Left Ventricular Blood Flow During Aortic Pressure Reduction in Hypertensive Dogs

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We measured left ventricular blood flow with radioactive microspheres during aortic pressure reduction in 10 open-chest, anesthetized dogs with left ventricular hypertrophy due to chronic hypertension and in 10 matched normotensive dogs. Heart rate and left atrial pressure were held constant, and autonomic reflexes were abolished with ganglionic blockade. Aortic diastolic pressure was lowered from baseline to 90, 75, and 60 mm Hg with an arteriovenous fistula. During aortic pressure reduction, a stepwise decline in the endocardial-to-epicardial flow ratio in hypertrophied hearts from 1.23±0.04 at baseline to 0.96±0.09 at a diastolic pressure of 75 mm Hg paralleled that in normal hearts and was not associated with any deterioration in left ventricular performance. However, a further fall in the endocardial-to-epicardial flow ratio to 0.76±0.10 at a diastolic pressure of 60 mm Hg in hypertrophied hearts exceeded that in normal hearts (0.92±0.05, p<0.05) and was accompanied by evidence of left ventricular isovolumic and end-systolic dysfunction. We conclude that in hearts with pressure-overload left ventricular hypertrophy, aortic pressure reduction causes a transmural blood flow redistribution from subendocardial to subepicardial muscle layers. At moderately low aortic pressures, this redistribution is more pronounced than in normal hearts and is associated with functional evidence of myocardial ischemia. (Hypertension 1991;18:665-673)

Several lines of evidence suggest that lowering aortic blood pressure in the setting of chronic hypertension may have deleterious effects on the heart. Experimental studies have demonstrated that in hearts with hypertension-induced left ventricular (LV) hypertrophy, LV isovolumic indexes1 and pump function2-3 are impaired at reduced aortic pressure levels that are well-tolerated by normal hearts. These findings are in accord with clinical studies that have noted either asymptomatic electrocardiographic changes4-6 or overt symptoms of myocardial ischemia7 after acute pressure reduction in hypertensive patients. Moreover, epidemiological studies that have described a U-shaped8 or J-shaped9 relation between the level of blood pressure after treatment and the incidence of cardiac mortality have led to the suggestion that excessive reduction of blood pressure with antihypertensive therapy might precipitate myocardial ischemia and infarction.10

Since animal studies using electrical pacing11 and coronary artery constriction12 have shown that the hypertrophied left ventricle is susceptible to subendocardial perfusion deficits, one possible explanation for any detrimental effects of aortic pressure reduction in hypertrophied hearts is an alteration in LV transmural blood flow patterns. We have previously shown that in normal hearts, moderate aortic pressure reduction redistributes LV blood flow from subendocardial to subepicardial muscle layers, without depression of LV isovolumic indexes or electrical evidence of myocardial ischemia.13 It is not known, however, if aortic pressure reduction similarly redistributes LV transmural flow in hypertrophied hearts and if differences in the extent of any redistribution are apparent at a level of aortic pressure associated with LV functional impairment. Accordingly, the aim of the present study was to compare LV transmural blood flow responses during acute aortic pressure reduction in normotensive dogs and those with well-compensated LV hypertrophy due to renovascular hypertension.

Methods

The study was performed in 20 conditioned adult male mongrel dogs. Ten had LV hypertrophy secondary to chronic renovascular hypertension and 10 were normotensive dogs with a similar range of body weights.

Induction of Hypertension

One-kidney renovascular hypertension was produced as previously described.1,14 Briefly, the left
Experimental Preparation

Normotensive and hypertensive dogs were anesthetized with intravenous sodium pentobarbitone (25 mg/kg bolus followed by a constant infusion of 6 mg/kg/hr), intubated, and artificially ventilated at an end-expiratory pressure of 4 cm H2O with oxygen-enriched room air. Arterial gas samples were analyzed frequently (Radiometer ABL1, Copenhagen, Denmark), and ventilation was adjusted to maintain arterial carbon dioxide tension between 35 and 40 mm Hg and pH between 7.3 and 7.4. Sodium bicarbonate was administered, as necessary, to correct any base deficits. Rectal temperature was kept between 36° and 38°C with a heated table and a thermostatically controlled water blanket.

