitant volume in the pigs, we used simple linear regression and calculated the correlation coefficient (r) and the standard error of estimate (SEE) for the regression line. In order to evaluate how much of the variability in the regurgitant volume was explained by the linear model we calculated r^2 . The calculated residuals from the linear regression between total peripheral resistance and the regurgitant volume were correlated with arterial compliance to investigate if changes in arterial compliance could explain the variation in regurgitant volume that was not accounted for by total peripheral resistance.

Results

HAEMODYNAMIC VARIABLES DURING AORTIC REGURGITATION

Data before and after a cage basket catheter was inserted into the aortic valve to produce acute aortic regurgitation, the haemodynamic effects of glyceryl trinitrate, and the haemodynamic variables at different regurgitant orifices in the pigs are shown in the table.

Figure 2 Relationship between regurgitant volume and total peripheral resistance at a regurgitant orifice area of $5-9 \text{ mm}^2$ in the pigs. The linear regression line with the calculated value of the correlation coefficient (r) and the standard error of estimate (SEE) is shown.

Figure 3 Relationship between regurgitant volume and total peripheral resistance in the computer model for four different values of the regurgitant orifice resistance $(0.5, 1.0, 2.0, 4.0 \text{ mm} \text{ Hg} \text{ s} \cdot \text{m}^{-1})$.

The degree of unfolding of the spiral wires of the cage basket catheter determined the size of the regurgitation. The simulated aortic regurgitation decreased mean and diastolic aortic pressures, while heart rate, systolic aortic pressure, and arterial compliance did not change. The rate of pressure equalisation across the regurgitant orifice expressed as the pressure half time (without glyceryl trinitrate) was shortened as the impairment of valve closure increased. In the computer model, decreasing the regurgitant orifice area, increased the regurgitant volume at all levels of arterial compliance as expected (fig 1).

EFFECT OF TOTAL PERIPHERAL RESISTANCE ON REGURGITANT VOLUME

When total peripheral resistance was reduced or increased at a given regurgitant orifice area in the pigs, the regurgitant volumes increased and decreased, respectively (fig 2). In the group of most data points (regurgitant orifice area of 5-9 mm²) and widest range of total peripheral resistance, 83% of the variance in regurgitant volumes could be explained by variations in total peripheral resistance. We found a strong correlation between total peripheral resistance and regurgitant volume for all regurgitant orifices by simple linear regession, except in the group of smallest regurgitant orifice where the correlation was weak. Since the smallest regurgitant orifice gave very little regurgitant flow and therefore had a high degree of uncertainty in measuring variation due to changes in haemodynamic variables, this group was excluded from the comparisons. The same qualitative relationship between total peripheral resistance and regurgitant volume was found in the computer model (fig 3). At a regurgitant orifice of 30 mm² and a constant value of arterial compliance of 1 ml⁻mm Hg⁻¹, the regurgitant volume fell from 50.4 to 17.1 ml and the regurgitant fraction fell from 0.57 to 0.25 when total peripheral resistance was reduced from 3.0 to 0.5 mm Hg·s·ml⁻¹.

EFFECT OF ARTERIAL COMPLIANCE ON REGURGITANT VOLUME

We could not disclose any relationship between arterial compliance and regurgitant volume in the pigs. An experimental problem was that it was impossible to vary arterial compliance substantially without influencing total peripheral resistance. In order to evaluate the influence of arterial compliance on the regurgitant volume compared to peripheral resistance, both variables were given the same denomination by expressing arterial compliance (C) as an inverse value multiplied by the inverse value of heart rate (HR) in seconds $(1 \cdot C^{-1} \cdot HR^{-1})$. By plotting the residuals from the linear regression between total peripheral resistance and regurgitant volume versus the inverse value of arterial compliance and heart rate, we could not show any relationship between arterial compliance and regurgitant volume independent of changes in total peripheral resistance (fig 4).

The effect of arterial compliance on regurgitant flow was then evaluated in the computer model. Figure 5 shows that changes in arterial compliance had hardly any effect on the regurgitant volume except at the smallest regurgitant resistance. The change in regurgitant volume due to changes in arterial compliance was probably due to the model assuming all arterial blood volume in one lumped compliance. The amount of blood available for regurgitation is thus reduced when arterial compliance is lowered.

GLYCERYL TRINITRATE IN AORTIC REGURGITATION

A 10 mg dose of intravenous glyceryl trinitrate reduced regurgitant volumes and regurgitant fractions significantly (table). We reduced the aortic pressure by about 40% using glyceryl trinitrate during regurgitation. Total peripheral resistance was reduced by about 50% and arterial compliance increased markedly.

Figure 4 There was no relationship between the residuals from the linear regression analysis between total peripheral resistance versus regurgitant volume and the inverse value of arterial compliance and heart rate at a regurgitant orifice area of $5-9 \text{ mm}^2$ in the pigs. This indicates that changes in arterial compliance did not account for the changes in the regurgitant volume that were not explained by the straight line model in fig 2.

Figure 5 (A) Relationship between regurgitant volume and the inverse value of arterial compliance and heart rate in the computer model for four different values of the regurgitant orifice resistance $(0.5, 1.0, 2.0, 4.0 \text{ mm Hg} \text{ s} \text{ mm}^{-1})$, and (B) the relationship between regurgitant fraction and the inverse value of arterial compliance and heart rate in the same model. Heart rate was constant at 60 beats min⁻¹ while arterial compliance was varied. There was a distinct reduction in the regurgitant volume and fraction for the largest regurgitant orifice area when arterial compliance was decreased.

Discussion

The present study shows that there is a strong relationship between total peripheral resistance and regurgitant volume in aortic valve incompetence. Increased total peripheral resistance increases the regurgitant volume at a given regurgitant orifice area. This relationship was found in the pigs both before and after intravenous glyceryl trinitrate, and in the computer simulation of aortic regurgitation. These findings are also in accordance with several studies that have shown positive effects of afterload reduction by vasodilators in patients with aortic regurgitation.¹² Neither is there any evidence that there is any difference between acute and chronic aortic regurgitation and the effect of vasodilators in reducing regurgitant flow.3

Arterial compliance was of small if any importance compared to total peripheral resistance regarding the regurgitant volume. It was very difficult to vary arterial compliance without affecting mean aortic pressure and thereby total peripheral resistance in our experimental model. Multiple regression analysis, whereby we attempted to disclose an influence of arterial compliance, was negative. This was confirmed in the computer model. The small influence of arterial compliance at large regurgitant areas may be due to the model, but the influence was anyhow weak.

Arterial compliance, which is defined as the increment in volume produced by an increment of pressure, is closely related to arterial wall stiffness. Arterial compliance is one of the determinants of afterload, and earlier studies have shown that decreased arterial compliance increases left ventricular systolic wall tension.⁵ Hence an increase in arterial compliance during aortic regurgitation should reduce left ventricular wall tension and afterload and in turn improve the volume load in the left ventricle. Although we found no, or only small, effect of arterial compliance on regurgitant volume, increased arterial compliance may still be favourable in patients with chronic aortic regurgitation.

Our study demonstrates the vasodilator effect of glyceryl trinitrate with a marked reduction in peripheral resistance, and the efficacy of vasodilator therapy in acute aortic regurgitation. The beneficial decrease in the regurgitant volume with glyceryl trinitrate seemed to be the result of reduced peripheral resistance, although reduced reflections of pressure and flow waves from the periphery and back to the central arteries might have contributed to this reduction in the regurgitant volume independent of the changes in peripheral resistance.^{13 14} Effects of glyceryl trinitrate on wave reflections could not be separated from changes in peripheral resistance in the present study. Still, the experimental study alone cannot exclude the possibility that increased arterial compliance enhanced the positive effect of reduced total peripheral resistance with glyceryl trinitrate in aortic regurgitation. Klepzig et al³ found in an experimental model of acute aortic regurgitation in dogs that a reduction of 40% in mean aortic pressure by glyceryl trinitrate reduced the regurgitant flow by about 60% which is in accordance with our results.

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Paper IV

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1 Introduction

SEVERAL DOPPLER methods are available for grading aortic regurgitation semiquantitatively (CIOBANU et al., 1982; KITABATAKE et al., 1985; ZHANG et al., 1986; TEAGUE et al., 1986; LABOVITZ et al., 1986; MASUYAMA et al., 1986; PERRY et al., 1987). Good correlations have been obtained between Doppler and angiographic grades (mild, moderate, severe), but none of the methods can quantify the regurgitant orifice or the regurgitant volume. At best these methods divide regurgitations into a few subgroups, but have a large element of uncertainty. It would be useful to have a reliable Doppler method for quantifying aortic regurgitation.

We have developed a method of quantifying aortic regurgitant orifice and volume based on noninvasive Doppler measurements of aortic flow velocity, blood pressure measurements, and a parameter estimation technique. The estimation is based on a Windkessel arterial model. The method was validated in pigs.

