Compression Induced by RV Pressure Overload Decreases Regional Coronary Blood Flow in Anesthetized Dogs

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ABSTRACT

Pulmonary artery constriction (PAC), a model of right ventricular (RV) pressure overload, flattens or inverts the septum and may flatten the left ventricular (LV) free wall. Finite Element (FE) analysis predicts that such deformations may cause substantial compression. This study tests the hypothesis that deformation-induced myocardial compressive stress impedes coronary blood flow (CBF). coloured microspheres (~2x10⁶) were injected into the left atrium of 13 open-chest anesthetized dogs under control conditions and during PAC, which decreased the end-diastolic trans-septal pressure gradient (LV – RV) from 1.6±1.3 to –3.4±1.7 mmHg. Septal and LV deformation were assessed using 2-D echocardiography and, by FE analysis, the hydrostatic component of stress. Post-mortem, a 2.5-cm wide, LV equatorial ring was divided into 16 endocardial and epicardial samples. PAC decreased CBF in the FE-predicted compression zones, areas with the greatest compression having the greatest reductions in CBF. During PAC, compression reached a maximum of 25.3±1.8 mmHg on the (LV) endocardial sides of the RV insertion points, areas that saw CBF decrease from 1.05±0.08 to 0.68±0.05 mL/min/g (P<0.001), more than 30%. CBF decreased (from 1.08±0.07 to 0.81±0.07 mL/min/g; P<0.001) on the RV side of the mid-septum, an area with as much as 16.0±1.0 mmHg of compression. Overall, average compressions of 10 mmHg decreased CBF by approximately 30%. We conclude that acute RV pressure overload deforms the septum and LV and induces compressive stresses that reduce CBF substantially. This may help explain why some patients with pulmonary hypertension and no critical coronary disease have chest discomfort indistinguishable from angina pectoris.

Keywords: diastole, mechanics, regional blood flow, microspheres, ventricles
Abbreviations

CBF - Coronary blood flow
FE - Finite Element
LV - Left ventricle
LVEDP - Left ventricular end-diastolic pressure
PAC - Pulmonary artery constriction
RV - Right ventricle
RVEDP - Right ventricular end-diastolic pressure
TSP - Trans-septal pressure (LVEDP – RVEDP)
INTRODUCTION

Patients with RV hypertension may have symptoms indistinguishable from angina pectoris, despite having no critical coronary disease (13,21). If RV diastolic pressure exceeds LV pressure, the septum may be mechanically deformed and shifted leftward (10).

Previously, we used Finite Element (FE) analysis to study the canine ventricular septum under control conditions and when pulmonary artery constriction (PAC) caused RV diastolic pressures to exceed those in the LV (18,19). Under control conditions, the septum was concave to the LV and wall stresses were low. During PAC, the septum was flattened or inverted and large compressive stresses developed in an arch-like pattern within it, stresses that might impede CBF. In the current study, we extended our previous work to examine the structural behavior and possible deformation of the LV free wall. Bending moments observed in the septum at the RV insertion points must be balanced by opposite bending moments in the LV free wall, which might flatten it. Coronary perfusion might be impeded in areas where there are high compressive stresses. To test these hypotheses, we measured CBF in 16 LV endocardial and epicardial regions using coloured microspheres and compared myocardial perfusion to deformation-induced compressive stress.

MATERIALS AND METHODS

Animal preparation and protocol. The experiments (approved by the institutional animal-care committee according to the standards defined by the Position of the American Heart Association on Research Animal Use) were performed on 13 open-chest, anesthetized dogs. Anesthesia was induced with 25 mg/kg IV thiopental and maintained with an infusion of a 25-mg/mL solution
(~100 mL/h) of fentanyl citrate. The dogs were ventilated with a constant-volume respirator (model 607, Harvard Apparatus Co., Inc.). The ECG was monitored and body temperature was maintained with a heating pad.

