Transmural Variation in Autoregulation of Right Ventricular Blood Flow

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We examined transmurally the right coronary autoregulatory flow response to varied perfusion pressures in 11 anesthetized, open-chest dogs. Right coronary artery flow was measured electromagnetically, and its transmural distribution was defined with 15-μm radioactive microspheres. Heart rate, mean aortic blood pressure, right ventricular systolic pressure, end-diastolic pressure, and \( \frac{dP}{dt} \) were constant. At 100 mm Hg, subepicardial flow averaged 0.48 ± 0.04 ml/min/g, and subendocardial flow averaged 0.56 ± 0.05 ml/min/g. In contrast to the left coronary circulation, right coronary autoregulation did not cause preferential subendocardial ischemia. As right coronary perfusion pressure was decreased from 100 to 40 mm Hg in five dogs, subepicardial and subendocardial flows were reduced similarly by 35–36%. As right coronary perfusion pressure was elevated from 100 to 150 mm Hg in six dogs, right ventricular subepicardial blood flow increased by 31%, whereas subendocardial coronary blood flow increased by 70%. Right ventricular subendocardial-to-subepicardial flow ratios averaged 1.15–1.20 for perfusion pressures of 40 to 120 mm Hg, and they increased to 1.36 ± 0.05 at 150 mm Hg. Right coronary artery autoregulatory closed-loop gain averaged 0.47 ± 0.06 between 70 and 100 mm Hg and was greater than zero from 40 to 120 mm Hg. Between 120 and 150 mm Hg, gain fell to −0.15 ± 0.10. Regional gain varied from 0.59 ± 0.10 to 0.44 ± 0.08 in subepicardium as pressure was decreased from 100 to 40 mm Hg. Subendocardial gains were similar to subepicardial gains over this pressure range. With increasing pressure, subepicardial gain was constant up to 120 mm Hg, but it fell to −0.03 ± 0.19 between 120 and 150 mm Hg. Subendocardial gain fell to −0.42 ± 0.27 between 100 and 120 mm Hg and to −0.78 ± 0.45 between 120 and 150 mm Hg. Thus, autoregulation is equipotent transmurally at pressures less than 100 mm Hg, but it is more potent in subepicardium at pressures greater than 100 mm Hg. (Circulation Research 1988;62:776-781)

**Materials and Methods**

Eleven mongrel dogs of either sex, weighing 15 to 24 kg, were anesthetized with sodium pentobarbital, 30 mg/kg i.v. initially, and supplemented as needed to maintain stable anesthesia. After tracheotomy, the dogs were ventilated by a respirator (Harvard Apparatus, South Natick, Massachusetts) with room air supplemented with oxygen to maintain normal arterial oxygen tension. A vinyl catheter was positioned in the inferior vena cava through a femoral vein for administration of supplementary anesthetic, heparin, and fluids. A second vinyl catheter was advanced into the thoracic aorta through a femoral artery to monitor aortic pressure. Right ventricular pressure was measured with a catheter-tipped transducer (Millar Instruments, Houston, Texas) inserted through the right jugular vein and across the tricuspid valve. The right ventricular pressure signal was differentiated electronically, and the positive derivative \( \frac{dP}{dt} \) was recorded.

The heart was exposed through a thoracotomy in the fourth right intercostal space. The right coronary artery was dissected free at its origin and a loose ligature was placed under it. After heparinization (500 U/kg), the right coronary artery was cannulated just distal to its origin with a stainless steel cannula (2.1 mm o.d., 1.4 mm i.d.). The right coronary artery was perfused with blood from a pressurized reservoir, which was supplied of the hyperperfused left coronary circulation. Thus, this investigation was conducted to define transmurally right coronary autoregulatory capability over a wide range of right coronary perfusion pressures.
with blood from the femoral artery by a roller pump. Right coronary perfusion pressure was measured at the tip of the perfusion cannula through a small-bore, fluid-filled catheter within the perfusion cannula. All fluid-filled catheters were connected to Statham P23Db pressure transducers (Gould, Cleveland, Ohio). Right coronary blood flow was measured electromagnetically with an FM 501 flowmeter and an EP 612 in-line flow transducer (Carolina Medical Electronics, King, North Carolina). Pressure and flow signals were recorded on an eight-channel polygraph (R611, Sensor Medics, Anaheim, California).