2 Materials and methods

2.1 Pig experiments

Six pigs (aged about 3 months, body weight 21.3 ± 2.3

First received 9th February and in final form 27th October 1989 © IFMBE: 1990 (SD) kg) were anaesthetised with pentobarbital, 700– 1000 mg intraperitoneally initially, and $3-4 \text{ mg min}^{-1}$ by continuous intravenous infusion. The pigs were tracheotomised and ventilated with a volume-regulated respirator (Model No. 613, Harvard Apparatus, Massachusetts). Blood gases were repeatedly measured on an IL 1306 pH/ blood gas analyser (Instrumentation Laboratories, Massachusetts). Body temperature was recorded by a rectal thermometer and kept at normal levels by a heating pad and wrappings. The urinary bladder was drained through a cystostomy.

A thoracotomy was performed by splitting the sternum, and the heart was exposed by a pericardiotomy and suspended in a pericardial cradle. A saline-filled polyvinyl catheter (no. 7F) was introduced through the apex of the left ventricle and placed in the left ventricular outflow tract for recording of left ventricular pressure. Similar catheters (no. 7F) were introduced through the left carotid artery and internal jugular vein to record the pressures in the ascending aorta (placed approximately 2 cm above the valve) and in the right atrium. All catheters were stiff and short to obtain resonant frequencies (tap test) above 60 Hz after connection to Statham P231D transducers. The transducers were statically calibrated against a mercury manometer with zero pressure referred to the left ventricular midlevel.

Acute aortic valve regurgitation was produced by

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opening a cage basket catheter (Laboratorie Porges, Paris) inserted into the aortic valve. This type of catheter is normally used to remove kidney stones by means of retractable spiral wires which balloon out to impair valve closure when the catheter is pulled back, but which create hardly any stenosis during systole. The catheter was advanced from the right carotid artery and the position was verified by echocardiography (CFM-700, Vingmed, Oslo, Norway). The amount of aortic regurgitation was altered by opening or closing the basket.

Through the left femoral artery a catheter with an inflatable balloon tip (Fogarty occlusion catheter, 22F) was placed in the descending aorta. Increase in afterload was obtained by inflating the balloon. A few seconds after deflating the inflated balloon, pronounced reduction in afterload pressure was obtained.

Two electromagnetic flow probes (12-16 mm ID, Skalar Instruments, Delft, The Netherlands) were placed snugly around the ascending aorta and around the pulmonary artery close to the valves. Before regurgitation was induced, aortic and pulmonary mean flows were calibrated to give the same volume by calculation of a fixed calibration factor in the computer analysis program (see below). The physiological discrepancy between pulmonary and aortic flow due to coronary flow was disregarded. Regurgitant aortic volume was measured as the difference between systolic aortic and pulmonary stroke volumes, because it is difficult to determine the baseline of the aortic flow probe recording during regurgitation, and it was therefore difficult to use only the aortic flow probe to measure the regurgitant volume. Cardiac output was measured as pulmonary flow, and the regurgitant fraction was measured as the ratio between regurgitant volume and systolic aortic stroke volume. Total peripheral resistance was determined as mean arterial pressure minus mean right atrial pressure divided by cardiac output.

All signals were continuously recorded on a Mark VII WR 3101 Graphtec Linearecorder at paper speeds of 1 or 50 mm s^{-1} . The signals were also stored by a digital computer (PDP-11/23 Plus with A/D convertor, Digital Equipment Corp., Massachusetts) connected to the recording systems. The analogue-to-digital conversion system worked with a sampling rate of 10 ms in each channel. Doppler examinations were performed with a CFM-700 Vingmed system utilising a 2·0 or a 2·5 MHz transducer. The regurgitant velocities were measured in the continuous-wave mode, and the transducer was placed directly on the left ventricle where the best signal was obtained.

2.2 Calculations

A Windkessel model and parameter estimation were used to estimate the regurgitant orifice, and from this value the regurgitant volume was calculated. The Windkessel model contained one capacitance C and one resistance Rto represent the systemic arterial bed, and in diastole a nonlinear resistance was introduced at the aortic valve to account for the backflow into the left ventricle.

If the volume of the arterial system is denoted by V, the continuity equation is

$$\frac{dV}{dt} + q_{out} = q_{in} \tag{1}$$

where q_{out} is flow out of the arterial system to the venous system and q_{in} is flow into the system from the ventricle. In regurgitation q_{in} has a negative value during diastole, and

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if dV/dt is multiplied by P_a/P_a , i.e. 1, eqn. 1 during diastole is

$$\frac{dV}{dt}\frac{P_a}{P_a} + q_{out} = -q_{reg} \tag{2}$$

where P_a is the arterial pressure and q_{reg} is regurgitant flow.

Total arterial compliance is defined as

$$C = \frac{dV}{dP_a} \tag{3}$$

The outflow of blood into the venous system is assumed to be proportional to the pressure difference

$$q_{out} = \frac{P_a - P_{ven}}{R} = \frac{P_a}{R} \quad P_a \gg P_{ven} \tag{4}$$

where P_{ven} is the venous pressure.

The drive pressure of the regurgitant jet, which is the difference between the aortic pressure and the left ventricular pressure P_v can approximately be estimated from the simplified Bernoulli equation:

$$P_a - P_V = 4v^2 \tag{5}$$

where v is the jet velocity in $m s^{-1}$; P is in mm Hg.

The continuity equation for the regurgitant flow is:

$$q_{reg} = Av = \frac{A}{2}\sqrt{P_a - P_v} \tag{6}$$

where A is the regurgitant orifice area.

By substituting $4v^2 + P_v$ (eqn. 5) for P_a in eqn. 4, $(4v^2 + P_v)/R$ (eqn. 4) for q_{out} in eqn. 2, C (eqn. 3) for dV/dP_a in eqn. 2, and Av (eqn. 6) for q_{reg} in eqn. 2, we obtain a differential equation for the regurgitant jet velocity in diastole:

$$\frac{dv}{dt} = -\frac{1}{2RC}v - \frac{P_v + RC}{8RCv}\frac{dP_v}{dt} - \frac{A}{8C}$$
(7)

The equation is a nonlinear differential equation for the regurgitant velocity which can be measured noninvasively with ultrasonic Doppler techniques. It contains three parameters: peripheral resistance R, arterial compliance C and regurgitant orifice area A, and an unknown function of left ventricular pressure $P_{\rm p}(t)$.

To make the system observable one needs more information. First, we assumed that the function of left ventricular pressure could be set to zero at the beginning of diastole and that it could be represented by a linearly increasing function throughout diastole. The last part of diastole was not used for the estimation. Secondly, we measured aortic systolic flow, and systolic and diastolic arterial pressures to obtain three more relationships between peripheral resistance, arterial compliance, and regurgitant orifice area.

Aortic systolic flow can be obtained noninvasively using aortic subvalvular velocity and area assessed by Doppler and two-dimensional ultrasonic imaging, respectively. Systolic and diastolic arterial pressures may be obtained by cuff.

Combining eqns. 1, 3, 4 and 6 we obtain the following differential equation for aortic pressure during systole:

$$\frac{dP_a}{dt} + \frac{P_a}{RC} = \frac{1}{C} q_s \tag{8}$$

where q_s is a ortic systolic flow. If t = 0 at the beginning of systole, then $P_a(0)$ is diastolic pressure P_d and $P_{a max}$ is

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systolic pressure P_s . T_s is the duration of systole, and the aortic pressure at the closure of the aortic valve P_c is calculated from the regurgitant jet using the Bernoulli equation $4v_{max}^2$, as long as the early diastolic ventricular pressure is assumed to be zero.

Integration of eqn. 8 over systole yields relationships between peripheral resistance, arterial compliance and regurgitant orifice area when the derivatives of both P_a and q_a are assumed to be zero at the beginning and end of systole. We then obtain:

$$C(P_c - P_d) + \frac{P_{s\,mean}\,T_s}{R} = V_s \tag{9}$$

where P_{smean} is the mean aortic pressure during systole and V_s is the systolic volume. From this equation we can express arterial compliance as a function of peripheral resistance R:

$$C = \frac{V_s - P_{s\,mean} \frac{T_s}{R}}{P_c - P_d} \tag{10}$$

The peripheral resistance is by definition:

$$R = \frac{P_{mean}(T_s + T_d)}{V_s - V_{reg}}$$
(11)

where T_d is the duration of diastole, P_{mean} is the mean aortic pressure over the cardiac cycle and V_{reg} is the diastolic regurgitant volume. Eqn. 6 shows that the regurgitant flow is a function of the regurgitant orifice and velocity. Thus, V_{reg} can be substituted with the regurgitant orifice multiplied with the regurgitant velocity integral. The mean systolic and aortic mean pressures are approximately estimated from the diastolic, systolic and closure pressures as:

$$P_{s\,mean} = P_d + 0.7(P_s - P_d) \tag{12}$$

$$P_{mean} = \frac{2P_d + P_s}{3} \tag{13}$$

Eqn. 12 is an empirically derived formula used in our laboratory, which correlates well with invasive pressure recordings in pigs. Based on measurements that may be obtained noninvasively, one may now relate both peripheral resistance and arterial compliance to the regurgitant orifice, and eqn. 7 then contains in essence only one independent parameter, the regurgitant orifice area A.

