Effect of Flow Reduction on Coronary Blood Flow Heterogeneity (43517)

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Abstract. **The purpose of this study was to test the hypothesis that under reduced flow conditions, spatial heterogeneity (segment-to-segment variability) of myocardial blood flow would be inversely proportional to the rate of perfusion and that vasoconstriction would alter this relationship in anesthetized open-chest dogs. A carotid-left circumflex coronary artery shunt was created. Coronary blood flow determinations employed the radioactive microsphere technique. Fifty tissue samples were obtained from the affected left ventricle, including subepicardial and subendocardial samples. The coefficient of variation (CV = 100 × SD/mean), an index of spatial heterogeneity, was computed. Flows were obtained under three separate conditions: control, a 50% flow reduction in the circumflex artery, and vasopressin infusion, in which the administered dose reduced circumflex artery flow by 50%. The within-animal CV increased from a control of 18 ± 9 to 45 ± 25 with partial occlusion and 46 ± 18 with vasopressin. No significant differences in CV were found between the two reduced flow conditions. A significant linear relationship between CV and mean coronary flow was found ($r = 0.51$, $P < 0.001$) over the entire range of flows studied (CV = −0.34*flow + 50.91) for control, 50% occlusion, and vasopressin treatment. The correlation was significantly improved ($r = 0.69$) using the equation CV = (1319.06/flow) + 4.44. Thus, the relative heterogeneity of coronary blood flow increased with reductions in coronary blood flow, regardless of the means of flow reduction.** [P.S.E.B.M. 1993, Vol 202]

Coronary blood flow is regulated to maintain an acceptable balance between O_2 supply and O_2 demand in the myocardium. At the same time, there is substantial variability associated with parameters of O_2 supply and usage within the same region of the heart, e.g., tissue partial pressure of O_2 (1, 2), high energy phosphates (3, 4), and coronary venous O_2 saturation (5, 6). Previous studies suggested that flow is not uniform throughout the heart (3, 7–10). This spatial heterogeneity of coronary flow, quantitated by Marcus *et al.* (11) with radioactive microspheres, occurs among adjacent tissue samples from the same region of the heart. Other flow techniques have also shown coronary blood flow heterogeneity (7, 12). Heterogeneity of flow and regional O_2 saturation also exist in ischemic myocardial regions (11, 13, 14). Physiologic unevenness of O_2 supply during flow restrictions may cause uneven cellular function or damage.

The mechanisms that control this spatial heterogeneity of coronary blood flow are unknown. We have reported that variability in myocardial flow (spatial heterogeneity) is inversely related to the flow rate in the rabbit heart (8). To our knowledge, there are no reports on whether lowering blood flow will increase spatial heterogeneity. There may be an effect of vascular tone of small coronary arterioles on the relationship between spatial heterogeneity and flow (15, 16). Conway *et al.* (15) reported that vasopressin reduced spatial heterogeneity, whereas Gorman *et al.* (16) reported that vasodilation, with dipyridamole at fixed flow, increased heterogeneity.

The present study tested the hypothesis that the variability of coronary blood flow was inversely related to the flow rate and that vasoconstriction would modify this relationship in the dog heart. Our study helped to determine the degree of spatial heterogeneity during flow restriction, as reported by others (11, 17), and the

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role of vascular tone in its control. We concluded that flow reduction increased the relative variability of coronary flow, whether it was caused by vasoconstriction or by partial occlusion. This indicated a relative independence of spatial heterogeneity on the degree of arteriolar vasoconstriction under low flow conditions.

Materials and Methods

Mongrel dogs of either sex, ranging in weight from 13 to 21 kg, were used in this study. The dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv). This dose was supplemented as required. Polyethylene catheters were inserted into a femoral artery and vein and into the carotid artery. Arterial catheters were used for measurement of blood pressure and heart rate, for blood sampling and for coronary perfusion. The venous catheter was used for injection of additional anesthetic as required. The trachea was cannulated and the animal was mechanically ventilated with a Harvard respirator. Arterial blood gases were monitored and maintained by adjustment of the respirator. The lungs were periodically overinflated to prevent atelectasis.