**Measurement of Regional Myocardial Blood Flow**

Myocardial blood flow was measured from tissue trapping of 15 ± 3-μm microspheres1 labeled with gamma-emitting radionuclides, 125I, 99mTc, and 113Sn (NEN, DuPont, Wilmington, Delaware). Before injection, the microspheres were dispersed in a solution of 10% dextran and agitated in an ultrasonicator and in a vortex mixer. For each flow measurement, 2 × 10^6 specifically labeled microspheres were injected directly into the right coronary perfusion line proximal to a 4-ml mixing chamber containing a rotating magnetic stirrer. Injection of the microspheres had no detectable effect on heart rate or right ventricular pressure or right coronary blood flow. Duplicate arterial reference blood samples were collected through 18-gauge needles inserted into the perfusion line distal to the mixing chamber beginning 10 seconds before microsphere injection. These samples were collected at a constant rate by an Isomatic 7624-02 micropump (Cole-Parmer, Chicago, Illinois) at approximately 2 ml/min for 3 minutes. Adequacy of microsphere mixing in the blood perfusate was verified by finding similar radioactivities in the duplicate reference blood samples. Injection of India ink into the perfusion line at the conclusion of the experiment clearly delineated the perfusion field of the right coronary artery. The hearts were excised, and the dyed perfusion area was weighed. The perfused tissue was frozen to facilitate sectioning. Four samples were cut from the center of perfused right ventricular free wall, and these samples were divided into three layers (subendocardium, midcardium, and subepicardium) of about equal thickness. Subendocardial and subepicardial samples were analyzed for radioactivity; these samples weighed 1.30 ± 0.12 and 1.27 ± 0.11 g, respectively.

Tissue samples and blood reference samples were analyzed for radioactivity with a gamma spectrometer (Packard Instrument, Downers Grove, Illinois). Isotope separation and blood flow computations were performed with an IBM microcomputer. Blood flow required to account for the radioactivity in myocardial tissue samples was calculated from the equation of Heymann et al12:

\[
MBF = Fr \times \frac{Rt}{Rr}
\]

where MBF is myocardial blood flow (ml/min), Fr is the reference blood sampling rate (ml/min), Rt and Rr are the radioactivities (cpm) of the tissue and reference samples, respectively. MBF was divided by the tissue sample weight and is reported as milliliters per minute per gram. Myocardial blood flow values determined for the outer and inner sections of each of the four right ventricular samples were averaged to compute mean subepicardial and subendocardial blood flows, respectively. The endo/epi ratio was calculated for each of the transmural samples, and the four values obtained in each heart were averaged.

**Experimental Protocols**

In Group 1, five of the 11 dogs, right coronary perfusion pressure was reduced in 10-mm Hg steps from 100 to 40 mm Hg. At perfusion pressures of 100, 70, and 40 mm Hg, steady-state coronary blood flows and other hemodynamic variables were recorded, and radioactive microspheres were injected.

In Group 2, six of the 11 dogs, right coronary perfusion pressure was increased in 10-mm Hg steps from 100 to 150 mm Hg. At the perfusion pressures of 100, 120, and 150 mm Hg, steady-state coronary blood flows and other hemodynamic variables were recorded, and radioactive microspheres were injected.

**Quantitation of Autoregulation**

The autoregulatory capabilities of the subepicardial and subendocardial regions of the right ventricular free wall were evaluated at each perfusion pressure by computing the autoregulatory closed-loop gain, Gc:

\[
Gc = 1 - \frac{\Delta F/F}{\Delta P/P}
\]

where \(\Delta F\) is the change in coronary blood flow observed when coronary perfusion pressure is changed by \(\Delta P\) and \(F\) is the flow observed at pressure \(P\) before the change in perfusion pressure. Values of gain between 0 and 1 indicate partial autoregulation and reach a maximal value of 1 when flow stays constant despite changes in perfusion pressure.

**Statistical Analyses**

Data are reported as mean ± SEM. Differences between observations made at different perfusion pressures within groups were tested with an analysis of variance, randomized complete block design (ANOVA), and the Student-Newman-Keuls procedure. Comparisons of regional blood flows and autoregulatory gains at corresponding perfusion pressures were tested with the Student's t test for paired data. Presence or absence of autoregulation was determined by comparing the autoregulatory gain to zero with the t test. These statistical procedures have been described by Zar.14 Differences were regarded as statistically significant at \(p<0.05\) unless otherwise stated.