To express the regurgitant orifice area, eqn. 7 is rewritten as:

$$A = -\frac{dv}{dt} \, 8C - \frac{4v}{R} - \frac{P_v + RC}{Rv} \frac{dP_v}{dt} \tag{14}$$

The regurgitant orifice area was obtained by a parameter estimation technique. Parameter estimation is a method of determining unknown or uncertain parameters in a model. The number of parameters that can be determined will depend on the nature of the model and the number of measurements. To estimate the regurgitant orifice we used the extended Kalman filter. We defined the regurgitant velocity as the first state variable x_1 and the regurgitant orifice as the second state variable x_2 (JAZWINSKY, 1970). The parameter estimation technique then gave an estimate of the regurgitant orifice.

In the present experiments we wanted to examine the validity of the parameter estimation technique for estimating the regurgitant orifice area. To minimise errors in the measurements we used aortic systolic flow as obtained with the electromagnetic flow probe, and calculated the mean systolic and mean aortic pressures from the invasive aortic pressure. By ultrasonic Doppler measurements we obtained the velocity of the regurgitant jet, and the aortic pressure at the closure of the aortic valve according to eqn. 5. Signals from 3-5 heartbeats at stable haemodynamic conditions were averaged before all calculations.

GORLIN and GORLIN (1951) described a formula to calculate the relationships between pressure, area and flow through stenotic valves. Ask *et al.* (1986) described a similar formula for flow through regurgitant valves:

$$q = C_d A_0 \sqrt{\frac{2}{\rho} (p_1 - p_2)}$$
(15)

where q is regurgitant flow, C_d is a 'discharge coefficient', A_0 is the regurgitant orifice, ρ is the density of blood, and $p_1 - p_2$ is the pressure difference across the valve. Downstream from the orifice and close to the hole the jet is characterised by a contraction of the flow. The point along the jet where the jet area is minimum is termed the vena contracta. The discharge coefficient is defined as: $C_d = C_v C_c$, where C_c , the coefficient of contraction, is the ratio of the area of the jet at the vena contracta A_c to the area of the orifice A_o . C_v is a velocity coefficient of the ratio of the actual velocity against the velocity for frictionless flow. For the orifice type of hole C_v is essentially 1. For realistic pressure differences and a sharp-edged orifice larger than $0.1 \,\mathrm{mm}$ in diameter, the coefficient C_d has been found experimentally to be constant and equal to 0.61.

The parameter estimation method, however, gave an estimate of the *effective* area of flow, i.e. the area of the jet at the vena contracta A_c . We therefore compared our estimates with the effective area calculated from Ask's formula with a discharge coefficient of 1, giving the following equation for the effective area:

$$A_{c} = \frac{q}{\sqrt{\frac{2}{\rho}(p_{1} - p_{2})}}$$
(16)

 A_c was calculated as the average of the instantaneous values throughout diastole.

3 Results

17 samples with different degrees of insufficiencies, aortic pressures and peripheral resistances were analysed (Table 1, Fig. 1). The regurgitant fractions measured electromagnetically ranged from 0.06 to 0.58.

Estimates of the regurgitant orifice varied from 2.1 to

Table 1 Haemodynamic variations in the samples analysed

Sample, pig		HR, beats min ⁻¹	MAP, mm Hg	TPR, mm Hg s ml ⁻¹	CO, ml beat ^{~1}	RF
1	(5)	95	81	2.5	22.8	0.18
2	(5)	95	64	2.3	32-8	0.54
3	(6)	85	56	1.8	24.2	0.22
4	(6)	79	56	1.5	29.0	0.22
5	(1)	77	58	3.2	16.0	0.19
6	ú	75	67	4.3	19.5	0.41
7	(2)	117	62	2.1	22.2	0.31
8	(3)	120	74	2.2	24.8	0.37
9	(3)	119	78	2.4	25.3	0.39
10	(4)	94	89	1.6	36-4	0.06
11	(5)	96	85	2.0	30.0	0.22
12	(2)	111	50	1.9	24.4	0.42
13	(5)	97	72	2.4	33-2	0.53
14	(6)	80	54	1.5	30-2	0.28
15	(n)	76	64	3.5	17.3	0.22
16	(6)	83	71	2.9	22.9	0.31
17	(5)	93	61	2.6	32-1	0.59

HR: heart rate; MAP: mean aortic pressure; TPR: total peripheral resistance; CO: cardiac output; RF: regurgitant fraction.

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Fig. 1 Pressure and flow traces from one of the analysed samples from pigs

 23.5 mm^2 . Fig. 2 shows the estimated orifices against the regurgitant areas calculated from the invasive data using eqn. 16. The regression equation of calculated orifice from invasive data against estimated orifice was y = 1.3352 + 0.8113x with a correlation coefficient of 0.88. The mean difference between the two methods (Ask's and parameter estimation) was 0.3 mm^2 , and +2SD and -2SD (95 per cent confidence interval) of the difference



Fig. 2 Regurgitant orifice calculated from the invasive data (ASK's formula, 1986) against estimated area

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were 5.1 mm^2 and -4.5 mm^2 , respectively. Hence the parameter estimation estimate did not deviate significantly from the effective orifice area as calculated from eqn. 16.

A second evaluation of the model and the parameter estimation scheme was to multiply the estimated area by the noninvasive velocity integral of the regurgitant jet to estimate the regurgitant volume. The estimated against measured volume is shown in Fig. 3. The regression equation of measured regurgitant flow against estimated flow was y = 1.1554 + 0.8731x with a correlation coefficient of 0.95. The mean difference between measured and estimated volume was 0.1 ml, and +2SD and -2SD of the difference were 2.9 ml and -3.1 ml, respectively. Hence, there was no statistical deviation betwen the two methods.

To examine how different variables $(V_s, P_v, P_c, P_{mean}, P_{s mean})$ influenced the estimated areas, we varied each of these variables by \pm 30 per cent (\pm 15 per cent for the mean pressures), one variable at a time, as inputs into the estimator. Results are shown in Table 2. With no variation in these variables the regurgitant area was $16\cdot 2 \text{ mm}^2$. Inaccuracies in mean aortic pressure P_{mean} and mean systolic pressure $P_{s mean}$ had the biggest influence of the estimated area. P_{mean} 15 per cent above and below the 'true' value caused a difference as large as $6-8 \text{ mm}^2$.



Fig. 3 Regurgitant volume measured with electromagnetic flow against regurgitant volume estimated from the parameter estimation technique

Table 2 Variations in estimated area when one measured parameter was changed \pm 30 per cent (\pm 15 per cent for mean pressures). With no variation in these variables the area was 16.2 mm²

Parameter measured	Variations in area, mm ²				
$V_s \pm 30$ per cent	15.9	14.5			
$P_{v}(t) \pm 30$ per cent	18-3	12.1			
$P_{c} \pm 30$ per cent	15-9	14.7			
$P_{\rm mere} \pm 15$ per cent	10.3	24.4			
$P_{\text{mean}} \pm 15 \text{ per cent}$	19-5	12.3			

 V_s : systolic volume; $P_v(t)$: left ventricular pressure; P_c : aortic pressure at closure of the aortic valve; P_{mean} : average aortic pressure, P_{smean} : average aortic pressure during systole.

The sensitivity for inaccuracies in tracing the contour of the regurgitant velocity curve was analysed by manually tracing exaggerated erroneous traces above and below the upper velocity contour (Fig. 4). Such tracings above and below the used contour of a small insufficiency gave areas of $4\cdot1$ and 7 mm^2 , respectively, while the 'true' value was $4\cdot8 \text{ mm}^2$ (Fig. 4 left panels). The corresponding regurgitant volumes were 7.4 and 10.8 ml with a 'true' value of $8\cdot3 \text{ ml}$.

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Fig. 4 Doppler velocity curves (small insufficiency to the left and large insufficiency to the right) of the regurgitant jet from the experiments with a copy below showing where a line along the maximum velocity envelope was drawn (in the middle). Top and bottom tracings were made to illustrate how an incorrect tracing could influence the estimated area. See Results

For a large insufficiency with an estimated area of 17.8 mm^2 , exaggerated tracings above and below the probable contour gave areas of $12.2 \text{ and } 18.0 \text{ mm}^2$, respectively. The corresponding volumes were 15 and 18.5 ml with a 'true' value of 21.4 ml.

4 Discussion

This study presents a method for quantifying aortic regurgitant orifice and volume from the velocity of the regurgitant jet measured by Doppler, and from measurement of aortic systolic flow, and peak systolic and enddiastolic arterial pressures.

An advantage of this method is that it includes the influence of total peripheral resistance and arterial compliance on regurgitant flow. In contrast, Doppler pressure halftime is a method of quantifying the degree of aortic regurgitation by evaluating the rate of pressure equalisation across the regurgitant orifice from the regurgitant velocity curve (TEAGUE et al., 1986). However, this method neglects the influence on the pressure half-time of factors other than the degree of regurgitation, such as total peripheral resistance, arterial compliance and compliance of the left ventricle. We have previously shown that total peripheral resistance has substantial influence on pressure half-time (SLØRDAHL et al., 1987), and the validity of methods based on pressure half-time alone is therefore questionable. We consider that a reliable method to evaluate aortic regurgitant flow should include all principal determinants of the overall haemodynamic conditions on both sides of the valve.

