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Changes in coronary perfusion pressure cause changes in myocardial contractile function and oxygen consumption (MVO_2), particularly in the right ventricle (RV). This study determined the effects of right coronary (RC) perfusion pressure (RCP) on RC vascular volume (RCV) and its relationship to MVO_2 of *in situ*, working canine hearts, and also investigated whether changes in MVO_2 are due primarily to altered RCP or RC blood flow (RCF). In 15 open chest, anesthetized dogs, the RC artery was cannulated and perfused with arterial blood diverted from a femoral artery. To blunt RCP-induced changes in RCF, vasopressin was infused into the RC perfusion line in seven dogs. RCV was measured by an indicator dilution method as RCP was varied without vasopressin (RCP = 60, 100, 140, and 180 mmHg) and with vasopressin (RCP = 60 and 100 mmHg). Without vasopressin, changes in RCP induced changes in MVO_2 which were associated with changes in RCV and RCF. With vasopressin, increasing RCP from 60 mmHg to 100 mmHg produced no changes in RCF, RCV, or MVO_2. These results indicate that RCP-induced changes in RV MVO_2 are mediated by RCV and/or RCF, but not by RCP *per se*.

CORONARY PERFUSION PRESSURE-INDUCED CHANGES IN CORONARY VASCULAR VOLUME IN THE CANINE RIGHT VENTRICLE

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LIST OF ABBREVIATIONS

1.	AoP	Aortic pressure
2.	dP/dt_{min}	Minimum rate of ventricular pressure development
3.	dP/dt_{max}	Maximum rate of ventricular pressure development
4.	HR	Heart rate
5.	LV	Left ventricle
6.	RC	Right coronary
7.	RCF	Right coronary blood flow
8.	RCP	Right coronary perfusion pressure
9.	RCV	Right coronary vascular volume
10.	RV	Right ventricle
11.	RVPs	Right ventricular systolic pressure
12.	RVPd	Right ventricular diastolic pressure

CHAPTER I

INTRODUCTION

Myocardial contractile function and oxygen consumption (MVO_2) are influenced by coronary perfusion pressure if coronary autoregulation is compromised (1, 2, 8, 11, 21, 22). The observation that myocardial oxygen consumption and contractile strength are changed by coronary perfusion is called "Gregg's phenomenon." This "Gregg's phenomenon" (11) has been ascribed to various causes (9), but its mechanism has not been unequivocally delineated. Recently we demonstrated a close correlation between changes in coronary vascular volume, systolic stiffness, and MVO_2 in left ventricle (LV) (4). Since right coronary (RC) autoregulation is less potent than left coronary autoregulation (10, 19, 23, 24), the Gregg phenomenon is particularly prominent in the right ventricle (RV). Also, RV differs significantly from LV in wall thickness, systolic pressure, work performance, oxygen consumption, and coronary blood flow. Thus, pressure-induced changes in RC vascular volume (RCV) might be pronounced, but no reports describe this relationship. Such information would be helpful in understanding the marked effect of RC perfusion pressure (RCP) on RV MVO_2. In this investigation, the effects of RCP on RCV were determined and compared with previously reported data for the left ventricle.

In the presence of poor coronary autoregulation, changes in coronary perfusion pressure produce concurrent changes in coronary blood flow. Our laboratory reported that

increased coronary blood flow with or without increased coronary perfusion pressure increased left ventricular contractile force and MVO_2 (12), although the effect of increased flow was greater if pressure increased concurrently. On the other hand, in some studies a change in flow without a change in pressure did not alter myocardial oxygen consumption (3, 5, 16). Therefore, whether coronary perfusion pressure or coronary blood flow plays a dominant role in coronary pressure-induced changes in MVO_2 is controversial.

We attempted to differentiate the effects of RCP and RCF on RV MVO_2 by using vasopressin, a potent coronary arteriolar vasoconstrictor (14), to prevent RCP-induced changes in RCF. Since most coronary volume is post-arteriolar, elevation of RCP was expected to have little effect on right coronary vascular volume in the presence of vasopressin. Thus, this approach determined if altered coronary perfusion pressure in the absence of pressure-induced changes in coronary flow and vascular volume would affect RV MVO_2.

CHAPTER II

MATERIALS AND METHODS

Surgical preparations

This investigation was approved by the Institutional Animal Care and Use Committee of the University of North Texas Health Science Center at Fort Worth and conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (NIH publication 85-23, revised 1985). Adult mongrel dogs (n = 15) of either sex weighing 18-31 kg were anesthetized with pentobarbital sodium (30 mg/kg iv). Anesthesia was maintained with supplemental administration of pentobarbital sodium (3-4 mg/kg iv) as needed. The dogs were intubated and subsequently ventilated by a Harvard respirator with room air supplemented with oxygen.