LV, RV, and aortic pressures were measured using 6-F micromanometer-tipped catheters (Millar Instruments, Inc., Houston, Tex.), inserted via peripheral vessels. Aortic flow was measured using an ultrasonic flow meter (Transonic Systems Inc., Ithaca, N.Y.). The heart was repositioned in the pericardium, which was reapproximated with loose sutures at its margins (22). A short injection catheter was placed in the left atrial appendage for the injection of microspheres. A catheter was also placed in the femoral artery for withdrawal of blood samples during microsphere injections. A pneumatic constrictor (14-16 mm, In-Vivo Metrics, Healdsburg, Calif.) was placed on the pulmonary artery to increase RV pressure transiently and change the end-diastolic trans-septal pressure gradient (LVEDP – RVEDP). Pressures and flows were recorded simultaneously with 2-D echocardiography (Hewlett-Packard Sonos 1000, Palo Alto, Calif.); an LV minor-axis view at the level of the papillary muscles was recorded using a 2.5-MHz trans-esophageal probe held on the surface of the RV free wall. Pressures, flow, and the ECG were amplified (VR16, Electronics for Medicine / Honeywell, White Plains, N.Y.), digitized at a sampling rate of 200 Hz, filtered to 100 Hz, recorded (Cardiosoft, Sonometrics Inc., London, Ontario), and analyzed (CVWorks, Advanced Measurements, Calgary, Alberta).

After surgery, the dogs were allowed to stabilize. To make the interventions as uniform as possible, 3 or 4 trial PAC’s were performed initially, before injection of the microspheres.

Under control conditions, 1-2x10^6 15:-m coloured microspheres (Dye-Trak, Triton Technology, San Diego, Calif.) were injected into the left atrium and flushed with saline (6). A
pump withdrew blood from the femoral artery at a rate of 14.8 mL/min. The pump was turned on 15 s before and remained on for 45 s after the injection. This was repeated during PAC, using a different colour of microspheres. In each animal, we achieved a negative trans-septal gradient and observed substantial septal flattening or inversion before injecting the microspheres. Blood samples (~25 mL) were placed in 50 mL centrifuge tubes and mixed with a solution of Triton-X, a hemolysing reagent.

**Analysis.** Echocardiographic images were digitized by tracing the endocardium and epicardium of the LV and the RV endocardial surface of the septum and the RV insertion points (Echo Analysis; v. 1.05, Advanced Measurements, Calgary, Alberta). The curvature (1/radius of curvature) of the septum and the LV free wall were calculated. Analysis of the images provided the shapes and dimensions (i.e., LV and RV diameters and wall thicknesses) used in the FE model.

As described previously (18,19), FE analysis was performed in a “reverse” fashion. The control and deformed shapes were known from the echocardiographic images and, for each case, the stiffness of the muscle and pericardium were modified until the modeled shape and size best matched the echo images. Principal stresses and the hydrostatic component of stress were determined. The pericardial stiffness (14) used was approximately 10 times higher than the myocardial stiffness. The FE model was developed using PATRAN (version 5.4; MSC Software Corp., Santa Ana, Calif.) and solved using ABAQUS (version 6.27; Abaqus, Inc., Pawtucket, R.I.). The pericardium was modeled as congruent with the LV and RV free walls, separated by slide-line elements that allowed free relative movement. The simplest form of hyperelastic
material behaviour defined in ABAQUS - a form of the neo-Hookean law – was utilized to relate strain to stress.

Post-mortem, an equatorial LV ring approximately 2.5-3.5 cm wide was divided into 8 radial sections, each divided into endocardial and epicardial layers (Figure 1). The septum and the LV free-wall were each divided into three sections, with the RV insertion-point segments making up the remaining two sections. The wet weight (approximately 4-8 grams) of each of the 16 sections was recorded. All blood and tissue processing techniques and procedures were performed according to guidelines (1) and as described elsewhere (11). To control for possible microsphere loss during tissue analysis, 5,000 microspheres of an unused colour were added to each tube as an internal control. Samples were digested with potassium hydroxide, and microspheres were reclaimed via washing (with detergent and ethanol), centrifugation, and aspiration. The samples were then air-dried for 1-2 days before the dye from the microspheres was extracted with dimethyl formamide and analyzed using absorbance spectrophotometry (Model 6300, Jenway Inc., Essex, England). Using the blood samples as standards for known blood flow, the blood perfusion through the tissue samples could then be calculated for both control and PAC conditions.