The chest was opened at the left fifth intercostal space, and a partial pericardiotomy exposed the heart. A shunt was made connecting a carotid artery to the left circumflex coronary artery. Cannulation of the circumflex artery required less than 2 min of ischemia. Large bore tubing was used except for approximately 1 cm of PE-90 tubing inserted into the coronary artery. Pressure in the cannula was determined 1 cm from the circumflex artery. Blood flow was assessed with an in-line extracorporeal flow probe connected to a Biotronix flow meter. A screw clamp was placed on the shunt for adjustment of the flow. A catheter was inserted into the left atrium for injection of radioactive microspheres. Aortic pressure, coronary perfusion pressure (Statham P23Db transducers), and heart rate were recorded on a Beckman R-411 recorder. Blood samples were obtained from the femoral artery catheter. Blood PO_2, PCO_2, and pH were determined using a Radiometer blood gas analyzer (model ABL 330).

In all dogs used in these studies after a period of initial stabilization, measurements of blood pressures and heart rate were obtained along with an anaerobic arterial blood sample. A dose of approximately 2×10^6 microspheres (3M, Minneapolis, MN), 15 ± 3 μm in diameter and labeled with either ^{141}Ce, ^{85}Sr, or ^{46}Sc, was vortexed for 2 min, injected as a 0.5-ml bolus into the left atrial catheter, and then flushed with 1.0 ml of saline. A single reference blood sample was withdrawn from the femoral artery at a rate of 7 ml/min, starting 30 sec before the injection of microspheres and continuing for a period of 2 min. A brief oclusion (15 sec) was performed to ensure the reactivity of the circumflex vascular bed.

After the control measurements were obtained, the screw clamp on the shunt was tightened to reduce flow to approximately 50% of its control value. Fifteen minutes later, measurements were obtained for arterial and coronary pressures, blood gases, and heart rate. An alternately labeled set of radioactive microspheres was injected as described. Upon completion of all measurements the occlusion was released and a 30-min recovery period was allowed. Vasopressin was infused directly into the coronary perfusion catheter at a dose of 2–8 mU/kg/min, which was sufficient to reduce coronary flow to the circumflex region by about 50%. Fifteen minutes later, measurements were obtained for arterial and coronary pressures, blood gases, and heart rate. An alternately labeled set of radioactive microspheres was used to determine coronary blood flow. The entire experimental protocol was completed in 10 dogs and partially performed in three additional animals.

Two additional dogs were used to determine the variability of coronary blood flow due to the technique itself. These animals were treated the same as the others except that a mixture of the three different microspheres was injected simultaneously. Separate comparisons were made in a flow-restricted and control area of the heart. Flow restriction was achieved by partial inflow blockage. This was performed in 24 samples in each region. If the microsphere technique produced ideal blood flow determinations, the three flow values obtained in each tissue sample in these dogs would be identical.

Upon completion of the experiment, Evans blue dye was injected into the coronary perfusion cannula and the heart was excised and frozen for tissue preparation and subsequent cutting. The atria, remnants of the aorta and pulmonary artery, the right ventricular wall, and fat tissue were discarded. A grid of 50 samples was made in the affected region (circumflex artery perfusion field) of the left ventricle. A control sample of six pieces was obtained from the nonaffected (left anterior descending artery perfusion field) region. The grid consisted of both subepicardial and subendocardial pieces with an average weight of 0.3–0.5 g, cut in the apex to base direction. The tissue samples were weighed and counted on an automatic gamma spectrometer (Packard 5230). Arterial blood samples obtained from the timed-reference samples were weighed and placed in the spectrometer along with the tissue samples. Appropriate corrections were made for activity overlap. Blood flows were calculated from the formula: $Fu = Fk \times Cu/Ck$, where Fu is the flow to any organ, Fk is the flow to the reference organ, Cu is the radioactivity in any organ, and Ck is the radioactivity in the reference organ (18, 19). We estimated at least 500 microspheres would be found in the lowest flow sample. Blood flow was expressed in ml/min/100 g tissue.