A catheter was inserted through the right femoral artery and advanced to the thoracic aorta for monitoring aortic pressure (AoP) and heart rate (HR). A second catheter was inserted into a femoral vein for administering supplemental pentobarbital sodium, heparin, donor blood, and sodium bicarbonate.

The heart was exposed through a right thoracotomy, and the fifth rib was removed. The pericardium was incised. A Millar catheter-tip transducer was inserted into the RV via an incision in the right atrial appendage to measure RV pressure (RVP) and its first derivative (RV dP/d*t*). The RC artery was isolated. After heparin (700

U/kg) was administrated intravenously for anticoagulation, the RC artery was cannulated and perfused at controlled pressure with arterial blood derived from the left femoral artery. The perfusion system consisted of a roller pump, a heat exchanger, an electromagnetic flow transducer, and a port for sampling RC arterial blood. A pressurized, temperature controlled reservoir with electromagnetic stirring bar was included in the perfusion system for nine experiments. In nine dogs, a coronary vein draining the area perfused by the RC artery was cannulated for collection of RC venous blood used for determining regional MVO_2. AoP, HR, RVP, and RV dP/d*t* were recorded continuously by a multichannel polygraph.

Right coronary perfusion pressure (RCP) and right coronary blood flow (RCF)

Coronary perfusion pressure was measured via a saline-filled catheter advanced through the perfusion line to the orifice of the coronary arterial cannula and attached to a pressure transducer. Coronary perfusion pressure was varied by adjusting the rate of a roller pump in six dogs, and the pressure in the sealed blood reservoir in nine dogs. RCF was measured with an electromagnetic flowmeter (Carolina Medical Electronics model FM502).

Right coronary vascular volume (RCV)

An indicator dilution method was used to measure coronary vascular volume in the region perfused by the RC artery. Red blood cells were obtained from the

experimental dog and labeled *in vitro* with ^{51}Cr (7). For each measurement of coronary vascular volume, 0.20-0.25 ml of labeled blood (25 μCi ^{51}Cr/ml) was injected into the RC perfusion line near the cannulation site. Myocardial radioactivity was monitored by a collimated NaI scintillation detector positioned over the RC-perfused region. ^{51}Cr clearance curves were recorded on a Soltec model 1243 recorder connected to the Tennelec gamma analysis system. The mean transit time ($\bar{T}$) of the ^{51}Cr-labeled cells was calculated by integrating the ^{51}Cr clearance curve according to the following equation:

$$\bar{T} = \sum_{0}^{t_{max}} tR(t)\,\Delta t \,/\, \sum_{0}^{t_{max}} R(t)\,\Delta t$$

where change in time (Δt) = 1 s, R (t) is radioactivity at time t, and t_{max} is the time required for R(t) to reach baseline. Recirculating peaks were eliminated by curvilinear extrapolation of the clearance curve. The rise in background due to recirculation was compensated by linear extrapolation of background activity from the pre-injection value to the stable post-injection value. Coronary vascular volume was calculated as the product of coronary blood flow and labeled cell mean transit time.

Blood gas data and myocardial oxygen consumption (MVO_2)

RC arterial and venous blood were collected anaerobically and analyzed for pH,

Po_2, and Pco_2 on a Ciba-Corning model 238 pH/blood gas analyzer. Arterial blood gases were kept normal by adjusting respiratory rate, tidal volume, and fractional inspired O_2 concentration, and by administering sodium bicarbonate. Oxygen content of blood samples was measured with an Instrumentation Laboratory model 282 CO-Oximeter, and myocardial oxygen consumption was calculated from the coronary flow and the arterio-venous oxygen content difference.

Blood Lactate

Blood lactate analyses were performed in six dogs to determine if intracoronary vasopressin infusion caused anaerobic metabolism indicative of myocardial ischemia. The lactate content of arterial and coronary venous blood samples was determined with a L-Lactate Analyzer. Lactate extraction was calculated as the difference of arterio-venous lactate content.

Experimental protocol

In six dogs, RCP was varied in 40-mmHg steps from 100 mmHg to 60 mmHg, then from 100 mmHg to 140 mmHg, and then further to 180 mmHg. RCV was measured at each coronary perfusion pressure level, when RCF had reached a steady state after each change in RCP.

In nine dogs, RCP was changed from 140 mmHg to 100 mmHg, and then from 100 mmHg to 60 mmHg. RCV and MVO_2 were measured at these pressures with

steady state RCF. In seven of these dogs, an infusion of synthetic vasopressin (American Regent Laboratories, Inc.) into RC perfusion line near the coronary cannulation site was then begun with RCP at 60 mmHg. The vasopressin was diluted in saline to a concentration of 0.2-0.5 U/ml, and the infusion rate was adjusted so that RCF stayed constant as RCP was raised from 60 to 100 mmHg. RCV and RV MVO_2 were determined with RCP at 100 mmHg and with RCF similar to that recorded with RCP at 60 mmHg prior to vasopressin infusion. The vasopressin infusion was continued, and RCP was increased to 140 mmHg. RCF increased as RCP was elevated from 100 to 140 mmHg, but the vasopressin infusion blunted the pressure-induced rise in RCF. Under these conditions, RCV and RV MVO_2 were again determined.