The surgical preparation was as described previously. Briefly, the chest was opened in the fourth or fifth left intercostal space, and a high-fidelity micromanometer (model P 4.5, Konigsberg Instruments, Oxnard, Calif.) was inserted through the cardiac apex to record LV pressure. A large bore cannula, introduced sutures. An arteriovenous (AV) fistula was constructed between the thoracic aorta and an external vertebral spines as the zero reference level. The surgical preparation was as described previously. Briefly, the chest was opened in the fourth or fifth left intercostal space, and a high-fidelity micromanometer (model P 4.5, Konigsberg Instruments, Oxnard, Calif.) was inserted through the cardiac apex to record LV pressure. A large bore cannula, connected to a reservoir, was inserted into the left atrial cavity to control mean left atrial pressure. The reservoir was filled with room-temperature carbon dioxide tension between 35 and 40 mm Hg and pH between 7.3 and 7.4. Sodium bicarbonate was administered, as necessary, to correct any base deficits. Rectal temperature was kept between 36° and 38°C with a heated table and a thermostatically controlled water blanket.

Hemodynamic Measurements

Aortic and left atrial pressures were measured with strain gauge transducers (model P23D, Statham Instruments, Oxnard, Calif.), using the midthoracic vertebral spines as the zero reference level. The isovolumic indexes dP/dtmax (the maximal rate of rise of LV pressure) and dP/dtmin (the rate of rise of LV pressure at a developed pressure of 40 mm Hg) were obtained from a differentiator having a linear output (±5%) up to a frequency of 90 Hz. LV, aortic, and left atrial pressures were monitored with an eight-channel paper recorder (model M19, Devices Limited, Welwyn Garden City, England) and were recorded on a multichannel tape recorder (model 3960 or 3968A, Hewlett-Packard, Palo Alto, Calif.) for subsequent analysis.

Measurement of Myocardial Blood Flow

LV blood flow was measured with approximately 1 million 15-μm radioactive microspheres labeled with one of six randomly chosen labels (113Ce, 51Cr, 113Sn, 85Sr, 99Nb, and 48Sc; New England Nuclear, Boston, Mass.). The microspheres were mixed for 10 minutes by ultrasonification and manual agitation and were flushed into the left atrial cavity over 30–40 seconds with 15 ml saline. A reference sample was withdrawn at a constant rate of 12 ml/min from an aortic catheter with a mechanical pump (model...
940A, Harvard Apparatus, South Natick, Mass.), starting 5–10 seconds before injection and ending 75–90 seconds after injection. The atriya, great arteries, epicardial fat, large coronary vessels, valves, and right ventricular free wall were removed from the fixed hearts. The left ventricle was divided into subendocardial, inner midwall, outer midwall, and subepicardial layers. This dissection yielded 84 separate tissue samples. In normal dogs, the subendocardium, inner midwall, outer midwall, and subepicardium comprised 25.0±0.5 (mean±SEM), 19.6±0.3, 21.8±0.4, and 33.6±0.8%, respectively, of total LV weight. The corresponding proportions for the hypertensive dogs were 24.3±0.3, 19.2±0.2, 21.4±0.3, and 35.1±0.7%.

The radioactivity of the reference and tissue samples was measured in a through-hole gamma counter (model 5130, Packard Instrument Co., Downer’s Grove, Ill.). The radioactivity of each isotope peak in the tissue samples was obtained by stripping away the contribution of background and the Compton areas of higher energy isotopes with a computer program. Blood flow was calculated from the relation:

\[ Q_{\text{Tissue}} = Q_{\text{Reference}} \times R_{\text{Tissue}} / R_{\text{Reference}} \]

where \( Q \) is flow (ml/min) and \( R \) is radioactivity (counts/min). In each animal, subendocardial, inner midwall, outer midwall, subepicardial, and total LV blood flows were obtained by appropriate summation of the individual sample flows. All flows were normalized to 100 g of wet tissue.

