

BASIC RESEARCH

Effect of load alterations on the effective regurgitant orifice area in chronic aortic regurgitation

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Heart 2002;88:397–400

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Accepted 12 June 2002

Objective: To evaluate the load dependence of effective regurgitant orifice area (ROA) in an animal model of chronic aortic regurgitation.

Methods: Eight sheep were studied 10–20 weeks after the surgical creation of aortic regurgitation. After baseline studies, 500 ml of blood, angiotensin II, and nitroprusside were infused sequentially. Electromagnetic flow meters were used as reference standards to determine aortic regurgitation volume. The time–velocity integral was acquired using the continuous wave Doppler method.

Results: Baseline aortic regurgitant volume varied from 8 ml (regurgitant fraction 28%) to 29 ml (59%), with a mean (SD) value of 17 (8) ml; mean ROA was 0.15 (0.05) cm². During angiotensin II infusion, aortic regurgitation volume (20 (8) ml) and mean diastolic aortoventricular pressure gradient (62 (18) mm Hg) increased by 26 (16)% and 48 (64)%, respectively ($p < 0.01$ for both). ROA did not change (0.16 (0.06) cm², $p = 0.15$). During nitroprusside infusion, aortic regurgitant volume (13 (7) ml, $p = 0.05$) and diastolic pressure gradient (25 (13) mm Hg, $p < 0.05$) decreased. ROA did not change (0.15 (0.05) cm²). When analysing 32 stages together, aortic regurgitant volume ($r = 0.78$, $p < 0.01$) and regurgitant fraction ($r = 0.55$, $p < 0.01$) correlated well with ROA. However, diastolic pressure gradient ($r = 0.28$) was not significantly correlated with ROA.

Conclusions: In an animal model of chronic aortic regurgitation, ROA did not change with load alterations.

Although the value of long term vasodilator treatment in chronic aortic regurgitation has been established, its mechanism remains controversial. Convincing beneficial effects on systolic function have been reported, with a reduced aortic regurgitation volume,^{1–6} even without significant changes in heart rate and blood pressure.⁷ Because the regurgitation volume is determined by the diastolic aortoventricular pressure gradient, the regurgitant orifice area (ROA), and diastolic filling time,⁸ the effect of vasodilators was assumed to be mediated through a reduction of aortic pressure. However, a significant reduction in diastolic pressure with long term vasodilator treatment is difficult to accomplish, because most patients with aortic regurgitation have low aortic diastolic pressures before treatment. Thus the load dependence and dynamic nature of the ROA have been proposed as possible mechanisms to explain the benefit of vasodilator treatment in chronic aortic regurgitation. Reimold and colleagues demonstrated the load dependence of effective ROA in an animal model of acute aortic regurgitation,⁹ and reported the same result in an in vitro model using calf heart and aorta.¹⁰ However, there have been no reports of chronic animal models with ventricular and aortic remodelling. We therefore undertook the present study to evaluate the load dependence of ROA with changes of loading conditions in an animal model of chronic aortic regurgitation.

METHODS

Animal model of aortic regurgitation

We studied eight juvenile sheep, mean (SD) weight 43 (6) kg. Aortic regurgitation was created surgically by incising the free edge of the right coronary ($n = 4$) or non-coronary cusp ($n = 4$) and after 10–20 weeks the animals were returned to the laboratory.

Instrumentation and data acquisition

An electromagnetic flow probe (model EP455, Carolina Medical Electronics Inc, King, North Carolina, USA) was placed around the pulmonary artery just above the pulmonary valve sinuses. Another electromagnetic flow probe was placed snugly around the skeletonised ascending aorta distal to the coronary ostia and proximal to the brachiocephalic trunk. Both flow probes were connected to flow meters (model FM501, Carolina Medical Electronics) and these were connected to a physiological data recorder (ES2000, Gould Inc, Cleveland, Ohio, USA). Calibration factors for the flow probes were corrected before each measurement, and zero baseline was adjusted so that the forward minus the backward aortic flow volumes equalled the pulmonary forward flow volume. Stroke volumes and aortic regurgitation volumes were determined by planimetry of the aortic forward flow signal recordings and of the regurgitant flow signal recordings, respectively. We inserted 5 French catheter tipped micromanometer pressure transducers (Millar Instruments, Houston, Texas, USA) into the ascending aorta through a carotid artery and into the left ventricle through the left ventricular apex for simultaneous recording of left ventricular and aortic pressures.