After each experiment, india ink was injected into the RC perfusion line. The dyed area was defined as the area perfused by the RC artery. Tissue mass of the perfusion area was estimated by weighing the dyed area of the right ventricle. Thus, the units for RCF, RCV, MVO_2, and lactate uptake were expressed as ml/min/g, ml/100 g, ml/min/100 g, and μmol/min/100 g, respectively.

Statistical analysis

A one-way analysis of variance for repeated measures (ANOVA) was used to analyze hemodynamic variables, RCV, and MVO_2 during varied RCP. Differences were considered significant if $P < 0.05$. When significance was found with ANOVA, a Student-Newman-Keuls test was then used to identify specific significant differences.

A *t* test was used to compare values at RCP of 100 and 140 mmHg without and with vasopressin. In addition, linear regression was used to analyze relationships between RCP and RCV, and between RCP and RCF.

CHAPTER III

RESULTS

Hemodynamic variables

Table 1 presents hemodynamic data from 15 dog hearts. Changes in RCP had no significant effect on AoP, RVPs, RVPd, RV dP/dt_{max}, RV dP/dt_{min}, or HR. Table 2 presents data from seven experiments in which vasopressin was infused following recording of hemodynamic data at RCP of 60 mmHg. Vasopressin infusion caused no significant effects on RVPs, RVPd, RV dP/dt_{max}, RV dP/dt_{min}, or HR at RCP of 100 and 140 mmHg compared to the untreated condition at these pressures (Table 1 and 2). In the presence of vasopressin, changes in RCP from 60 to 100 mmHg had no significant effect on AoP, RVPs, RVPd, RV dP/dt_{max}, RV dP/dt_{min}, or HR. When RCP was increased further to 140 mmHg, small but significant decreases in RVPs, RV dP/dt_{min}, and HR were observed compared to values at RCP of 60 mmHg (Table 2).

Right coronary vascular volume (RCV)

Individual measurements of RCV without vasopressin are presented in Fig. 1. A significant, positive effect of RCP on RCV is evident ($P < 0.0001$). RCV data are summarized in Table 3. At the baseline level (RCP = 100 mmHg), mean RCV was 8.8 ± 0.7 (ml/100 g). RCV fell 31% following the reduction of RCP to 60 mmHg. When

Table 1. Hemodynamic variables without vasopressin

	RCP (60 mmHg) (n = 15)	RCP (100 mmHg) (n = 15)	RCP (140 mmHg) (n = 15)	RCP (180 mmHg) (n = 6)
RCP (mmHg)	59.0 ± 0.7	100.7 ± 0.7	140.2 ± 0.2	180.0± 0.0
AoP (mmHg)	90.4 ± 3.3	92.1 ± 3.1	90.4 ± 3.4	81.4 ± 2.9
RVPs (mmHg)	23.8 ± 1.3	23.6 ± 1.0	22.1 ± 1.0	21.7 ± 3.2
RVPd (mmHg)	2.1 ± 0.8	1.7 ± 0.5	2.1 ± 0.4	1.7 ± 0.3
RV dP/dt_{max} (mmHg/s)	550 ± 78	577 ± 71	544 ± 64	425 ± 75
RV dP/dt_{min} (mmHg/s)	-681 ± 63	-700 ± 61	-688 ± 60	-513 ± 38
HR (beats/min)	143 ± 6	142 ± 6	140 ± 6	146 ± 11

Values are means ± SE; n = no. of dogs; RCP = coronary perfusion pressure; AoP = mean aortic pressure; RVPs = right ventricular systolic pressure; RVPd = right ventricular end-diastolic pressure; RV dP/dt_{max} =maximum rate of right ventricular pressure development; RV dP/dt_{min} = minimum rate of right ventricular pressure development; HR = heart rate.