The purpose of estimating the regurgitant orifice was not to find the anatomical orifice, as proposed by the original formula of Ask *et al.* (1986) (eqn. 15), but to find the effective area of flow to be used in the continuity equation to calculate regurgitant volumes. The difference between the anatomical and the effective area of flow will vary with the anatomical shape of the regurgitant orifice (Ask *et al.*, 1986). It is difficult to obtain noninvasive information about the anatomical shape of the regurgitant orifice, and we also consider this parameter to be of less interest than the effective area.

In all parameter estimation techniques inaccuracies in the measurements used as inputs will influence the estimated value. The importance of each measurement for the final result will be different. In our model the most influential input was the mean aortic pressure over the heart cycle (Table 2). Inaccuracies in V_s and P_c (calculated from maximum velocity of the regurgitant jet), together with an incorrect constant in the assumption that the $P_v(t)$ was linearly increasing, had considerably less influence on the regurgitant orifice area. Nor was the method very sensitive to incorrect tracings of the regurgitant velocity curve (Fig. 4).

Our method is more elaborate than the pressure halftime method, because it requires measurement of two pressures, i.e. peak systolic and end-diastolic aortic pressures, and systolic flow, in addition to the Doppler registration of the regurgitant jet velocity, which is common in both methods. In principle, all measurements may be obtained noninvasively. Peak systolic pressure and end-diastolic pressure may be obtained by cuff measurements. Aortic systolic flow can be calculated from subvalvular aortic diameter (two-dimensional ultrasonic imaging) and the systolic time velocity integral (pulsed Doppler, SKJAERPE et al., 1985). As mentioned above, the most critical measurement is actually that of mean aortic pressure. There seems to be close agreement between arm systolic pressure measured by cuff and the intra-arterial peak pressure, whereas diastolic cuff pressures tend to be significantly higher (11-15 mm Hg, for fat patients 30-36 mm Hg) than intraarterial pressures in some studies (FORSBERG et al., 1970). Two studies of patients with aortic regurgitation showed different results with regard to diastolic pressure. RAGAN

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and BORDLEY (1941) did not find a significant difference between cuff and intra-arterial diastolic pressure, as opposed to KOTTE *et al.* (1944), who found that the cuff pressures were significantly higher than intra-arterial pressures. We consider that measurement of mean aortic pressure may be performed accurately enough to give reasonable accuracy of the area and regurgitant volume estimates.

In conclusion, we have developed and tested a new method to quantify aortic regurgitation, based on noninvasive (Doppler) measurement of regurgitant jet velocity, measurement of aortic systolic flow, and measurement of two arterial pressures. The method seems promising with respect to obtaining quantitative estimates of regurgitant orifice area and volume in patients.

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Authors' biographies



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Regurgitant volume in aortic regurgitation from a parameter estimation procedure.

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Running head: REGURGITANT VOLUME IN AORTIC REGURGITATION

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ABSTRACT

The regurgitant volume and regurgitant orifice area as well as total peripheral resistance and arterial compliance were estimated in a cardiovascular hydromechanical simulator and in 10 patients with aortic regurgitation. A parameter estimation procedure based on a simple model of the cardiovascular system, Doppler measurements of the regurgitant jet, aortic systolic flow, and systolic and diastolic blood pressures was used. In the cardiovascular simulator the estimated regurgitant orifice area was compared to a hole in the disk of a mechanical aortic valve. In the patients the regurgitant fraction was compared to semiquantitative grading from echocardiography routinely performed in our laboratory. In the hydromechanical simulator, the estimated regurgitant orifice area of 26.5 ± 3.5 (SD) mm² (n=9) was not different from the true value of 24 mm². In the patients there was a fair relationship between the estimated regurgitant fraction and the semiquantitative grading. The estimated regurgitant orifice areas varied between 1.6 and 31.2 mm². The estimated mean values of total peripheral resistance and arterial compliance were 1.67 ± 0.55 mmHg·s/ml and 1.30 ± 0.42 ml/mmHg, respectively.

INDEX TERMS: Doppler echocardiography; arterial compliance; regurgitant orifice area; total peripheral resistance; characteristic impedance

INTRODUCTION

Previous investigations have demonstrated the difficulties in quantitating aortic regurgitation noninvasively from Doppler echocardiography. Several methods have been proposed to quantitate aortic regurgitation such as evaluating the rate of pressure equalization (pressure half-time) across the regurgitant orifice from a continuous wave Doppler recording (10), or evaluating the maximal length, area and thickness of the regurgitant jet at its origin relative to the size of the outflow tract by Doppler color flow mapping (6), or calculating the regurgitant fraction or the end diastolic flow velocity in the aortic arch by pulsed wave Doppler (11,12), or calculating the regurgitant volume from systolic aortic and pulmonary volume flow determined by two-dimensional Doppler echocardiography (4). None of these methods has won universal acceptance. The purpose of the present study was to test the hypothesis that the regurgitant volume and orifice area could be estimated from a parameter estimation procedure based on a simple model of the cardiovascular system. Input data to the procedure were Doppler measurements of the regurgitant jet and aortic systolic flow, and systolic and diastolic blood pressures. The method was first evaluated in a cardiovascular hydromechanical simulator. Secondly we applied the parameter estimation procedure in patients to assess its clinical feasibilty.

MATERIALS AND METHODS

Hydromechanical simulator. A cardiovascular hydromechanical simulator driven by an electropneumatic unit was used (8). 'Cardiac' output was measured by a Pitot device positioned between a delay tube simulating the venous bed and an 'atrium'. 'Cardiac' output was accurate to ± 0.1 l/min between 2.0 and 7.0 l/min. 'Aortic' regurgitation was produced by drilling a hole of 24 mm² in the disk of a mechanical 'aortic' valve. The pressure gradient across the 'aortic' valve was obtained via Statham P23ID pressure transducers connected to fluid-filled catheters positioned in the 'ventricle' and at the 'aortic' root. Various resistances were placed at the outlets of the elastic tubes. To simulate and evaluate the estimation procedure at various hemodynamic conditions we varied 'cardiac' output and the peripheral resistance in a random manner. Total peripheral resistance was determined as mean 'arterial' pressure divided by 'cardiac' output.

As inputs to the parameter estimator we used the regurgitant jet velocity obtained with continuous wave Doppler, 'aortic' systolic and diastolic blood pressures from the Statham pressure transducers and total systolic flow through the 'aortic' valve from the regurgitant volume added to the mean 'cardiac' output measured with the Pitot device. Continuous wave Doppler recordings were made by a CFM 700 (Vingmed, Oslo, Norway) using a 2 MHz transducer from a fixed position on the aortic arch. All measurements from the flow velocity curves were averaged over at least 5 consecutive 'cardiac' cycles.

Study population. The study population consisted of 10 patients with chronic aortic regurgitation who underwent a standard physical examination, M-mode and twodimensional echocardiography, and complete pulsed and continuous wave Doppler echocardiographic examination. The severity of aortic regurgitation was graded semiquantitatively as 'trivial', 'mild', 'mild to moderate', 'moderate', 'moderate to severe' or 'severe'. The grading was done from the general impression of the echocardiographic examination attaching importance to the intensity of the jet, the jet height vs. the size of left ventricular outflow tract, pressure half-time, flow reversal in descending aorta with an estimation of the regurgitant fraction, and left ventricular size and function.

Pressure half-time was defined as the time required for the maximum velocity to fall from peak velocity to peak velocity divided by $\sqrt{2}$ (3). The regurgitant fraction in the descending aorta was calculated as the ratio of diastolic to systolic flow. Each flow was the product of the corresponding time-velocity integral times a corresponding aortic crosssectional area. Each aortic cross-sectional area was equal to the square of an aortic diameter times $\pi/4$. Systolic and diastolic diameters were the maximum and minimal diameters obtained from suprasternal M-mode recordings. Corresponding time-velocity integrals were obtained from pulsed wave Doppler with the sample volume in the descending aorta close to the aortic isthmus.

The regurgitant volume and the regurgitant orifice area were estimated from the parameter estimation procedure. The input variables were simular to those in the hydromechanical simulator: 1) the aortic regurgitant jet obtained from continuous wave

Doppler, 2) systolic and diastolic aortic blood pressures obtained with cuff and 3) systolic flow obtained from the left ventricular outflow tract subvalvular diameter (from twodimensional echocardiography) and velocity (from pulsed wave Doppler) (7). The arterial blood pressure was measured auscultatory in the right arm with the patient in the supine position. The systolic and diastolic pressures were defined by the appearance and disappearance of Korotkoff sounds. The blood pressures were measured nearly simultaneously to the Doppler measurements of the regurgitant jet.

Two-dimensional echocardiograms were recorded with commercially available phased array echocardiographs using a variety of standard transducers, but all echocardiograms used in the parameter estimation procedure were recorded with a CFM-700 (Vingmed, Oslo, Norway) using an annular array transducer (2.5 MHz/2.0 MHz). The echocardiograms (both two dimensional and Doppler recordings) were transferred from the digital replay memory of the CFM-700 to a Macintosh II computer (Apple Computer, Inc., Cupertino, California) for processing after the examinations.

Calculations. To estimate the regurgitant orifice a three-element Windkessel model, i.e., a r-C-R model, of the arterial tree was used. C is arterial compliance, R is total peripheral resistance and r is the characteristic resistance of aorta, i.e., the model representation of the aortic characteristic impedance. To simulate regurgitation in diastole a nonlinear resistance was introduced in parallel to the aortic valve to account for the backflow into the left ventricle.

