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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LONDON
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TAVISTOCK SQUARE, LONDON WC1
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 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.5–6 Another important point about arterial compliance is that due to the non-linear elastic properties of artery walls, i.e., 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 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 Graphitec Linearrecorder 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 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:

\[
C = \frac{Q_{in} - A_s/R}{P_s - P_d}
\]

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 \(P_s\) 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:

\[
q = C_d A_o \sqrt{\frac{2}{\rho} (p_1 - p_2)}
\]
Haemodynamic variables in the pigs with and without aortic regurgitation. Samples with four different calculated regurgitant orifices areas were used. Values are means(SD)

<table>
<thead>
<tr>
<th>Regurgitant area (mm²)</th>
<th>RF</th>
<th>Regurgitant volume (ml)</th>
<th>Aortic pressure (mm Hg)</th>
<th>Stroke volume (ml)</th>
<th>Compliance (mm Hg.s/ml)</th>
<th>TPR (mm Hg.s.ml⁻¹)</th>
<th>PHT (ms)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>Systolic</td>
<td>Diastolic</td>
<td>0</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Control (n=16)</td>
<td>0</td>
<td>0</td>
<td>82.1(8.3)</td>
<td>99.5(9.8)</td>
<td>63.4(7.7)</td>
<td>26.6(6.5)</td>
<td>0.57(0.13)</td>
<td>1.79(0.52)</td>
</tr>
<tr>
<td>GTN (n=6)</td>
<td>0</td>
<td>0</td>
<td>41.7(5.5)</td>
<td>68.2(9.9)</td>
<td>27.0(4.0)</td>
<td>26.4(3.0)</td>
<td>1.46(0.64)</td>
<td>0.82(0.09)</td>
</tr>
<tr>
<td>Control [2.4(1.7), n=24]</td>
<td>0.07(0.05)</td>
<td>2.0(1.3)</td>
<td>84.2(6.5)</td>
<td>101.5(7.2)</td>
<td>65.3(6.6)</td>
<td>30.3(5.6)</td>
<td>0.68(0.13)</td>
<td>1.83(0.39)</td>
</tr>
<tr>
<td>5-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control [6.5(1.0), n=25]</td>
<td>0.22(0.10)</td>
<td>5.3(1.4)</td>
<td>78.8(11.9)</td>
<td>95.1(14.7)</td>
<td>59.0(11.4)</td>
<td>26.2(5.9)</td>
<td>0.57(0.10)</td>
<td>2.65(1.01)</td>
</tr>
<tr>
<td>GTN [6.7(1.6), n=6]</td>
<td>0.12(0.07)</td>
<td>2.8(1.3)</td>
<td>46.3(13.9)</td>
<td>70.2(14.1)</td>
<td>32.1(13.1)</td>
<td>23.1(10.9)</td>
<td>1.65(0.86)</td>
<td>1.25(0.50)</td>
</tr>
<tr>
<td>15-19</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Control [17.2(1.4), n=6]</td>
<td>0.37(0.02)</td>
<td>8.8(0.9)</td>
<td>74.2(3.1)</td>
<td>99.4(3.0)</td>
<td>52.9(1.6)</td>
<td>23.8(1.3)</td>
<td>0.64(0.14)</td>
<td>2.29(0.30)</td>
</tr>
<tr>
<td>GTN [16.5(1.2), n=5]</td>
<td>0.25(0.03)</td>
<td>6.3(0.9)</td>
<td>43.3(3.6)</td>
<td>77.5(2.5)</td>
<td>23.9(11.9)</td>
<td>25.0(4.4)</td>
<td>1.61(0.43)</td>
<td>1.24(0.25)</td>
</tr>
<tr>
<td>28-32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control [30.6(1.3), n=6]</td>
<td>0.53(0.05)</td>
<td>16.7(3.2)</td>
<td>64.5(7.8)</td>
<td>88.2(4.8)</td>
<td>41.7(6.4)</td>
<td>31.2(3.8)</td>
<td>0.68(0.10)</td>
<td>2.34(0.24)</td>
</tr>
</tbody>
</table>

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

where q is regurgitant flow, \( C_a \) is a “discharge coefficient”, \( A_r \) is the regurgitant orifice, \( \rho \) 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: \( C_a = C_v C_c \), where \( C_v \) is the coefficient of flow jet contraction, \( C_c \) is the area of the jet at the vena contracta, \( A_r \) is the area of the orifice, \( A_v \), \( C_v \) 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 \( C_v \) 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 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.

![Graph](image_url)

**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 ml mm Hg⁻¹).

![Graph](image_url)

**Figure 2** Relationship between regurgitant volume and total peripheral resistance at a regurgitant orifice area of 5-9 mm² 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.
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·C⁻¹·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.

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 equilibration 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 resistance, i.e., increasing 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 regression, 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.
Compliance, resistance, and glyceryl trinitrate in aortic regurgitation

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 mm Hg s ml⁻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. 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.

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. 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. 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 al 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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