A one-way analysis of variance was used to determine significant differences in the hemodynamic parameters and blood gases between treatments. A two-

way analysis of variance with repeated measures was used to determine significant differences in mean coronary blood flow, standard deviation, and coefficient of variation (CV) with respect to treatment and regions. The latter statistic is defined as (SD/mean flow) × 100 and is a relative measure of the dispersion of flow values. The Duncan multiple range test was used to determine sources of significant difference in the analysis of variance, where applicable. Least squares regression analysis was used to determine significant correlation between standard deviation or CV and mean flow on an overall, treatment, and regional basis. Values are presented as mean ± SD. A $P < 0.05$ was considered significant in all analyses.

Results

Values for hemodynamic parameters, arterial blood gases, and pH for all treatments are presented in Table I. Analysis of variance showed no significant differences in aortic blood pressure, heart rate, PaO_2, $PaCO_2$, or pH between the various treatments. Coronary blood flow, as determined by electromagnetic flow meter, was reduced to approximately half of its control value by both the partial occlusion and vasopressin infusion (Table I). Coronary perfusion pressure was significantly lowered by partial occlusion of the carotid to circumflex artery shunt, but it was not significantly affected by vasopressin.

Under control conditions, coronary blood flow within the perfusion field of the carotid to circumflex artery shunt averaged 71 ± 24 (within-animal CV = 18 ± 9) ml/min/100 g and this was similar to the flow in the left anterior descending coronary artery perfusion field, which had a mean value of 76 ± 24 ml/min/100 g. No significant control subepicardial versus subendocardial regional differences were found in either mean flow, standard deviation, or CV; therefore, data are presented as mean data. The subendocardial/subepicardial flow ratio averaged 1.03 ± 0.22 in control conditions. Coronary blood flow determined with radioactive microspheres dropped approximately 40% with partial occlusion of the shunt to 44 ± 20 ml/min/100 g and to a similar value with vasopressin infusion (42 ± 13 ml/min/100 g). The subendocardial to subepicardial flow ratio was 0.93 ± 0.20 with partial occlusion and 0.87 ± 0.38 during vasopressin infusion. Under these reduced flow conditions, the within-animal CV was significantly higher (partial occlusion, 45 ± 25; vasopressin, 46 ± 18; $P < 0.01$) than the control value. There was no significant difference in CV between the two reduced flow conditions.

Overall linear regression analysis of paired CV and mean coronary blood flow data is presented in Figure 1. No differences were found in the relationship of flow and CV between the partial occlusion and vasopressin treatment groups, so all data were combined. A significant correlation ($r = 0.51$, $P < .001$) was found for the equation CV = −0.34*flow + 50.91. The correlation was significantly improved ($r = 0.69$) using the equation CV = (1319.06/flow) + 4.44. When blood flow was reduced by either treatment, there was a significant correlation between mean flow and its standard deviation: SD = 0.12*flow + 8.48 ($r = 0.37$). The reductions in flow were greater than the reductions in standard deviation. Thus, spatial heterogeneity appears to be inversely related to mean coronary flow over the range of mean flows studied in this experimental model (22–138 ml/min/100 g).

When least squares analysis was applied to the subepicardial and subendocardial regions separately, similar regression equations were generated. The equation of best fit for the subepicardial region was CV = (1052.92/flow) + 3.05 ($r = 0.53$). The analysis for the subendocardium generated the equation CV = (1632.23/flow) − 3.14 ($r = 0.79$). The correlation was higher in the subendocardium, although the difference between the regression equations was not statistically significant.