From the three-element arterial model we obtain an expression for the arterial pressure (P_a) throughout the cardiac cycle (see appendix):

$$P_{a}(t) = e^{-t/T}[P_{a}(t=0) + \frac{1}{C} \int_{0}^{t} e^{\tau/T}q(\tau) d\tau] + rq(t)$$
(1)

where q is flow through the aortic valve, T = RC, and τ is the time variable of the integration. If t=0 at the beginning of systole, $P_a(0)$ is equal to diastolic pressure, P_d . $P_a(t_c)$ is also equal to the diastolic pressure since t_c is the duration of the heart cycle. P_a maximum is peak systolic pressure, P_s . The aortic pressure at the closure of the aortic valve, P_c , was calculated from the regurgitant jet using the simplified Bernoulli equation ($P_c=4v^2$, P in

mmHg, v in m/s) by assuming that the early diastolic ventricular pressure was zero. If $P_a(0)$ and P_a maximum are assumed to be the diastolic and systolic pressures obtained with cuff measurements, we obtain the aortic pressure at four different times through the heart cycle.

Eq.(1) solved for $t = t_c$ with regard to T is:

$$\frac{1}{T} = \frac{1}{t_c} \ln \left[1 + \frac{1}{P_d C_0} \int_0^{t_c} e^{\tau/T} q(\tau) \, d\tau \right]$$
(2)

For chosen initial values of the characteristic resistance ($r=0 \text{ mmHg}\cdot s/ml$), arterial compliance (C=2 ml/mmHg) and total peripheral resistance (R= 2 mmHg\cdot s/ml), we obtained a T (=R·C) estimate by use of a fixed-point iteration procedure. For the given estimates of T and C we then estimated new R and r values with help of another parameter estimation technique (2 points boundary value problem), demanding that the aortic pressure curve went through the four observed pressure values, i.e., P_d, P_s, P_c, P_d (see appendix). The new R and r were inputs to a new estimation of T (and C) and so forth until convergence was achieved. In 4 patients we experienced problems with making the parameter estimation to converge to stable C estimates. In these cases, the procedure was stopped when the R value was stable. The reason for this problem might have been that the input variables were not accurate enough to bring all parameter solutions to full convergence.

The peripheral resistance is by definition:

$$R = P_{mean}(t_s + t_d) / (Q_s - Q_{reg})$$
(3)

where P_{mean} is mean aortic pressure over the cardiac cycle, Q_s is the systolic volume, Q_{reg} is the diastolic regurgitant volume, and t_s and t_d are the durations of systole and diastole. The mean aortic pressure was calculated as:

$$Pmean = (P_d t_d + P_s t_s) / t_c$$
(4)

Having obtained an estimate for R, and using the measured values of Q_s and P_{mean} , the regurgitant volume was calculated from Eq.(3):

$$Q_{reg} = (Q_s R - P_{mean}(t_c)) / R$$
(5)

Since the regurgitant flow is a function both of the regurgitant orifice and the velocity (the continuity equation for the regurgitant flow), the regurgitant orifice area (Reg.Area) was calculated from the equation:

$$\operatorname{Reg.Area} = \operatorname{Qreg} / \operatorname{VTI}_{\operatorname{reg}}$$
(6)

where VTI_{reg} is the velocity time integral of the regurgitant jet measured and calculated from the Doppler recording in diastole.

Statistics. All mean values are given \pm the standard deviation (SD).

RESULTS

There was an excellent relationship between the estimated regurgitant orifice area and the true regurgitant orifice area of the mechanical aortic valve in the cardiovascular hydromechanical model (Table 1). The estimated regurgitant orifice area was 26.5 ± 3.5 mm² (true value 24 mm²) during different hemodynamic situations when total peripheral resistance varied between 0.57 and 2.22 mmHg·s/ml, mean aortic pressure varied between 69 and 107 mmHg, and the regurgitant volume varied between 2.4 and 4.2 l/min. Mean difference between the observed regurgitant volume and the estimated regurgitant volume was -3.1 ± 5.0 ml (Fig. 1).

In 10 patients with aortic regurgitation there was a fair relationship between the regurgitant fraction estimated by parameter estimation and the semiquantitative evaluation based on echocardiography (Fig. 2). Since the clinical evaluation resulted in qualitative categories only, the relation cannot be described by a statistical procedure. The estimated regurgitant orifice areas varied between 1.6 and 31.2 mm² (Table 2). The estimated values of total peripheral resistance and arterial compliance were within the physiological range

with mean values of 1.67 ± 0.55 mmHg·s/ml and 1.30 ± 0.42 ml/mmHg, respectively.

The sensitivity of the parameter estimation procedure was demonstrated by changing the input variables \pm 10 per cent, one variable at a time, as inputs to the estimator in one patient (Table 3). With no variation the estimated regurgitant orifice area was 2.2 mm². Greatest deviation was found when diastolic pressure was changed 10 per cent.

DISCUSSION

The present study demonstrates that regurgitant orifice area, regurgitant volume, total peripheral resistance and arterial compliance can be estimated from noninvasive measurements of blood pressure, systolic flow through the aortic valve and the regurgitant jet. The experiments in the cardiovascular simulator demonstrated that excellent results could be obtained with ideal input variables. The study in patients showed that one might also obtain acceptable results in a clinical situation. The possibility to estimate the studied parameters arose from earlier studies in pigs where the same parameters were estimated using an estimation procedure that required information about diastolic left ventricular pressures (9). Both estimates as inaccuracies in the input variables might influence the results to variable degrees. This was shown in the sensitivity analysis which indicated that errors both in the systolic and diastolic pressures as well as errors in measuring systolic flow had great influence on the results. However, the mutual importance of errors in the input variables will depend on the hemodynamic situation that is studied.

The problem encountered in some of the patients with obtaining stable estimates of arterial compliance indicated that the input variables were not accurate enough. In the present study the greatest inaccuracies were probably in the noninvasive blood pressure measurements. The auscultatory method of indirect blood pressure measurement to estimate systolic and diastolic pressures might have not been accurate enough for our purpose. A possible solution to enhance the quality of the results is to use the oscillometric principle to determine brachial artery pressure, which is proved to be more reliable than auscultatory measurement (1). The parameter estimation might become more accurate if estimates of the

ascending aortic pressure obtained with a carotid pulse tracing calibrated from an automatic blood pressure meter are used as input into the parameter estimation procedure.

One of the advantages of the present approach is that both arterial compliance and total peripheral resistance are included in the estimation procedure. In an earlier study we showed that the pressure half-time is influenced both by total peripheral resistance and by arterial compliance (8), and a similar influence of total peripheral resistance on flow reversal in the descending aorta can be expected. Parameter estimation from a vascular analog therefore gives a more complete impression of the total hemodynamic situation during aortic regurgitation and not only an estimate of the regurgitant volume.

One of the main problems in developing quantitative Doppler methods for aortic regurgitation is the selection of a reference method. Aortography has long been regarded as the only useful investigation for grading aortic regurgitation, but angiographic assessment of the severity of aortic regurgitation is often at variance with the measured regurgitant volume index (2). The use of angiography has also decreased due to the introduction of noninvasive methods. Gated blood pool scanning and magnetic resonance imaging enables right and left ventricular stroke volumes to be compared in order to calculate the regurgitant fraction (5,13), but a disadvantage is that other lesions producing regurgitation or shunting need to be excluded. No specific echocardiographic method has won universal acceptance as to quantitate the severity of aortic regurgitation, but reasonable assessments of the severity are done from a general impression of the echocardiographic study as done in the present study.

In conclusion, the present study demonstrates the possibility to estimate noninvasively the regurgitant volume and the regurgitant orifice area in aortic regurgitation. Methods and procedures to obtain more precise and accurate measurements of the input variables are however needed before this method is fully assessed and acceptable for clinical use.

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Cardiac output	Mean aortic pressure	Total peripheral resistance	Heart rate	Regurgitant volume	Estimated regurgitant volume	Estimated regurgitant orifice area
(l/min)	(mmHg)	(mmHg·s/ml	(beats/min)	(1/min)	(l/min)	(mm ²)
3.9	72	1.12	89	2.8	3.4	29.6
4.5	86	1.19	73	3.5	4.4	31.0
2.9	107	2.22	73	4.2	4.0	23.0
3.3	101	1.88	72	4.0	3.8	23.8
5.3	68	0.69	72	2.4	2.4	24.2
6.0	69	0.57	105	2.7	2.7	26.3
5.6	75	0.81	106	3.0	4.0	32.2
4.7	82	1.04	107	3.3	3.5	24.8

109

3.8

3.8

23.6

3.5

95

1.68

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TABLE 1. Hemodynamic variables and estimated parameters in the cardiovascular model with a regurgitant orifice area of 24 mm^2 .

TABLE 2. The results from the parameter estimation method in 10 patients compared to the semiquantitative grading from Doppler echocardiography done by an experienced reader.