**Results**

Systemic arterial blood was analyzed frequently to ensure that blood gas variables of the coronary perfusate remained at physiological levels (\(P_{O2} = 108 ± 8\) mm Hg, \(P_{CO2} = 29.2 ± 1.7\) mm Hg, \(pH 7.40 ± 0.02\)). Since hemodynamic and blood flow values for Groups...
1 and 2 at 100 mm Hg coronary perfusion pressure were not significantly different according to the t test for unpaired data, these values were averaged. Hemodynamic values at each right coronary perfusion pressure are presented in Table 1. Mean aortic blood pressure, right ventricular systolic pressure, end-diastolic pressure, and dP/dt were not significantly altered by increasing or decreasing right coronary perfusion pressure. Heart rates were similar within groups.

Total right coronary blood flow measured in the perfusion line is plotted as a function of coronary perfusion pressure in Figure 1. Right coronary artery flow varied with coronary perfusion pressure, but mild inflections at 70 and 100 mm Hg suggested the presence of more effective pressure-flow autoregulation in this range. Autoregulatory closed-loop gain averaged +0.33 ± 0.05 between perfusion pressures of 40 and 70 mm Hg, +0.47 ± 0.06 between 70 and 100 mm Hg, and +0.27 ± 0.09 between 100 and 120 mm Hg. These gains were significantly greater than zero, indicating the presence of moderate autoregulation. Gain averaged -0.15 ± 0.10 between 120 and 150 mm Hg, indicating absence of autoregulation at elevated right coronary perfusion pressure.

When total right coronary blood flow measured both by in-line electromagnetic flow transducer (X) was compared with the average transmural flow determined by microspheres (Y), the points could be fitted by a straight line through the origin with the equation, \( Y = 1.09X - 0.01 \) (\( r = 0.96, p < 0.01 \)). The slope was not significantly different from 1.0.

The relation between coronary perfusion pressure and transmural blood flow in right ventricular free wall is shown in Figure 2. Subepicardial and subendocardial flows fell significantly but similarly (−35% and −36%, respectively) when right coronary perfusion pressure was decreased from 100 to 40 mm Hg. Subepicardial blood flow increased significantly by 31% and subendocardial blood flow by 70% (\( p < 0.05 \)) as coronary perfusion pressure was increased from 100 to 150 mm Hg.

To further compare the autoregulatory capabilities of right ventricular subepicardium and subendocardium, regional autoregulatory closed-loop gains were computed for each change in perfusion pressure (Figure 3). Subepicardial gains varied from +0.59 ± 0.10 to +0.44 ± 0.08 as perfusion pressure was decreased from 100 to 40 mm Hg. Subepicardial gains varied from +0.52 ± 0.14 to +0.44 ± 0.07 over this pressure range. All regional hypotensive gains were significantly greater than zero. For the pressure increment from 100 to 120 mm Hg, subepicardial gain averaged +0.43 ± 0.09. This value was significantly greater than zero and similar to values observed in Group 1 when pressure was reduced. Although subepicardial autoregulation remained moderately effective up to 120 mm Hg, subendocardial gain fell significantly to near zero. A further increment in right coronary perfusion pressure to 150 mm Hg caused the gain of both regions
to fall significantly, but subepicardial gain remained significantly greater than subendocardial gain.

Transmural ratios of blood flow in the right ventricular free wall are plotted as functions of coronary perfusion pressure in Figure 4. Endo/epi ratios were similar, and they averaged between 1.15 and 1.20 for right coronary perfusion pressures of 40 to 120 mm Hg. At 150 mm Hg, the endo/epi ratio was significantly increased to 1.35 ± 0.05.

Discussion

There were four important findings in this study:
1) The distribution of blood flow across the right ventricular wall was not altered by coronary hypotension. 2) Blood flow was distributed preferentially to right ventricular subendocardium during coronary hypotension. 3) Moderately effective pressure-flow autoregulation was observed in subepicardial and subendocardial regions of the right ventricular wall at perfusion pressures between 40 and 100 mm Hg. 4) Autoregulation failed first and more severely in right ventricular subendocardium at pressures above 100 mm Hg.