RESULTS

Hemodynamic, dimensional, and global flow measurements obtained during control conditions and PAC are shown in Table 1.

Finite element analysis. Figure 2 shows distributions of the hydrostatic component of stress that develop under control conditions (A) and during PAC (B) in a representative experiment.
The hydrostatic component of stress, an invariant of the stress tensor, is the mean of the three normal components of stress. Compressive hydrostatic stress will tend to decrease myocardial volume and tensile or ‘decompressive’ hydrostatic stress will tend to increase myocardial volume. For a homogeneous isotropic material, hydrostatic stress causes changes in volume rather than shape, as opposed to deviatoric stress which changes shape but not volume. We recognize that the myocardium with its changing muscle fibre angles and blood vessel network is not isotropic but, given its sponge-like character, we feel that the volumetric effect is more important for flow and, therefore, that the hydrostatic component of the stress tensor is more fundamentally related to flow than deviatoric stress. During control conditions, the perimeter of the LV (including the septum) was quasi-circular and stresses were low, as reported previously (18,19). The pericardium was under moderate circumferential (and thus hydrostatic) tension.

During PAC, RVEDP exceeded LVEDP, making the trans-septal pressure gradient negative (Table 1). As illustrated by the typical data shown in Figure 2, the septum flattened or inverted with maximal hydrostatic compression near the insertion points and at the RV side of the mid-septum, consistent with the arch-like pattern of compressive circumferential stresses observed in a septum-only model (18,19). The maximum hydrostatic compression near the insertion points increased from 7.5±1.1 (SEM; control) to 25.3±1.8 mmHg during PAC while the maximum hydrostatic compression on the RV side of the septum increased from 4.3±0.8 to 16.0±1.0 mmHg. Hydrostatic tension (decompression) increased opposite these areas of high compression in the myocardium. In the LV epicardial regions near the RV insertion points, hydrostatic tension increased from −11.5±1.0 mmHg at control to −24.1±0.2 mmHg, while on the LV side of the mid-septum tension increased from −8.5±0.6 to −20.8±1.7 mmHg (by convention, tension is
negative). The pericardium showed high circumferential tension and thus high hydrostatic tension (Figure 2; Panel B). These stress distribution patterns were similar in all dogs. The curvature of the septum changed from $0.276\pm0.015$ to $-0.125\pm0.011$ cm$^{-1}$ and, for the LV free wall, from $0.349\pm0.023$ to $0.274\pm0.015$ cm$^{-1}$. (All reported differences were significant at $P<0.001$ unless otherwise stated.)

Bending moments during control conditions and PAC are shown in Figure 3. Control bending moments (A) were small, the deviations being caused by slight tension at the RV insertion points. During PAC (B), substantially larger bending moments developed in the septum as the insertion points were pulled radially (due to larger RV circumferential forces) and the center of the septum was pushed leftward by the negative trans-septal pressure gradient, causing inversion. These bending moments were transmitted to the LV free-wall, causing the flattening. Data from the 6 other dogs whose bending-moment data were analyzed were similar (C and D).

**Coronary blood flow.** CBF in the 16 LV regions (see Figure 1) is shown for a typical animal in Figure 4 under control and PAC conditions. In each animal, CBF consistently decreased in the regions of the RV insertion points (LV endocardial side) and on the RV side of the mid-septum.

Average CBF was calculated for 13 dogs in each of the 16 LV regions (Figure 5, Panels B and D). Under control conditions, the mean LV CBF was $1.07\pm0.08$ mL/min/g but was lower in the posterior (13) and epicardial mid-free wall (11) regions ($0.78\pm0.07$ and $0.80\pm0.06$ mL/min/g, respectively), regions that were gravitationally dependent in this model (Figure 5B).
During PAC, mean arterial pressure decreased (from 78.5±8.2 to 47.5±8.0 mmHg) and mean LV CBF decreased to 0.76±0.07 mL/min/g. CBF decreased most in the endocardium at the RV insertion points (Regions 2 and 10), from 1.03±0.08 (control) to 0.57±0.04 mL/min/g with PAC; CBF on the epicardial side of the insertions (Regions 1 and 9) was unaffected by PAC. CBF in the RV side of the mid-septum (Region 5) also decreased significantly (Figure 5D). CBF on the LV side of the mid-septum (Region 6) remained in the normal range during PAC.