Two-dimensional Echocardiography

LV 2-D echo views were obtained with a 5 MHz medium focus phased-array transducer and 77020AC ultrasound system (Hewlett-Packard, Andover, Mass.). For each view, stop-frame images were triggered with a surface electrocardiogram at two instances in the cardiac cycle. The first was at the point of positive dP/dt\(_{\text{max}}\). As positive dP/dt\(_{\text{max}}\) occurs well before aortic valve opening in our preparation, LV dimensions at this instant were assumed to be equivalent to those at end diastole. The second was at 20 msec before negative dP/dt\(_{\text{max}}\), which corresponds to LV end systole (more precisely, end ejection). Satisfactory end-systolic LV major and minor axis images were obtained in eight normotensive dogs and all 10 hypertensive animals.

LV dimensions were obtained directly from videotape recordings with an onboard analysis program, using the trailing-leading edge method to define endocardial and epicardial outlines. Average LV wall thickness was calculated as the difference between the equivalent radii of the minor axis internal (\( A_i \)) and external cross-sectional areas. The length of the major axis (\( L \)) was measured between the cardiac apex and a point lying midway along the plane of the mitral valve annulus. The left ventricle was assumed to have prolate ellipsoid geometry so that LV cavity volume equaled \( 2/3 \times A_i \times L \).

End-systolic Pressure–Volume and Wall Stress–Volume Relations

The pressure volume points at end systole were fitted to the line of best fit using least-squares linear regression. The slope of this relation, the end-systolic elastance (\( E_s \)), is a measure of LV systolic chamber function that is relatively independent of cardiac loading conditions. This is an advantage over isovolumic indexes, which become quite load dependent at lower aortic pressures. The end-systolic pressure–volume relation was obtained during stepwise lowering of aortic blood pressure with the AV fistula. As mean left atrial pressure was held constant during this intervention, LV end-diastolic volume underwent only minor changes. However, stroke volume increased, and LV end-systolic volume therefore decreased. The number of points used to construct an end-systolic pressure–volume relation ranged between four and seven in the hypertensive dogs and four and six in the normal animals, each point representing a different steady-state level of aortic pressure. LV end-systolic pressure was assumed to be equivalent to aortic dicrotic notch pressure. LV volume at each point was calculated using the average of the 2-D echo LV minor axis cross-sectional area and major axis length measurements from five cardiac cycles.

To assess myocardial properties in normotensive and hypertensive dogs, the corresponding end-systolic wall stress–volume relation was calculated using the formula for a prolate ellipsoid. Circumferential wall stress, the major component of LV wall stress, was thus equivalent to

\[ 1.36[P-D/4H][(2L^2-D^2)/(L^2+D-H)] \]

where \( P \) is aortic dicrotic notch pressure (mm Hg), \( D \) is minor axis internal diameter (mm), \( L \) is major axis dimension (mm), \( H \) is wall thickness (mm), and 1.36 is the conversion factor (mm Hg to g/cm²).

Statistical Analysis

Results were analyzed with standard statistical tests. The effect of blood pressure reduction on LV blood flow and isovolumic indexes was assessed with two-way and three-way analysis of variance. The between-pressures and, with the blood flow data, the between-regions sums of squares were orthogonally partitioned into individual degrees of freedom. Significant differences between normotensive (N) and hypertensive (HT) dogs during aortic pressure reduction were assessed from

\[ t = \Delta(HT-N)/(SE^2_N+SE^2_{HT})^{0.5} \]

with \((n_N+n_{HT}-2)\) degrees of freedom, where \( \Delta(HT-N) \) is the difference between the response of the hypertensive and normal dogs and \( SE \) is the appropriate standard error from each analysis of variance. Differences in the end-systolic pressure–volume and end-systolic wall stress–volume relations between normotensive and hypertensive dogs were evaluated with
Hemodynamics and Isovolumic Indexes