All operative and animal management procedures were approved by the animal care and use committee of the National Heart, Lung, and Blood Institute. Preoperative, intraoperative, and postoperative animal management and husbandry methods are described in detail elsewhere.¹¹

Echocardiography

All echocardiographic studies were performed on a commercially available system (Power Vision, Toshiba Corporation, Tokyo, Japan) with a 3.5 MHz transducer. From the apex, and using liver tissue as a standoff (2 cm thickness), continuous wave Doppler tracings of the regurgitant signal were recorded under the guidance of colour Doppler flow imaging while

Table 1 Haemodynamic characteristics of each stage

	HR (beats/min)	MAP (mm Hg)	SV (ml/beat)	ARV (ml/beat)	DPG (mm Hg)	ROA (cm ²)
Baseline	111 (20)	76 (24)	34 (13)	17 (8)	45 (16)	0.15 (0.05)
Blood	111 (23)	91 (22)	39 (15)	19 (9)	54 (10)	0.16 (0.05)
Angiotensin II	105 (14)	107 (14)*	41 (16)*	20 (8)*	62 (18)**	0.16 (0.06)
Nitroprusside	98 (18)	46 (11)*	31 (15)	13 (7)**	25 (13)**	0.15 (0.05)

Values are mean (SD).

* $p < 0.01$, ** $p < 0.05$ v baseline.

ARV, aortic regurgitant volume; DPG, diastolic aortoventricular pressure gradient; HR, heart rate; MAP, mean aortic pressure; ROA, regurgitant orifice area; SV, stroke volume.

adjusting the orientation of the interrogating beam carefully. The continuous wave Doppler tracings were digitised for off-line analysis. The time-velocity integral and pressure half times of the aortic regurgitation jets were measured in three consecutive beats and the average of the measurements was used.

Calculations

The ROA was calculated by both invasive and Doppler echocardiographic methods.

With a modification of the Gorlin equation using aortic regurgitation volume (ARV), diastolic filling period (DFP), and the mean diastolic pressure gradient between the aorta and left ventricle [P1–P2], ROA was calculated as:

$$\text{ROA} = \frac{\text{AR volume}}{(50.4)(\text{DFP})\sqrt{[P1 - P2]}}$$

ROA was also determined using continuous wave Doppler echocardiography as the ratio of the aortic regurgitation volume, obtained by electromagnetic flow meters, to the time-velocity integral (TVI) of the aortic regurgitation jet, obtained by echocardiography. Then:

$$\text{ROA} = \frac{\text{AR volume}}{\text{TVI of AR jet}}$$

The regurgitant fraction was calculated as backward aortic flow volume per minute divided by forward aortic flow volume per minute.

Study protocol

After the measurement at baseline, three different loading conditions were studied. Firstly, 500 ml of warm blood were transfused over 30 minutes. Secondly, an intravenous infusion of angiotensin II at a dose of 10–20 µg/min (Peptide Institute, Osaka, Japan, provided by Tanabe Seiyaku Co, Tokyo, Japan) was given to increase mean aortic pressure by 15 mm Hg. Thirdly, nitroprusside was infused at a dose of 100–200 µg/min to decrease mean aortic pressure by 15 mm Hg. Measurements were done after the haemodynamic changes had stabilised in each stage.

Statistical analysis

Data are presented as mean (SD). Heart rate, aortic regurgitation volume, mean diastolic aortoventricular pressure gradient, and ROA were compared between baseline and each loading condition by the paired Student *t* test. The ROA calculated by continuous wave Doppler was compared with that determined by catheterisation using linear regression analysis. Statistical analyses were undertaken using a statistical package (STAT VIEW 1988, Abacus Concepts Inc). A probability value of $p < 0.05$ was considered significant.

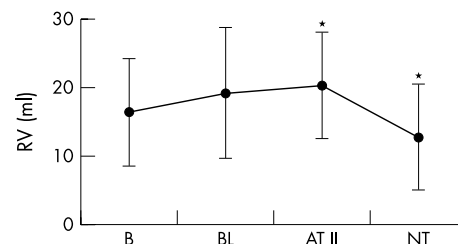


Figure 1 The changes in aortic regurgitant volume (RV) with load manipulations. AT II, angiotensin II; B, baseline; BL, blood; NT, nitroprusside. * $p < 0.01$ v baseline.

RESULTS

Haemodynamic measurements for the four different stages are given in table 1.

Correlation between Doppler echocardiographic data and invasive data

There was good correlation and agreement between effective ROA calculated by continuous wave Doppler echocardiography and determined by the catheterisation procedure ($r = 0.93$, $p < 0.01$; mean (SD) difference: 0.01 (0.02) cm²).