Regional myocardial blood flow was computed from tissue content of radioactive microspheres, a technique widely used in coronary research.1 Previous studies have demonstrated close agreement between flow measurements made by the microsphere technique and other procedures,12-15 and this was verified in the current study by the similarity of flows measured electromagnetically and by microspheres. Accuracy of regional blood flow measurements made with microspheres depends on their complete entrapment in small vessels of the coronary circulation. At normal coronary perfusion pressure, arteriovenous shunting of 15-μm microspheres across the coronary circulation averaged 1.1% and ranged from 0% to 3.8%.16 Elevated coronary perfusion pressure increases arteriovenous shunting of smaller, 9-μm microspheres,16 but the linear relation observed between flows measured electromagnetically and by microspheres indicated that shunting of 15-μm microspheres did not increase at elevated pressures in this study.

In the left ventricular free wall, flow to subendocardium is reduced to a greater extent than is flow to subepicardium during severe coronary hypotension.7-9
Thus, coronary hypotension reduces more rapidly coronary reserve in left ventricular subendocardium, although a pharmacologically demonstrable reserve remains at coronary pressures as low as 30 mm Hg. In the present study, we found that the transmural distribution of flow across the right ventricular wall was not altered by right coronary hypotension. This finding is consistent with differences in the left and right coronary artery phasic flow patterns. Intramyocardial pressure in the left ventricle is sufficiently high to impede flow to subendocardium during systole, so most left coronary flow occurs during diastole. With left coronary dilation in the presence of hypotension, the transmural gradient of vascular tone required to compensate for subendocardial underperfusion during systole is compromised, and ischemia becomes more severe in subendocardial tissue.

In the right ventricle, systolic intramyocardial pressure has little effect on right coronary artery flow. Selective systolic or diastolic perfusion of the right coronary circulation does not alter the normal distribution of flow across the right ventricular wall. However, when right ventricular pressures are elevated in right ventricular hypertrophy or acute pulmonary artery hypertension, right coronary hypotension causes transmural maldistribution of blood flow similar to that caused by hypotension in the normal left ventricle.

Another explanation for the unaltered flow distribution across the right ventricular wall during hypoperfusion might be a preferential distribution of collateral blood flow to subendocardium. This explanation is unlikely because coronary collateral blood flow is small during acute right coronary hypotension. We recently delineated the mechanism of attenuated pressure-flow autoregulation in the right coronary circulation. The present study confirms our previous findings of blunted right coronary autoregulation as assessed by measurements of total right coronary flow and extends those findings to a regional basis. Over the range of pressures where effective autoregulation of total right coronary flow is observed (Figure 1 and Yonekura et al), both the subepicardium and the subendocardium show similar but moderate autoregulatory capabilities (Figure 3). Our regional flow measurements showed that the initial decline in right coronary autoregulation is due to selective failure of the subendocardial vasculature to autoregulate (Figure 3). With further increases in perfusion pressure, both subepicardial and subendocardial vasculature failed to autoregulate, but flow increased more in subendocardium. Redistribution of flow to left ventricular subendocardium during coronary hypertension has been previously reported. Our current findings suggest that subendocardial resistance vessels of the right ventricle, like those of the left, are less well adapted to regulate flow in the face of increased perfusion pressure. However, the subendocardial vessels of the right coronary circulation lost their autoregulatory capability at 120 mm Hg, whereas those of the left coronary circulation autoregulated as effectively as subepicardial vessels up to approximately 145 mm Hg. Only at approximately 195 mm Hg was a more pronounced failure of left ventricular subendocardial autoregulation observed by Boatwright et al. The tendency for right coronary autoregulation to fail at lower perfusion pressures is consistent with our earlier finding of displacement of right coronary autoregulatory potential capability toward lower perfusion pressures.

The influence of perfusion pressure on right ventricular oxygen consumption and the resultant blunting of right coronary autoregulation is probably due to increased oxygen requirements of myocytes stretched by a distended vasculature, that is, the garden hose effect. Enlargement of vessels would occur more readily in the right ventricle because of its thinner wall and lower wall tension compared with the left ventricle. Another factor may be a smaller tissue pressure in right ventricular myocardium, especially during systole. The current findings suggest that the most distensible coronary vessels in the canine heart are those of the right ventricular subendocardium. Although we were not able to measure right ventricular oxygen consumption in specific transmural regions, we speculate that subendocardial oxygen consumption would increase first and more extensively than subepicardial oxygen consumption as right coronary perfusion pressure is elevated. This question merits examination with methods sensitive to changes in local, transmural venous oxygen content.

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References


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