The hydrostatic component of stress was also averaged over each of the 16 LV regions for control and PAC conditions and is shown in Figure 5 (Panels A and C). In each region, averaged hydrostatic stress was close to 0 mmHg under control conditions (Panel A). With PAC, the greatest change was again seen at the (LV) endocardial regions of the RV insertions (Regions 2 and 10). Averaged hydrostatic compression here increased from 2.43±0.74 (control) to 12.31±0.87 mmHg with PAC. The averaged stress in the epicardial sides of the insertions (Regions 1 and 9) was not affected by PAC. Hydrostatic stress also changed significantly at the mid-septum. On the RV side, averaged hydrostatic compression increased (from 1.38±0.51 to 7.93±0.46 mmHg) while, on the LV side, hydrostatic tension increased, from −4.99±0.25 to −10.01±0.85 mmHg.

Hydrostatic stress patterns can be compared to flow patterns in Figure 5. Under control conditions, averaged stresses close to 0 mmHg corresponded to normal flows in all regions. With PAC, however, both the hydrostatic stress and flow patterns changed in a systematic way. In regions where averaged hydrostatic compression was high (e.g., Regions 2 and 10), there was a corresponding large reduction in CBF. In areas where hydrostatic stress was unaffected (e.g.,
Regions 1 and 9; epicardial side of RV insertions) or where hydrostatic tension developed, normal CBF was maintained.

Figure 6 compares the averaged hydrostatic component of stress with coronary blood flow in an individual dog. While no relationship is evident for control conditions (Panel A), an inverse relationship becomes evident for PAC (Panel B). CBF decreased as hydrostatic compressive stress increased.

Figure 7 (pooled data) compares averaged hydrostatic stresses and CBFs for control (Panel A) and PAC (Panel B). Again, it shows that the regions with the greatest decreases in CBF with PAC correspond to the areas with the greatest hydrostatic compression. Also, the area with the largest CBF corresponds to the area with the greatest hydrostatic tension/decompression (Region 6). Increased hydrostatic compression decreased CBF.

**DISCUSSION**

Our FE model of the septum predicted an arch-like pattern of compression during PAC as it flattened and sometimes inverted (18,19) and earlier we had demonstrated that end-diastolic septal segment length continued to shorten as the septum inverted, suggesting that compression was occurring (3). Figure 2 illustrates that the deformation caused by PAC induces increased hydrostatic compression in the RV-insertion regions and in the RV side of the mid-septum, consistent with the compressive circumferential stresses demonstrated by Nelson et al. (see their Figure 6 (19)). Finally, Figure 5 and Figure 7 demonstrate that these regions of hydrostatic compression correspond to regions of reduced CBF. This reduction in CBF probably occurs predominantly during diastole, when perfusion pressures are lower and CBF is greatest.
While it is clear that regions of compression correspond to regions of reduced CBF, Figure 7 also suggests that hydrostatic tension (i.e., decompression) increases CBF, at least relatively. The myocardium has often been described as sponge-like so it might be expected that hydrostatic decompression would increase vessel diameter and CBF. During PAC, aortic perfusion pressure decreased substantially, decreasing LV CBF overall. However, in regions of decompression, this decrease appears to be less or even negligible, presumably due to the CBF-enhancing effect of hydrostatic decompression.

According to the FE analysis, myocardial and pericardial stiffnesses increased during PAC. The compressive stresses that impede CBF might also cause congestion, which has been shown to increase tissue stiffness (9,20,26).