Baseline haemodynamics and regurgitant volume

At baseline, aortic regurgitation volume measured by electromagnetic flow meters varied from 8 ml (regurgitation fraction 28%) to 29 ml (59%), with a mean value of 17 (8) ml. Mean aortic pressure and heart rate were 76 (24) mm Hg and 111 (20) beats/min, respectively. Mean diastolic aortoventricular pressure gradient was 45 (16) mm Hg. Effective ROA ranged from 0.08–0.21 cm² with a mean value of 0.15 (0.05) cm².

Effect of load manipulations

With a 500 ml blood transfusion, mean aortic regurgitation volume and diastolic aortoventricular pressure gradient increased to 19 (9) ml and 54 (10) mm Hg, respectively (NS v baseline). The effective ROA did not change significantly (0.16 (0.05) cm²). During angiotensin II infusion, the aortic regurgitation volume increased to 20 (8) ml, a 26 (16)% increase ($p < 0.01$). In addition, the mean diastolic aortoventricular pressure gradient increased by 48 (64)% to 62 (18) mm Hg ($p < 0.01$). However, the effective ROA did not change significantly (0.16 (0.06) cm²; $p = 0.15$). During nitroprusside infusion, the aortic regurgitation volume decreased by 23 (35)%, to 13 (7) ml ($p = 0.05$); the mean diastolic pressure gradient decreased by 42 (28)% to 25 (13) mm Hg ($p < 0.05$); and the effective ROA did not change significantly (0.15 (0.05) cm²). The changes of regurgitant volume, mean diastolic aortoventricular pressure gradient, and ROA with load manipulations are shown in figs 1, 2, and 3.

Regression analysis

When the haemodynamic data from all 32 stages were analysed together, aortic regurgitation volume correlated well

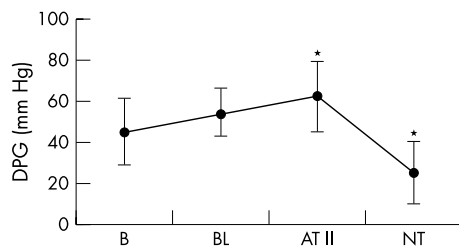


Figure 2 The changes in mean diastolic aortoventricular pressure gradient (DPG) with load manipulations. AT II, angiotensin II; B, baseline; BL, blood; NT, nitroprusside. * $p < 0.01$ v baseline.

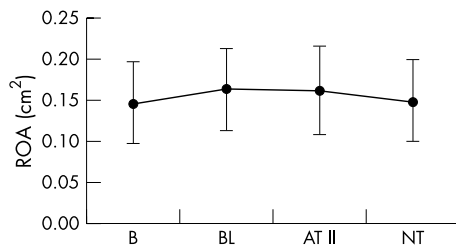


Figure 3 The changes in regurgitant orifice area (ROA) with load manipulations. AT II, angiotensin II; B, baseline; BL, blood; NT, nitroprusside.

with ROA ($r = 0.77$, $p < 0.01$) and mean diastolic aortoventricular pressure gradient ($r = 0.63$, $p < 0.01$). ROA also showed a significant negative correlation with pressure half time ($r = -0.63$, $p < 0.01$). In a stepwise multiple linear regression, the correlation was improved by combining ROA with the diastolic aortoventricular pressure gradient ($r = 0.89$, $p < 0.01$). Aortic regurgitation volume ($r = 0.78$, $p < 0.01$) and regurgitant fraction ($r = 0.55$, $p < 0.01$) showed good correlations with ROA. However, mean aortoventricular pressure gradient was not correlated with ROA ($r = 0.28$).

DISCUSSION

Valvular heart diseases have been shown to be dynamic, with changes in stenotic and regurgitant orifice area occurring in response to altered loading conditions.^{12–13} However, the dynamic nature of the aortic regurgitant orifice area is controversial, and it has been suggested that this variable is unresponsive to changes in aortic pressure.¹⁴ However, Reimold and colleagues reported variation in the orifice area depending on aortic pressure in an animal model of acute aortic regurgitation.⁹ Furthermore, aortic pressure dependence of the orifice area has also been demonstrated in an in vitro model,¹⁰ and changes of orifice area during diastole were observed in patients with chronic aortic regurgitation.¹⁵ These observations suggest that dynamic alteration of the orifice may be a mechanism whereby vasodilator treatment reduces regurgitant volume and left ventricular volume. This is plausible because it is difficult in practice to reduce diastolic blood pressure significantly in patients with chronic aortic regurgitation, as they already have low diastolic pressures. Other investigators have reported a reduction in regurgitant volume without any significant changes in heart rate or blood pressure.⁷