In the dogs used to test flow variation, coronary blood flow in the flow-restricted region averaged 38 ml/min/100 g and the between-sample CV was 43%. The coefficient of variation of flow determinations using the three simultaneously injected radioactive microspheres per tissue sample was 10%. In the region without flow restriction, flow averaged 67 ml/min/100 g and the between-sample CV was 19%. The CV for the within-

Table I. Hemodynamic and Blood Gas Data for Control, Partial Occlusion, and Vasopressin Treatment[a]

	Control	50% Occlusion	Vasopressin
Mean aortic blood pressure (mm Hg)	90 ± 18	77 ± 26	95 ± 24
Mean coronary blood pressure (mm Hg)	86 ± 18	63 ± 23[b]	93 ± 23
Coronary blood flow (ml/min)	32 ± 23	16 ± 11[b]	19 ± 16[b]
Heart rate (beats/min)	163 ± 28	157 ± 31	140 ± 23
PaO_2 (mm Hg)	66 ± 13	73 ± 13	70 ± 14
$PaCO_2$ (mm Hg)	31 ± 4	34 ± 4	30 ± 4
pH	7.43 ± 0.08	7.44 ± 0.09	7.37 ± 0.10

[a] Values are presented as mean ± SD.
[b] Significantly different from control.

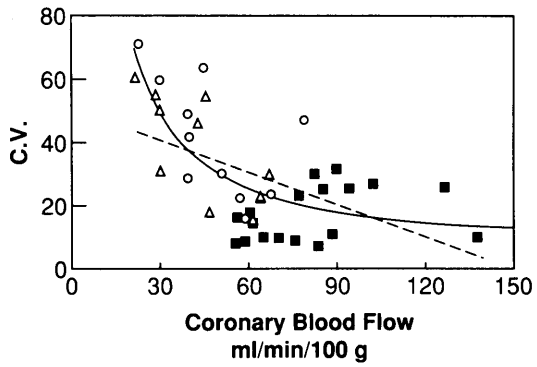

Figure 1. The relationship between flow variability of small myocardial regions shown as a coefficient of variation and average coronary blood flow in those segments during control (■), partial occlusion (△), and vasopressin infusion (○). Each point represents the mean and CV of the entire circumflex region (50 pieces) under that experimental condition. The linear regression equation of best fit was CV = −0.34*flow + 50.91 (r = 0.51, $P < 0.001$). The equation CV = (1319.06/flow) + 4.44 gave a better fit (r = 0.69).

region variability (among the three flow measures) averaged 8%.

Discussion

The major finding of this study was that spatial heterogeneity of coronary blood flow increased when blood flow was decreased in the dog heart. This is in agreement with a previous study by Conway and Weiss (8), who found that increasing blood flow decreased the spatial heterogeneity in the rabbit heart. The heterogeneity of coronary blood flow increased with decreasing flow, regardless of whether vasopressin was administered or flow was impeded with a screw clamp occlusion. This implies that the degree of vasoconstriction does not directly affect heterogeneity during flow restriction, but that the absolute level of flow is crucial.

While earlier studies supported substantial variability of coronary flow (7, 20), Marcus *et al.* (11) used the coefficient of variation, a mean coronary flow-normalized measure of flow dispersion, to quantitate spatial heterogeneity of flow. They determined that approximately half of the variability of flow was due to technique error and half due to true segment-to-segment variation in flow rate. We found a similar degree of methodologic error with injection of differently labeled radioactive microspheres (8), as have others (19). In the present report, variability related to methodologic errors accounted for between one fourth and one half of the total variability. The rest was related to true biological variability. The degree of spatial heterogeneity that we report is similar to that of previous investigations and exhibits no regional (subepicardial versus subendocardial) differences (8, 11, 21–23). There is also temporal heterogeneity of myocardial flow (11, 21), but this appears to be considerably less important than spatial heterogeneity (9).

The heart is a muscle that as a whole appears to be doing a relatively uniform level of work. However, when a given region of the heart is examined, it is clear that there is a wide variability in local blood flow (11, 22–24). In the present study, we have demonstrated that decreasing blood flow results in an increase in variability. We did not find any subepicardial versus subendocardial differences in the spatial heterogeneity of coronary blood flow under any of the experimental conditions tested. This lack of regional difference in flow variation has been reported by others (7, 8, 23). Our subendocardial to subepicardial flow ratios during flow restriction were similar to other reports during ischemia (3, 11, 14, 22). However, these values were not significantly different from the control ratio. This may be related to the slight pressure gradient in control causing a lowered flow ratio. This bed, however, did exhibit reactive hyperemia.