During PAC in this model (and probably in clinical pulmonary hypertension) the determinants of CBF were several and complex (12). There may have been reflex responses to the systemic hypotension that could not be evaluated in this model. Elevation of RV pressure not only displaced the septum but increased coronary sinus pressure and pericardial pressure. As shown by Watanabe et al. (27), with the pericardium present, an increase in LV pressure moves the CBF-perfusion pressure relation to the right, increasing the zero-flow intercept. We would expect that intramyocardial pressure would change as a function of regional compression but, in addition, there may have been effects of local deformation of the coronary vasculature (12). Finally, because no coronary vasodilators or autonomic blockers were given, autoregulatory mechanisms were likely active: it must be noted that, during PAC, CBF in many regions remained normal despite decreased perfusion pressure. The flow heterogeneity seen in Panel A of Figure 7 shows that factors other than compression can affect flow.
This study demonstrates that PAC substantially reduces regional CBF and that the regions with the greatest decrease in CBF corresponded to those with the greatest compressive stress. In reality, however, we may have underestimated the degree of CBF reduction. As illustrated by Figure 2, there were small regions where compressive stress was great (~25-30 mmHg) and in those particular regions CBF might have been reduced substantially more than the ~30% we measured, because we necessarily measured CBF averaged over much larger volumes of myocardium.

CBF within the septum and the LV free wall has been previously measured during PAC (4,5,7,23) but those investigators did not investigate possible regional differences. Sestier et al. (23) examined regional blood flow during PAC and found that blood flow to the endocardial layers was reduced, compared to epicardial blood flow. Gold and Bache (7) found similar results during mild PAC but smaller transmural changes during severe PAC. Fixler et al. (5) found transmural differences in the septum only. All these authors considered the differences to have been caused by reflex redistribution of flow. Sharma and Sashara (24) did not find significant CBF differences in the either the septum or LV free wall. A critical limitation of all these studies is that neither the septum nor the LV free wall was separated into smaller regions. Although the epicardial and endocardial layers were examined (providing information on transmural flow), possible local differences within the septum and free wall layers were not assessed.

**Clinical implications.** In patients with primary or secondary pulmonary hypertension and no critical coronary disease, angina-like symptoms might in fact be due to RV ischemia, but the mechanism of this ischemia has never been satisfactorily explained. It has been attributed to
increased RV oxygen consumption and, in some cases, compression of the left main coronary artery by a dilated pulmonary artery (2,17). However, because RV diastolic pressure is increased, decreasing or reversing the trans-septal gradient and flattening or inverting the septum, myocardial compression could also decrease CBF. Long-term CBF reduction from chronic diastolic compression may be moderated due to the possible effects of vascular or perivascular remodeling.

A similar mechanism may contribute to the well-recognized hypoperfusion of the septum observed in patients with left bundle branch block (LBBB). Although the septum is not displaced so profoundly or for so long, it does move leftward (posteriorly) in early diastole (when CBF is normally greatest) and at end-diastole (8). Very recently, Vernooy et al. demonstrated reduced CBF in their experimental model of LBBB and suggested that this was due to diminished regional oxygen demand (25). However, the LV re-adopts a more circular configuration during systole, even after being deformed during diastole (10), and the pattern of reduced CBF that they demonstrate agrees at least as well with our pattern of deformation-induced compression as it does with their pattern of reduced circumferential shortening. Thus, it is possible that this mechanism might also help to explain the abnormal perfusion pattern seen during myocardial scintigraphy and positron-emission tomography studies in patients with LBBB and no critical coronary disease (15,16,28).

**Limitations.** Our FE model does not account for several anatomical complexities (e.g., changing fibre angle, anisotropy, vessel orientation, the third dimension, etc.) and because we do not know the precise material behavior, we only seek to compare patterns of stress rather than
absolute values. However, the model still predicts a pattern of compression at end-diastole that, as demonstrated, corresponds to and presumably causes substantial reductions in CBF. Furthermore, it is clear that the fundamental imprecision of the microsphere method makes it unable to confirm or disprove even the degree of detail produced by this simple model; the additional detail provided by a more complex model could not be verified experimentally.

From our data, it is not clear whether the reduction in average LV CBF (from 1.07 to 0.76 mL/gm/min) is due more to decreased supply or to decreased demand, as the reduction in mean arterial pressure (from 78.5 to 47.5 mmHg) must imply substantial reductions in both supply and demand. Figure 7B implies that compression and decompression (tension) substantially explains the variance in CBF. However, we cannot rule out the possibility that diastolic compression and decompression respectively correlate with decreased and increased fibre length and, thus, systolic work. Whether work-related changes in demand fundamentally determine CBF in this circumstance awaits the results of further experimentation.