In the present study with an animal model of chronic aortic regurgitation, we could not detect a significant change in the effective ROA despite a 26% increase in regurgitant volume and a 48% increase in mean diastolic aortoventricular pressure gradient with an angiotensin II infusion. Similarly, although nitroprusside infusion resulted in a 23% decrease of regurgitant volume and a 42% decrease of aortoventricular pressure gradient, the ROA did not change. This finding contrasts with

previous results in an animal model of acute aortic regurgitation,⁹ where a 90% increase in the aortoventricular pressure gradient caused by dopamine increased the orifice area by 38%, and a 45% reduction in the pressure gradient caused by nitroprusside decreased the orifice by 28%. Furthermore, it was reported that the ROA gradually increased when aortic pressure was increased in an in vitro model,¹⁰ which suggests that alterations in aortic pressure change aortic root size and geometry and hence the orifice area.¹⁶ However, we did not observe any relation between percentage change in aortic pressure and orifice area, which is consistent with a previous report in patients with chronic aortic regurgitation.¹⁵

The apparent inconsistency of these findings probably reflects the differences between acute and chronic animal models. In chronic aortic regurgitation, left ventricular systolic function, left ventricular volume, and left ventricular and aortic compliance vary substantially in animal models, depending on the severity and duration of the aortic regurgitation. Furthermore, the healing process after incision of the leaflet may increase leaflet stiffness. These differences could affect the dynamic nature of the orifice. In addition, in our study the surgically created aortic regurgitation was more severe than in other comparable studies. For example, in our model the regurgitant volume ranged from 8–29 ml, and the ROA from 0.08–0.21 cm², compared with values of 2–11 ml and 0.02–0.18 cm², respectively, in the study by Reimold and colleagues.⁹ Because the dynamic nature of the orifice is inversely related to the severity of the regurgitation,¹⁵ it is likely that the orifices were less dynamic in our animals.¹⁷

Clinical implications

Evaluating the severity of aortic regurgitation is a difficult clinical problem. Several methods are currently used to estimate the regurgitant volume, such as radionuclide ventriculography, contrast aortography, and Doppler echocardiography. However, the influence of loading conditions on the regurgitant volume limits the clinical usefulness of these methods.

The effective ROA can be estimated using Doppler echocardiographic methods, including quantitative Doppler and colour Doppler flow convergence.^{17–19} In our present study, we showed that the ROA was not influenced by changes in the loading conditions. Thus the ROA may be more reliable than regurgitant volume for grading the clinical severity of aortic regurgitation when the loading conditions are altered.

Study limitations

We adjusted the baseline for the aortic flow recording until the forward minus the backward aortic flow volumes equalled the pulmonary forward flow volume. This method ignores coronary arterial flow runoff. However, we measured coronary arterial blood flow during ventricular diastole in three sheep in a preliminary study, and the coronary flow rate was small (0.13–0.23 l/min). The correlation coefficient for the regression of pulmonary forward flow versus aortic forward minus aortic regurgitation flow was 0.98 (SEE = 0.03 l/min).

In our animal model, aortic regurgitation was achieved by incising the free edge of one of the cusps. As the pathology of the leaflet and the location of the regurgitation orifice are important factors in orifice dynamics,¹⁰ our animal model may not be representative of all the causes of chronic aortic regurgitation. For example, regurgitation secondary to aortic root disease may have a different pattern of orifice area change from chronic regurgitation caused by fixed lesions, the latter being closer to our animal model.^{20–21}

In our study the changes in loading conditions were made by intravenous treatments, so they were necessarily of short duration. Thus our results may not be directly applicable to patients who are taking chronic vasodilators. In those patients the ROA may change over time, so a longer duration of vasodilator treatment may be warranted for analysing ROA in

chronic aortic regurgitation, which is important in clinical decision making.

Conclusions

In an animal model of chronic aortic regurgitation, ROA did not change significantly with load alterations. This has implications for the investigation of the severity of aortic regurgitation.

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IMAGES IN CARDIOLOGY

Coronary–pulmonary artery fistulae: blood flow pattern and effect on myocardial perfusion

In a man aged 65 years undergoing diagnostic coronary arteriography, a fistula was found arising from the circumflex coronary artery and entering a branch of the left pulmonary artery (panel A, black arrows), while exercise stress myocardial perfusion scintigraphy (^{201}Tl SPECT) showed normal distribution of the radiotracer. Estimation of blood flow using a Doppler guidewire (panel A, white arrows) revealed that the flow through the fistula was mainly during systole (panel B, diastolic to systolic velocity ratio (DSVR) 0.3), while the flow in the circumflex was mainly during diastole (panel C, DSVR 3.2). The latter provides a probable explanation of the ^{201}Tl SPECT findings, indicating that the fistula did not affect the myocardial perfusion.

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