						Param	eter			Echo
						Estim	ation			Report
No	Age	Sex	BP	PHT	RF	Reg.	RF	TPR	С	Clinical
	(yr)			ms	desc.	Area		mmHg·s/	ml/	grading
						mm ²		ml	mmHg	
1	83	F	195/82	433	0.35	1.6	0.05	1.52	0.86	Mi
2	67	М	130/55	761	0.30	13.5	0.45	1.90	1.52	Mi-Mo
3	31	М	135/53	495	0.40	21.6	0.43	1.17	2.09	Se
4	49	М	148/99	634	0.22	4.7	0.27	3.17	1.38	Mi
5	69	F	165/68	332	0.20	4.4	0.13	1.30	0.78	Mi-Mo
6	66	F	110/60	297	0.27	4.4	0.16	1.52	0.98	Mi-Mo
7	30	М	130/90	399	0.07	4.6	0.17	1.71	1.59	Tr
8	71	М	140/68	259	0.29	17.3	0.35	1.62	1.00	Mi
9	18	F	90/45	309	0.32	31.2	0.48	1.12	1.78	Mo-Se
10	58	F	138/80	524	0.13	6.6	0.18	1.64	1.00	Mi-Mo

No: Patient number, BP: blood pressure obtained by cuff, PHT: pressure half-time from continuous wave Doppler as a mean value of 4-5 recordings, RF desc.: regurgitant fraction calculated from pulsed wave Doppler in descending aorta and corrected for different aortic diameter in systole and diastole, Reg.Area: estimated regurgitant orifice area, RF: estimated regurgitant fraction, TPR: estimated total peripheral resistance, C: estimated arterial compliance, Tr: trivial, Mi: mild, Mi-Mo: mild-moderate, Mo-Se: moderate-severe, Se: severe.

TABLE 3. Variation in estimated regurgitant orifice area (in mm²) in one patient assessed by successive alteration of input variables by \pm 10 per cent. With no variation in these variables the estimated area was 2.2 mm².

input new value of A new valu	e of A
variables (mm ²) (mm	²)
P _s 2.0 3.2	
P _d 0.6 5.2	
P _c 2.2 2.2	
Qs 2.9 1.4	

 P_s : systolic pressure, P_d : diastolic pressure, P_c : end systolic pressure, Q_s : systolic flow, A: regurgitant orifice area.

APPENDIX

Expression for the aortic pressure from a three-element model

If the volume of the arterial system is denoted by V, the continuity equation is:

$$\frac{\mathrm{dV}}{\mathrm{dt}} + \mathbf{q}_{\mathrm{out}} = \mathbf{q}_{\mathrm{in}} \tag{1}$$

where q_{out} is flow out from the arterial system to the venous system and q_{in} is flow into the system from the ventricle, i.e. aortic systolic flow, q_s . In aortic regurgitation q_{in} is not zero in diastole, but is represented by the regurgitant flow leaking back into the left ventricle, q_r , giving the equation if $\frac{dV}{dt}$ is multiplied with $\frac{dP_a}{dP_a}$, i.e., 1:

$$\frac{\mathrm{d}V}{\mathrm{d}P_{a}}\frac{\mathrm{d}P_{a}}{\mathrm{d}t} + q_{\mathrm{out}} = q_{\mathrm{in}} = q \qquad (2) \qquad 0 \le t \le t_{\mathrm{S}}, q = q_{\mathrm{S}}$$

ts<t≤td, q=qr

where t_s is duration of systole, t_d is duration of diastole and P_a is the arterial pressure. The total arterial compliance is defined as:

$$C = \frac{dV}{dP_a}$$
(3)

The outflow of blood into the venous system is assumed to be proportional to the pressure difference:

$$q_{out} = \frac{P_a - P_{ven}}{R} = \frac{P_a}{R}$$
(4) $P_a \gg P_{ven}$

where Pven is the venous pressure.

In diastole the characteristic resistance, r, is assumed to be neglectable and is therefore set to zero. By combining Eq.(2), (3) and (4) we obtain the equation:

$$q = C\frac{dP_{a'}}{dt} + \frac{P_{a'}}{R}$$
(5)

where $P_{a'}$ is the arterial pressure when r is zero. In systole $P_a = P_{a'} + rq$, giving the equation for both systole and diastole:

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$$q = C \frac{dP_a}{dt} - C r \frac{dq}{dt} + \frac{P_a}{R} - \frac{r}{R} q \qquad (6)$$

Eq.(6) solved with regard to the arterial pressure through the heart cycle, is:

$$P_{a}(t) = e^{-t/T} [P_{a}(t=0) + \frac{1}{C} \int_{0}^{t} e^{\tau/T} q(\tau) d\tau] + rq(t)$$

which is the equation used in this paper.

Parameter estimation procedure



Eq.2
$$P_a(t) = e^{-t/T}[P_a(t=0) + \frac{1}{C} \int_0^t e^{\tau/T}q(\tau) d\tau] + rq(t)$$

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FIG. 1. Mean regurgitant volume of measured and estimated regurgitant volumes in the cardiovascular hydromechanical simulator versus the difference of the volumes.



FIG. 2. Relationship between the regurgitant fraction obtained from the parameter estimation procedure and the semiquantitative categorical assessment from Doppler echocardiography. The numbers refer to the patients in Table 1.







Left and Right Ventricular Volumes by Magnetic Resonance Imaging from a New Biplane Method.

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Abstract - A new biplane method using a shape factor for calculating left and right ventricular volumes by magnetic resonance imaging was developed. The ventricular volumes were calculated from one long axis image together with one to five short axis images. The deviation from a circular cross section of each ventricle was expressed by an overall shape factor defined by the areas measured in the short axis images in end diastole and end systole and the corresponding diameters measured in the long axis image. The algorithm for volume calculation was validated in phantoms. End diastolic and end systolic volumes were calculated in 16 healthy volunteers of both sexes in order to compare the left and right ventricular stroke volumes which were assumed to be equal. In four patients with chronic aortic regurgitation the regurgitant fractions were compared with a semiquantitative evaluation by echocardiography. In six differently shaped phantoms the mean difference between 'true' volume and calculated volume was $1.0 \pm$ 0.8 ml (standard error). The mean difference between measured left and right ventricular stroke volumes was 0.4 ± 2.0 ml, with a standard deviation of 8.0 ml in individual measurements. There was a reasonable correlation between the regurgitant fraction obtained by magnetic resonance imaging and the semiguantitative evaluation by echocardiography. It is concluded that the combined long and short axis approach gives reliable left and right ventricular volumes.

Keywords - ventricular volumes, shape factor, aortic regurgitation

1 Introduction

Previous investigations have demonstrated that magnetic resonance imaging can accurately quantitate left ventricular dimensions and volumes (DILWORTH et al., 1987; UNDERWOOD et al., 1988; BEYAR et al., 1990; CRANNEY et al., 1990; SEMELKA et al., 1990), and that right ventricular dimensions and volumes may be obtained in the same way (LONGMORE et al., 1985; UNDERWOOD et al., 1986; MARKIEWICZ et al., 1987; SECHTEM et al., 1987; SECHTEM et al., 1988). These methods are usually based on summation of volumes in short axis multiple slice images encompassing the entire ventricles. The purpose of this study was to develop a new biplane method which incorporated both rapid data acquisition and high enough accuracy to enable calculation of regurgitant volumes in aortic or mitral valve incompetence. The method incorporated a new idea of using a shape factor to describe the geometry of the ventricles for volume calculation. We describe the method, the validation in phantoms, and its first application in 16 healthy volunteers and four patients with chronic aortic regurgitation.

2 Materials and methods

2.1 Ventricular shape factor

The volume (V) of any object is

$$V = \int_{a}^{b} A(x) \, dx \tag{1}$$

where x is the coordinate along an arbitrary axis, $a \le x \le b$, and A(x) is the area of the cross-section at the position x. If every cross-section is circular with a diameter w(x), then

$$A(\mathbf{x}) = \frac{\pi}{4} \mathbf{w}(\mathbf{x})^2. \tag{2}$$

The circular approximation is often used for calculating the volume of the left ventricle, and in this case the x-axis would be the long axis of the heart. In order to use a similar formula as Eq. (2) for calculating the volumes of both ventricles, we introduced a shape factor, f(x), so that

$$f(x) = \frac{A(x)}{\frac{\pi}{4} w(x)^2} .$$
(3)

f(x) thus expresses the deviation from a circular cross section at the position x. We may also define an overall shape factor F so that

$$F = \frac{\int_{a}^{b} A(x) dx}{\frac{\pi}{4} \int_{a}^{b} w(x)^{2} dx}$$
(4)

The direction of the x-axis is in our context defined to be parallel to the long axis image and perpendicular to the short axis images. A numerical approximation for the shape factor of Eq. (4) is

$$F = \frac{\sum_{i=1}^{N} A(x_i)}{\frac{\pi}{4} \sum_{i=1}^{N} w(x_i)^2}$$
(5)

where we sum over N short axis images, x_i is the position of the i-th short axis image, A(x_i) is the area of the contour drawn in that short axis image, and w(x_i) is the width of the contour in the long axis view at the position x_i . The integral

$$I = \int_{a}^{b} w(x)^2 dx$$
 (6)

in Eq. (4) may be calculated numerically from the endothelial border drawn in the long axis image. The ventricular volume will then be

$$V = \frac{\pi}{4} F I.$$
 (7)

This volume formula is exact in the limit where one measures the areas in a large number of equidistant parallel images. It is also a good approximation when one has a small number of images since the shape factor f(x) of a ventricle usually depends little on x. The use of one shape factor for the whole ventricle minimizes the statistical measurement error (see Appendix).