We acknowledge that the relations we have described are somewhat vague with respect to time. Using the microsphere technique, we measured CBF averaged over a few cardiac cycles. Most CBF occurs during diastole. During systolic contraction, the normal compression exerted by the myocardium on the coronary vasculature is the greatest. However, during PAC, the septum is most distorted during diastole and resumes its normal curvature during systole (10) and, therefore, distortion-induced compression is a diastolic phenomenon. Arbitrarily, we have used end-diastolic pressure and dimension measurements as the basis of our finite-element analysis. Thus, we have related averaged CBF to diastolic distortion-induced compression.
A major concern in microsphere studies is the necessity to have a sufficient number in each sample to provide an accurate estimate of CBF. We limited our injections to no more than 1-2 million microspheres to minimize the effects of embolization on myocardial performance but were able to achieve at least at least 400 microspheres per sample, thus minimizing statistical uncertainty (1). However, this concern prevented us from analyzing even smaller samples. As suggested above, such an analysis might have shown variations in greater detail, corresponding even better to the large pixel-to-pixel gradations in compression (see Figure 2B).

Using the coloured-microsphere technique, microspheres might be lost during the recovery process. This was minimized by using microspheres of a different colour as an internal control.

This study was performed in open-chest dogs and the weight of the heart itself may have affected regional CBF. (We are not aware of other microsphere studies in open-chest dogs.) In principle, this apparent gravitational effect could be incorporated into the FE model.

**Conclusions.** Pulmonary artery constriction, a model of RV pressure overload, flattens and/or inverts the septum and flattens the LV free wall. Our finite-element model predicts that such deformations of these thick-walled structures may cause sufficient compression to impede CBF. We tested this hypothesis using coloured microspheres and showed that regional CBF is decreased by up to 30% and that the degree of reduction in regional CBF is predicted by the degree of hydrostatic compression in that region.
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Foundation for Medical Research (Edmonton).

DISCLOSURES

There are no conflicts of interest to disclose for any author.
REFERENCES


Table 1. Effects of pulmonary artery constriction

<table>
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<tr>
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<tr>
<td>Mean arterial pressure</td>
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<tr>
<td>Cardiac output</td>
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<td>Peak RV systolic pressure</td>
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<td>RVEDP</td>
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<tr>
<td>TSP</td>
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PAC, pulmonary artery constriction; LVEDP, LV end-diastolic pressure; RVEDP, RV end-diastolic pressure; TSP, trans-septal pressure (LVEDP – RVEDP); CBF<sub>LV</sub>, average LV coronary blood flow; means ± standard error of the mean; n = 13. All changes were significantly different at P<0.001 except for LVEDP (P=0.004).
Figure 1 – The LV freewall and septum, showing the 16 regions used for microsphere analysis of CBF.
Figure 2 – The hydrostatic component of stress for control conditions (Panel A) and for PAC (Panel B).
Figure 3 - Bending moments diagrams shown for control loading (A) and PAC (B) in a single animal. Bending moments for 7 dogs are overlaid in Panel C (control) and Panel D (PAC).
Figure 4 – Regional coronary Blood flow for an individual animal under control conditions (A) and with PAC (C).
Figure 5 – Panels A and C show mean hydrostatic stresses (in mmHg) for each region during control (A) and PAC (C) as calculated by FE Analysis (n=13). Panels B and D shows the corresponding mean CBF during control (B) and PAC (C).
Figure 6 - CBF versus hydrostatic stress plotted for an individual animal for control (Panel A) and PAC (Panel B).
Figure 7 – Mean CBF plotted against the mean hydrostatic component of stress for control (Panel A) and PAC (Panel B). Standard errors are shown (n=13). For PAC, the linear regression is shown (P<0.001). The location of each region is indicated by the number beside the point (refer to Figure 1). A dagger indicates that tension (decompression) in the region is greater after PAC and an asterisk indicates both that the compression is greater and CBF is less after PAC (P<0.001).