Compared with normal dogs, resting aortic blood pressures were approximately 25% higher in the hypertensive dogs, but matched at the reduced pressure levels (Table 2). In normal dogs, dP/dt\text{max} decreased by 5% \( (p<0.05) \) at ADP 60 mm Hg, but dP/dt\text{DPAE} was similar throughout the pressure reduction (Table 2). In hypertensive dogs, dP/dt\text{max} was initially maintained with lowering of aortic blood pressure but then fell by 15% at ADP 60 mm Hg \( (p<0.005) \). The latter decline was greater than in normotensive dogs \( (p<0.025) \) and was accompanied with a 10% decrease in dP/dt\text{DPAE} \( (p<0.005) \) (Table 2).

Left Ventricular Myocardial Blood Flow

Under baseline conditions, total LV blood flow in hypertensive dogs, 238±37 ml/min, was higher than in normotensive animals, 144±17 ml/min \( (p<0.05, \) unpaired \( t \) test), but a difference was not apparent when flow was indexed for LV weight (normotensive, 132±11; hypertensive, 179±24 ml/min/100 g). LV blood flow decreased progressively between control and ADP 60 mm Hg in both groups, falling by 36% to 115±20 ml/min/100 g in hypertensive dogs and by 28% to 95±11 ml/min/100 g in the normotensive animals (Figure 1A). This decrement in LV blood flow was not evenly distributed across the LV wall in either group, being greatest in the subendocardium, intermediate in the midwall layers, and least in the subepicardium (Figures 1B and 1C). In hypertensive dogs, subendocardial flow fell by 50%, from 117±16 to 59±7 ml/min/100 g between control and ADP 60 mm Hg. In normotensive dogs, subendocardial flow decreased by 36% (from 137±15 to 87±10 ml/min/100 g) in the same pressure interval. As a result of these disproportionate transmural flow changes, the endocardial-to-epicardial flow ratio fell stepwise during aortic pressure reduction in both groups (Figure 1D). Between control and ADP 75 mm Hg, the fall in the endocardial-to-epicardial flow ratio in hypertensive dogs (from 1.23±0.04 to 0.96±0.09) was similar to that in normotensive dogs (from 1.19±0.05 to 1.00±0.04). However, a marked drop in the endocardial-to-epicardial flow ratio to 0.76±0.10 in hypertensive dogs at ADP 60 mm Hg was greater \( (p<0.05) \) than a decrease to 0.92±0.05 present in normotensive dogs.

Left Ventricular End-systolic Pressure–Volume and Wall Stress–Volume Relations

During initial lowering of aortic pressure, the LV end-systolic pressure–volume points were linearly
related in both normotensive ($r=0.950\pm0.013$, $n=8$) and hypertensive dogs ($r=0.966\pm0.009$, $n=10$). The regression coefficients of this relation (i.e., $E_{es}$) ranged from 3.2 to 8.6 mm Hg/ml in normotensive dogs and from 4.2 to 17.3 mm Hg/ml in the hypertensive animals. Comparing the two groups, the pooled regression coefficient in the hypertensive dogs (6.4±0.5 mm Hg/ml) was significantly greater than that of the normotensive dogs, 4.5±0.5 mm Hg/ml ($p<0.025$) (Figure 2A). The corresponding LV circumferential end-systolic wall stress–volume relation was also linear in normotensive ($r=0.981\pm0.005$, $n=8$) and hypertensive dogs ($r=0.986\pm0.003$, $n=10$). However, in contrast to the end-systolic pressure–volume relation, the pooled regression coefficient in hypertensive dogs, $12.6\pm0.6$ g/cm²/ml was similar to that of normotensive animals, $12.4\pm0.6$ g/cm²/ml (Figure 2B).