The results of this study indicate that as flow is decreased its variability increases. The inverse nature of this relation between flow and CV of flow is consistent with the study by Sciacca *et al.* (25), who reported a significantly increased variability in a region of the myocardium receiving approximately two thirds of its normal flow. It is also consistent with the data which show that increasing flow in the rabbit heart decreases heterogeneity (8). However, Sestier *et al.* (23) did not report changes in CV with adenosine administration in dogs. Furthermore, the work of the Bassingthwaighte group has shown stability of local flow over time and condition (7, 9, 26). These are not necessarily conflicting reports, since relatively large changes in flow are necessary to change CV (8).

Significant heterogeneity has been reported in NADH fluorescence during lowered levels of myocardial oxygenation (17, 27). Heterogeneity of flow and regional venous O_2 saturation also exist in myocardial regions that are ischemic (11, 13, 14). Others have also shown heterogeneous patterns of myocardial flow, function, oxygenation, and microcirculation during myocardial ischemia (11, 28–32). From the results of the current study, it appears that the relative dispersion of flow increases in both the subepicardium and subendocardium as the level of flow decreases. There is evidence for some degree of flow reserve in ischemia (33, 34), which may explain some of the flow redistribution. This data may also help explain the increased levels of variability in many parameters during reduced oxygenation. There may be a nonlinear increase in heterogeneity at lowered coronary flow rates.

From the data presented, it is clear that the CV of coronary blood flow increased with decreasing flow regardless of the method by which flow was altered. Increasing the heterogeneity of myocardial blood flow when flow was decreased with a screw clamp is consistent with the data of Conway and Weiss (8) in rabbit. However, Conway *et al.* (15) found that intracoronary

vasopressin infusion improved autoregulation, and decreased spatial heterogeneity. We report here that vasopressin had the same effect on heterogeneity of coronary flow as partial occlusion. We did not study autoregulation, but found that vasopressin increased heterogeneity. Differences may be related to regional differences, the level of anesthetic, the degree of flow restriction or vascular tone during control or during partial occlusion. Gorman *et al.* (16) reported that vasodilation with dipyridamole at constant pressure would decrease flow heterogeneity in the guinea pig heart. We report that vasoconstriction without any significant change in perfusion pressure increased heterogeneity in the dog heart.

Flow restriction increases the heterogeneity of coronary blood flow, but this effect appears independent of vascular tone in a comparison between partial occlusion and vasopressin infusion. During flow restriction, some of the radioactive microsphere-determined flow may enter the circumflex area through collateral channels. The proportion of collateral flow could change with the different experimental conditions. The change in flow variability with rate may be related to small vessel tone, the anatomic branching pattern, or relatively temporally constant flow dispersion in the heart (9, 26, 35). There are reports that this heterogeneity may (3) or may not (4) be related to local levels of metabolic substrates or high energy phosphates. There is evidence that β-adrenergic receptors exert some control on myocardial flow heterogeneity (24, 36). It is not clear which, if any, of these factors explain the inverse relationship between coronary flow rate and flow heterogeneity.

In summary, we found that spatial heterogeneity of coronary blood flow increased when blood flow was decreased in the dog heart. The heterogeneity of coronary flow increased with decreasing flow, regardless of whether vasopressin was administered or flow was restricted with a screw clamp. This implies that the degree of vasoconstriction of small coronary arterioles does not directly affect heterogeneity during flow restriction, but that the absolute level of flow is crucial. Thus, any form of partial ischemia increases flow heterogeneity. Such flow heterogeneity may indicate that some areas are at higher risk of ischemia and cell death during flow restriction. Spatial heterogeneity in the heart has been reported in flow, venous O_2 saturation, myocardial tissue PO_2, high energy phosphates, NADH reduction, etc.

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