2.2 Imaging technique

The magnetic resonance imaging was performed on a Philips Gyroscan (Philips Medical Systems, Best, The Netherlands) system at 0.5 tesla and the images were transferred to a VAX 2000 (Digital Equipment Corp., Massachusetts, USA) workstation for post-processing. The employed image angulation procedure assumed that the patient was lying face up and head first in the magnet. A first scout view was a non-angulated transverse view. The second image was a two chamber long axis view of the left ventricle, perpendicular to the first transverse image. These two scout views were spinecho images obtained by using an echo-time (TE) of 20 ms and an acquisition matrix of 128x100 (reconstruction matrix of 256x256).

From the second view, and perpendicular to it, we planned the third view, a short axis view to be used for volume calculation. This was first planned as a long axis view, and we obtained the angle for the short axis view by adding or subtracting 90 degrees. The short axis images were spin-echo images acquired as Cycled Multi Slice, Multi Phase images, normally with five slices each in five different phases. The slice thickness was 10 mm, and there was a gap between slices of 5-10 mm, depending on the heart size. We used echo times of 20 ms, a variable acquisition matrix of typically 256x160 (reconstruction matrix of 256x256), 2 measurements, field of view of 350 mm, and an arrhythmia rejection window of 10 %. Perpendicular to the third view we planned a fourth view which was the true four chamber long axis view of the heart. The long axis images were rapid gradient echo images with 12 or 16 phases in one slice with an echo time of 15 ms, a flip angle of 40°, an acquisition matrix of typically 128x100 (reconstruction matrix of 256x256), 4 measurements, a field of view of 350 mm, and a time resolution of 25 to 50 ms.

Normally we used six images for calculating the volumes of the two ventricles in end diastole and end systole, i.e., five short axis images in parallel planes (third view) and the four chamber long axis view (fourth view). Ventricular stroke volumes were defined as the difference between end diastolic and end systolic volumes. Synchronization between the cardiac cycle and the imaging sequences was achieved by triggering from the R-wave of the electrocardiogram. Triggering was performed with a Hewlett-Packard (HP) telemetry system (Hewlett-Packard GmbH, Böblingen, Federal Republic of Germany).

The end diastolic image was identified 8 milliseconds after the R-wave, and end systole was identified as the image of smallest ventricular volumes. The images used for calculating the volumes were enlarged three times before the left and right ventricles were planimetered by one investigator on the VAX 2000. To ensure that the endothelial border was defined consistently, the contour in the long axis image was also plotted automatically in the short axis images where it intersected these, and vice versa (Fig. 1). This was a help in the cases where parts of an image had a loss of the endothelial border. All contours of the same phase were finally plotted in a quasi three dimensional projection as a visual check of the consistency of the endothelial border drawing (Fig. 2).

2.3 Phantoms

Six different phantoms of known volumes were used to validate the algorithm for volume calculation and the use of a shape factor. Four of them were water-filled balloons with different volumes and shapes which were placed in the magnet with similar axis as a human heart. Two phantoms were differently shaped glasses of water. The volumes were comparable to ventricular volumes and the resolution of the images was the same as in a standard heart examination.

2.4 Study subjects

16 healthy volunteers of both sexes (most of them athletes) without any evidence of valvular regurgitation, and four patients with chronic aortic regurgitation were studied. In the group of healthy subjects the stroke volumes of the left and right ventricle were assumed to be equal, while the difference in stroke volumes of the two ventricles in the patients with aortic regurgitation was assumed to represent the regurgitant volume.

The short axis image data of the 16 healthy volunteers were divided into four subgroups (I-IV) in order to assess how the number of short axis images influenced the calculation of the shape factor and the ventricular stroke volumes. In data group I, only the midventricular (third) short axis image was used in addition to the long axis image. In data group II, the middle and one or two short axis images closer to the apex were used in addition to the long axis image. In data group III, the long axis image. In data group III, the two short axis images closest to the base were used in addition to the long axis image. In data group IV, all short axis images obtained were used in addition to the long axis image.

2.5 Echocardiography

Nine of the subjects, i.e., six healthy volunteers and three patients, underwent an echocardiographic examination the same day to compare the stroke volume measurements of the left ventricle. The stroke volumes were determined from the subvalvular aortic

velocity curve and the subvalvular diameter assuming a circular outflow tract and a flat velocity profile (SKJAERPE et al., 1985).

In the four patients with chronic aortic regurgitation we compared the regurgitant fractions with the semiquantitative evaluation of a cardiologist by echocardiography. The latter procedure graded the aortic regurgitation as 'mild', 'mild to moderate', 'moderate', 'moderate to severe' or 'severe' from a combination of two-dimensional, M-mode, and Doppler echocardiography.

2.6 Statistics

All mean values are given \pm the standard error estimate of the mean (SE), while the numbers in brackets are the standard deviation of the measured values (SD). To study the agreement between the calculated left and right ventricular volumes and the agreement between left ventricular stroke volumes obtained by magnetic resonance imaging and by echocardiography, we plotted the difference against the mean value of the two measurements, and estimated the agreement by calculating the bias, i.e., the mean difference and its standard deviation.

3 Results

3.1 Phantoms

There was excellent agreement between the measured phantom volumes and the calculated volumes from the new algorithm in spite of wide variation in the shape factor (Table 1). The mean difference between the measured volumes and the calculated volumes was $1.0 \pm 0.8 \ (\pm 1.8)$ ml

3.2 Ventricular volumes

The mean end diastolic volume of the left ventricle in the healthy subjects was 151 $\pm 9 (\pm 36)$ ml, and the mean end systolic volume was $68 \pm 5 (\pm 19)$ ml. The mean end

diastolic volume of the right ventricle was $164 \pm 11 (\pm 43)$ ml and the mean end systolic volume was $81 \pm 7 (\pm 28)$ ml. The calculated shape factors and volumes of the ventricles are shown in table 2. The mean shape factor of the left ventricle was not significantly different from 1 and the shape factor of the right ventricle was approximately 2.

3.3 Stroke volumes

The mean left ventricular stroke volume using all short axis images in calculating the ventricular volumes was $83.4 \pm 5.0 (\pm 19.8)$ ml while the corresponding mean right ventricular stroke volume was $83.0 \pm 5.0 (\pm 20.0)$ ml. The mean difference between left and right ventricular stroke volumes was $0.4 \pm 2.0 (\pm 8.0)$ ml (Fig. 3). The ejection fractions for left and right ventricles were $0.54 \pm 0.02 (\pm 0.07)$ and $0.51 \pm 0.02 (\pm 0.07)$, respectively.

3.4 Number of short axis images

According to table 3, mean end diastolic and end systolic volumes did not change much using fewer short axis images in calculating the volumes, but the standard deviations of the stroke volumes and their differences increased. Left ventricular stroke volumes obtained by echocardiography in nine subjects matched excellently the left ventricular stroke volumes from magnetic resonance imaging in six subjects, but deviated by about 40 ml in three subjects (Fig. 4).

3.5 Aortic regurgitation

In four patients with chronic aortic regurgitation the mean left ventricular stroke volume was 149.1 ± 28.0 ml (± 56.0) and mean right ventricular volume was 83.4 ± 10.8 ml (± 21.7). The regurgitant fractions by magnetic resonance imaging were in good agreement with the semiquantitative evaluation by echocardiography (Table 4).
4 Discussion

This study demonstrates that both left and right ventricular volumes can be calculated from magnetic resonance imaging using a shape factor in the formula for volume calculation. The method allows, in principle, volume calculation from one long axis image and one or more short axis images. These are images that are obtained routinely in cardiac studies. The volumes calculated in the normal subjects were in accordance with other studies reporting left and right ventricular stroke volumes calculated from magnetic resonance images (SECHTEM et al., 1987; SECHTEM et al., 1988; WATANABE et al., 1986), even though our end diastolic and end systolic volumes tended to be somewhat larger. One reason might have been that most of our subjects were well-trained athletes known to have enlarged heart chambers. Another potential factor lies in systematic differences in the definition of the endocardial border among different observers. The regurgitant fractions calculated in four patients with chronic aortic regurgitation were reasonable compared to the gradings obtained by echocardiography.

4.1 Shape factor

The use of a shape factor makes the volume formula independent of preconceived left and right ventricular shapes. This is a new approach for volume calculation although GIBSON and BROWN (1975) have introduced a shape index to describe the left ventricle. Their shape index was defined as 4π (Area)/ (Perimeter)², and the purpose was to describe the shape of the left ventricle during different haemodynamic situations. We used diameter instead of circumference (perimeter) in our shape factor. The results showed that our shape factor handled both the complex geometry of the right ventricle and the approximate circular shape of the left ventricle cross sections. The principle of using a shape factor in volume calculation is not limited to magnetic resonance imaging, but can be applied in other imaging techniques like echocardiography. Simpson's rule,

which is a well recognized method for volume calculation, has also been applied to the right ventricle (WATANABE et al., 1982), but our formula gives a smaller statistical measurement error than Simpson's rule (see Appendix).