With progressive reduction of aortic blood pressure, the LV pressure–volume points deviated strikingly from the regression line. Further decreases in aortic pressure then produced increases in the end-systolic volume (i.e., LV dilatation) (Figures 3 and 4). This departure from linearity of the LV pressure–volume points was observed at an aortic diastolic pressure of $33\pm2$ mm Hg in normotensive dogs.
Two main findings have emerged from this study. First, in hearts with LV hypertrophy secondary to chronic hypertension, aortic pressure reduction decreases mean LV blood flow and redistributes transmural LV flow from subendocardial to subepicardial muscle layers. Second, this transmural redistribution in hypertrophied hearts is more pronounced than in normal hearts at moderately low aortic pressures and is then associated with depression of LV isovolumic and end-systolic indexes.

Normal LV end-diastolic dimensions in association with a greater LV wall thickness and wall-to-lumen ratio (Table 1) suggested that the hypertensive animals in our study had well-compensated concentric LV hypertrophy. The greater slope of the end-systolic pressure-volume relation in hypertrophied hearts (Figure 2A) was consistent with an increase in global LV systolic function. By contrast, the identical slope of the end-systolic wall stress-volume relation in the two groups (Figure 2B) indicated that performance was similar per unit area of myocardium. This implies that the increased global LV systolic function in the hypertrophied hearts of our study was attributable to increases in LV wall thickness and wall-to-lumen ratio, in the absence of any enhanced performance of individual muscle units.

Discussion

The latter notion is in accord with suggestions made in our previous study that characterized LV pump performance by the mean LV pressure–cardiac index relation and with the results of Sasayama et al on the compensated phase of LV hypertrophy after aortic constriction. Our finding of a similar baseline LV flow per unit weight in hypertensive dogs is in agreement with...
FIGURE 4. Minor axis two-dimensional echocardiographic views of the hypertrophied heart in Figure 3B. Upper panel: Image at the lower limit of the linear end-systolic pressure-volume relation (end-systolic pressure 100 mm Hg). Cross-sectional area of the left ventricular (LV) cavity is outlined by the dotted markers. Lower panel: Image after development of pronounced LV dilatation (end-systolic pressure 48 mm Hg), superimposed with the same area defined by markers in upper panel.

previous studies of LV pressure-overload hypertrophy.11,25-27 With aortic pressure reduction, average LV blood flow fell progressively in hypertrophied hearts suggesting that as in normal hearts, the metabolic cost of rises in cardiac output during aortic pressure reduction13 was far outweighed by the effect of associated decreases in LV wall stress.13 In agreement with other studies,11,12,25,26 the baseline LV endocardial-to-epicardial flow ratio was similar in normotensive and hypertensive animals. Reducing aortic diastolic pressure from 144 to 76 mm Hg in the hypertensive group of dogs produced a progressive decrease in the endocardial-to-epicardial flow ratio, signifying a redistribution of LV transmural blood flow from subendocardial to subepicardial muscle layers. On the basis of direct28 and indirect29 measurements of regional LV intramyocardial pressure, as well as computer modeling of transmural myocardial mechanics,30 we previously concluded that the transmural redistribution of LV blood flow in normotensive hearts during aortic pressure reduction was a physiological phenomenon related to nonuniform transmural changes in regional LV wall stress and metabolism.13 As the decrease in the endocardial-to-epicardial flow ratio during aortic pressure reduction in hypertensive dogs initially paralleled that in normotensive animals and was not associated with any evidence of LV dysfunction, it is likely that a similar process occurred in the hypertrophied hearts.

At an aortic diastolic pressure of about 60 mm Hg, the decline in the endocardial-to-epicardial flow ratio in hypertrophied hearts exceeded that in normal hearts. This greater decline in the endocardial-to-epicardial flow ratio was accompanied by significant reductions in the isovolumic indexes dP/dt\(_{max}\) and dP/dt\(_{max}\). Unlike normotensive dogs, where a small decline in dP/dt\(_{max}\) coupled to an unchanged dP/dt\(_{max}\) at a diastolic pressure of 60 mm Hg was due to early aortic valve opening before attainment of full isovolumic dP/dt\(_{max}\),13 the simultaneous and more marked falls in dP/dt\(_{max}\) and dP/dt\(_{max}\) in hypertrophied hearts at the same pressure were consistent with a depression of inotropic state.1 The greater decline in the endocardial-to-epicardial flow ratio at a diastolic pressure of 60 mm Hg was also associated with the emergence of a departure of LV pressure-volume points from the linear end-systolic pressure-volume relation. This departure closely resembled that reported in isolated hearts during reductions in coronary perfusion pressure below the lower limit of coronary autoregulation, a pattern that was presumed to result from the movement of pressure-volume points onto linear end-systolic pressure-volume relations with lesser slopes.32 The changes in isovolumic and end-systolic indexes at an aortic diastolic pressure of 60 mm Hg in hypertrophied hearts of our study were thus both indicative of a deterioration in LV function, and therefore highly suggestive of the onset of myocardial ischemia.