4.2 Biplane method

The advantages of a biplane approach for volume calculation have already been recognized (CRANNEY et al., 1990). Even though a short axis multiple slice approach has the theoretical advantage of encompassing the entire ventricles, the partial volume effects, especially in defining the valves, makes the method uncertain. Former studies have also shown that one slice techniques for calculating left ventricular volumes do not correlate as well to other methods as multi slice techniques (DILWORTH et al., 1987; UNDERWOOD et al., 1988; BUCKWALTER et al., 1986; VAN ROSSUM et al., 1988). Similarly, our data both emphasize the advantage of a biplane approach and show that several short axis images are needed to achieve acceptable identity between left and right ventricular stroke volumes in subjects without valve incompetence. With four or five short axis images in addition to the long axis image, the confidence interval (± 2 SD) was within ± 16 ml, which represents no serious error in the evaluation of the severity of regurgitation.

The need for four or five short axis images in addition to the long axis image was in some opposition to one of the purposes of the study, i.e. to develop a method which allowed rapid data acquisition. In cardiac studies there has to be a compromise between the accuracy of the method and the data acquisition time. However, in many cardiac evaluations using the present method the accuracy could be good enough with just one short axis image in addition to the long axis image, which implies that the volume of the right ventricle with its complex geometry can be calculated from only two images. In patients with wall motion abnormalities the number of short axis image should be as high as possible to include the differences of the shape of the ventricles that are induced by the wall motion abnormalities.

4.3 Stroke volumes

Equality of stroke volumes of both ventricles in normal subjects does not necessarily mean that the end diastolic and end systolic volumes were correct. However, the left ventricular stroke volumes obtained by two dimensional and Doppler echocardiography were similar to those calculated from magnetic resonance imaging. The discrepancy in three of the subjects between the two methods might show an inaccuracy in the calculations from magnetic resonance images, or the echocardiographic measurements. Since the ultrasound method uses the subvalvular diameter in calculating the cross-sectional area, and the diameter is squared in the area calculation used to calculate the stroke volume, the relative error of the stroke volume is necessarily rather large. However, the observed differences may have been real since the two examinations were done at a few hours difference and the stroke volumes of the subjects might have changed between the two examinations.

The results encourage continued validation of our method as a possible reference method for assessing single valve incompetence as well as for volume calculation at any cardiac disorder. The magnitude of the regurgitation is usually assessed by the qualitative grading of the regurgitant jet visualized during contrast cineangiography, but the method is imprecise and often inaccurate in assessing the severity of the incompetence (CROFT et al., 1984).

4.4 Conclusion

Our biplane and shape factor method in calculating left and right ventricular volumes from magnetic resonance imaging gave nearly identical stroke volumes from the left and right ventricles in subjects without valve incompetence. The difference in stroke volumes in patients with chronic aortic regurgitation correlated well with semiquantitative evaluation of the severity of valve incompetence by echocardiography. The method should be applicable for volume calculation in all kinds of cardiac disorders and the principle of using a shape factor should also be applicable for other imaging techniques like echocardiography.

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Figure legends

Fig. 1 A long axis image and a short axis image in end systole with and without the contours drawn of the ventricular borders in one patient with aortic regurgitation. The contour in the long axis image was also plotted automatically in the short axis image where it intersected this, and vice versa, in order to ensure that the endothelial border was defined consistently.

Fig. 2 Contours of left ventricular and right ventricular borders drawn in end diastole (left panel) and end systole (right panel) in one healthy subject. The independently drawn long and short axis borders are superimposed to allow a visual check of the consistency of the border definitions.

Fig. 3 The difference of left and right ventricular stroke volumes plotted against the mean left and right ventricular stroke volumes using all short axis images for the volume calculation in 16 healthy subjects.

Fig. 4 The difference between the stroke volumes obtained by magnetic resonance imaging (MRI) and by echocardiography (Echo) plotted against the mean of the two volumes in nine subjects.

Phantom	Measured	Calculated	Shape
	volume	volume	factor
	ml	ml	
1	196	192	0.95
2	117	115	1.02
3	113	115	2.74
4	108	109	1.04
5	135	134	1.10
6	133	132	1.03

Table 1. Measured and calculated volumes in the six phantoms, and the corresponding shape factors used for volume calculation.

1-4: water filled-balloons, 5-6: glasses of water.

Table 2. Mean end diastolic volume and mean end systolic volume of the left and right ventricles using all the short axis images, and the mean of the corresponding shape factors used for volume calculation in 16 healthy subjects. Values are given \pm the standard error estimate of the mean.

	Volume	Shape Factor	
	ml		
Left Ventricle			
ED	151± 9	1.004 ± 0.018	
ES	67 ± 5	1.006 ± 0.031	
SV	83.4 ± 5.0		
Right Ventricle			
ED	164 ± 11	1.97 ± 0.06	
ES	81 ± 7	1.94 ± 0.10	
SV	83.0 ± 5.0		

ED: end diastole, ES: end systole, SV: stroke volume.

Table 3. Mean end diastolic volume, mean end systolic volume and mean stroke volume of the left and right ventricles in relation to the number of short axis images used for volume calculation in 16 healthy subjects. See explanation to groups I-IV in text. All volumes are given \pm one standard deviation (SD). Mean difference is mean difference between left and right ventricular stroke volumes.

	Left			Right			Mean
	Ventricle			Ventricle			Difference
Group	EDV	ESV	SV	EDV	ESV	SV	SV
	ml	ml	ml	ml	ml	ml	ml
Ι	146±41	69±21	77.9±25.2	148±41	79±24	68.7±24.3	9.1±29.8
II	150±40	69±24	80.8±23.8	170±59	84±34	85.6±38.6	-4.7±32.2
ш	152±36	67±17	84.3±21.5	165±43	80±28	85.0±18.8	-0.8±15.2
IV	151±36	68±19	83.4±19.8	166±43	81±28	83.0±20.0	0.4±8.0

EDV: end diastolic volume, ESV: end systolic volume, SV: stroke volume.

Table 4. Regurgitant volumes and fractions in four patients with chronic aortic regurgitation assessed by magnetic resonance imaging. The degree of regurgitation was semiquantitatively evaluated by echocardiography.

Patient	Regurgitant	Regurgitant	Echo
No	Volume	Fraction	Evaluation
	ml		
1	27	0.20	Mild-Mod
2	137	0.62	Severe
3	33	0.37	Moderate
4	66	0.44	Mod-Sev

Mild-Mod: mild to moderate, Mod-Sev: moderate to severe.

APPENDIX

Numerical and statistical errors in volume formulas.

Consider a numerical volume formula of the form

$$V_{num} = \sum_{i=1}^{N} W_i A_i \tag{1}$$

where $A_1,..., A_N$ are measured areas of a series of parallel cross sections. $W_1,..., W_N$ are appropriate weight factors and typically they will be the slice thicknesses. The formula should be exact if all areas are equal, this implies the constraint on the weight factors that

$$\sum_{i=1}^{N} W_i = L = \text{the total length.}$$
(2)

If a circular area A is measured by the measurement of m points equally spaced around its perimeter, then the standard deviation of the measured area is

$$\sigma_{\rm A} = \sqrt{\frac{4\pi A}{m}} \sigma_{\rm P} \tag{3}$$

where σ_P is the standard deviation of the measurement of each position coordinate. Since one usually measures more points for a large area than for a small one, it is a reasonably good approximation to assume that σ_A is a constant, independent of the area.

With this approximation, if we assume that the errors in measured areas are independent and if we neglect the errors in the weight factors $W_1,..., W_N$, the standard deviation σ_V of the measured volume is given by the formula

$$\sigma_V^2 = \sigma_A^2 \sum_{i=1}^N W_i^2 = \sigma_A^2 \left(\frac{L^2}{N} + \sum_{i=1}^N (W_i - \frac{L}{N})^2 \right)$$
(4)

We see that σ_V is minimized when we take all weights equal,

$$W_1 = \dots = W_N = W = \frac{L}{N}$$
 (5)

This gives the volume by the sum of areas,

$$V_{num} = W \sum_{i=1}^{N} A_i$$
 (6)

Our volume formula, Eq. (7) in the text, is of the area-sum type with weight

$$W = \frac{\int_{i=1}^{b} w(x)^2 dx}{\sum_{i=1}^{N} w(x_i)^2}$$
 (7)

There is of course some error in the estimate of the common weight factor W. However, in any volume formula it is necessary to estimate the length of the object, and there is always an inherent uncertainty in this length estimate.

Note that Simpson's rule (SR), for N = 3,5,7,9,...,

$$V_{SR} = \frac{L}{3(N-1)} (A_1 + 4A_2 + 2A_3 + 4A_4 + \dots + 2A_{N-2} + 4A_{N-1} + A_N)$$
(8)

is not of the minimal variance type, since it uses unequal weights. Simpson's rule is an exact formula for integrating any cubic polynomial. However, there is no point in improving the precision of a numerical approximation, if the increase in the statistical measurement error is larger than the reduction in the numerical error. In other words, Simpson's rule should only be used for very accurate data.



Fig. 1





Fig. 2



Fig. 3





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