A likely basis for the greater decrease in the endocardial-to-epicardial flow ratio observed at an aortic diastolic pressure of 60 mm Hg in the hypertensive dogs of our study was an alteration in coronary pressure-flow relations. In normotensive hearts, LV coronary blood flow is "autoregulated," that is, maintained within narrow limits over a wide range of coronary perfusion pressures by pressure-dependent alterations in vascular resistance.33 Below the lower pressure limit of autoregulation, LV blood flow falls with pressure reduction,34,35 accompanied by evidence of myocardial ischemia.35 Autoregulatory capacity also exhibits transmural differences, with loss of autoregulation occurring in the subendocardium at higher pressures than in the subepicardium.34,35 Several studies have now demonstrated that autoregulation of coronary blood flow is preserved in hearts with LV hypertrophy secondary to chronic hyperten-
sion, but that the lower limit of autoregulation is shifted to a higher pressure level. Moreover, the limited subendocardial vasodilator response elicited in renal hypertensive dogs either with a coronary stenosis or intravenous infusions of adenosine suggests that loss of autoregulation in the subendocardium also precedes that in the subepicardium in hypertrophied hearts.

We propose that the greater decline in the endocardial-to-epicardial flow ratio in hypertrophied hearts in our study at an aortic diastolic pressure of 60 mm Hg can be explained by a shift in the lower limit of coronary autoregulation to a higher pressure level, combined with loss of autoregulation in the subendocardium preceding that in the subepicardium. Thus, between the baseline state and an aortic diastolic pressure of about 75 mm Hg, we speculate that both subendocardial and subepicardial flows were autoregulated in hypertrophied hearts but more pronounced falls in subendocardial flow (which resulted in a declining endocardial-to-epicardial flow ratio) were due to greater reductions in subendocardial wall stress and metabolism. However, at an aortic diastolic pressure of 60 mm Hg, subepicardial flow was still autoregulated, but subendocardial flow was not because its pressure-flow point lay below the lower limit of subendocardial autoregulation. The fall in subendocardial flow was thus exaggerated, resulting in a relatively greater decrease in the endocardial-to-epicardial flow ratio. Since studies using ultrasonic crystals in hypertrophied hearts indicate that subendocardial underperfusion produces not only subendocardial but also transmural dysfunction, this hypothesis would also account for our finding of an association between an accentuated decline in the endocardial-to-epicardial flow ratio and global impairment of LV performance.

Clearly, there are limitations in extrapolating results obtained from anesthetized animal experiments conducted under highly controlled conditions to the clinical setting. However, our experimental findings support the clinical observations that acute lowering of aortic pressure can produce ischemic electrocardiographic changes in hypertensive patients without significant coronary artery disease at a pressure level without effect in normotensive patients. It has been presumed that these ischemic changes are due to subendocardial underperfusion. Our results suggest that such underperfusion could arise from an exaggeration of a redistribution of LV transmural blood flow toward subepicardial muscle layers normally accompanying aortic pressure reduction. Moreover, if this exaggerated redistribution is mainly related to a shift of the lower limit of coronary autoregulation to a higher pressure level, then the persistence of this shift in patients, despite long-term pressure normalization, may also in part explain the paradoxical increase in mortality observed with reduction of arterial diastolic pressure below about 90 mm Hg with antihypertensive therapy.

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References

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