Table 2. Hemodynamic variables with vasopressin

	RCP (60 mmHg) (n = 7)	RCP (with vp) (100 mmHg) (n = 7)	RCP (with vp) (140 mmHg) (n = 7)
RCP (mmHg)	60.0 ± 0.0	100.0 ± 0.0	140.0 ± 0.0
AoP (mmHg)	92.9 ± 5.1	91.4 ± 3.9	95.0 ± 4.1
RVPs (mmHg)	22.0 ± 1.0	20.2 ± 1.5	19.2 ± 0.6*
RVPd (mmHg)	1.6 ± 0.8	1.4 ± 0.4	1.8 ± 0.7
RV dP/dt_{max} (mmHg/s)	513 ± 66	413 ± 24	363 ± 24
RV dP/dt_{min} (mmHg/s)	-775 ± 78	-700 ± 71	-588 ± 32*
HR (beats/min)	140 ± 7	131 ± 7	129 ± 9*

Values are means ± SE; n = 7; RCP = coronary perfusion pressure; vp = vasopressin treated group; AoP = mean aortic pressure; RVPs = right ventricular systolic pressure; RVPd = right ventricular end-diastolic pressure; RV dP/dt_{max} =maximum rate of right ventricular pressure development; RV dP/dt_{min} = minimum rate of right ventricular pressure development; HR = heart rate; vp = vasopressin; * $P <$ 0.05 vs RCP = 60 mmHg.

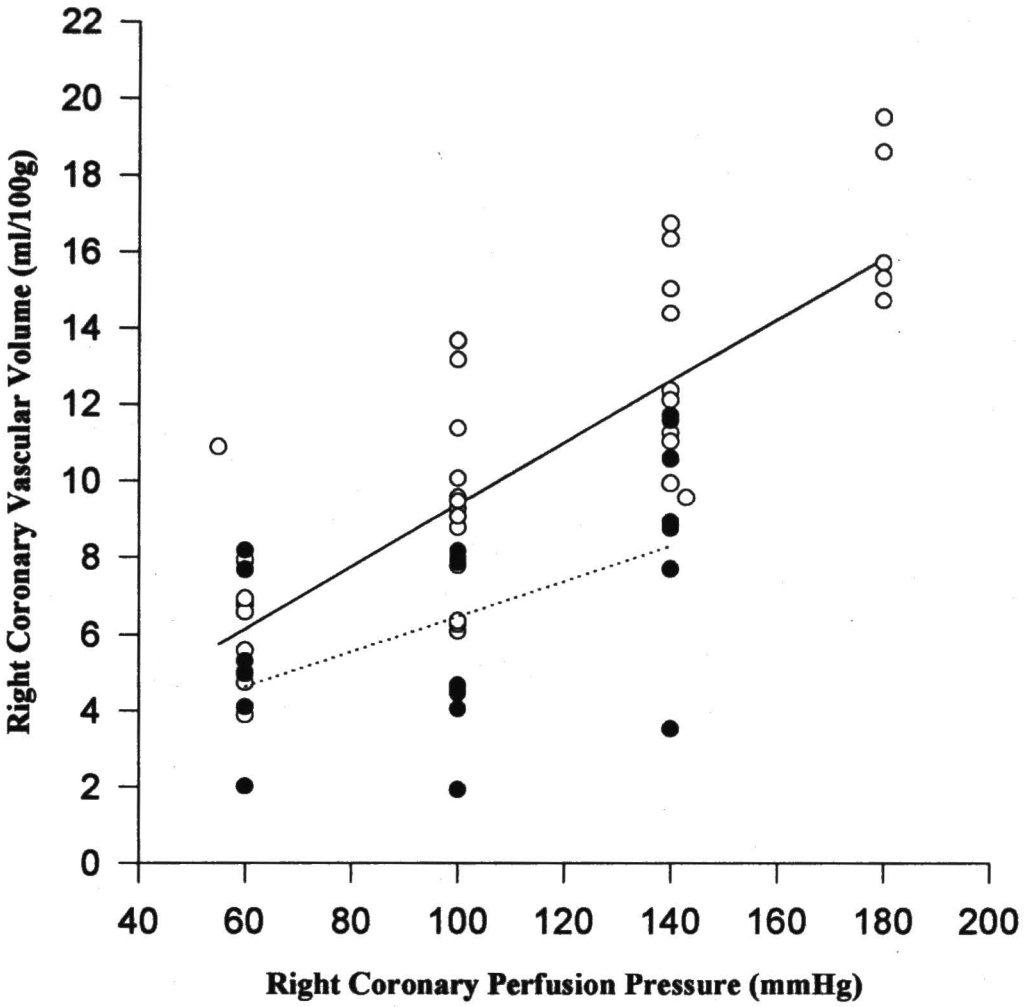

Fig. 1. Relationship between right coronary perfusion pressure (X) and right coronary vascular volume (Y) with (n = 7) and without vasopressin (n = 15). Open circles represent right coronary vascular volume without vasopressin. Filled circles represent right coronary vascular volume with vasopressin. The straight line illustrates the equation: $Y = 1.28 + 0.0813 \bullet X$; $R^2 = 0.674$; $P < 0.0001$. The dotted line illustrates the equation: $Y = 1.90 + 0.0458 \bullet X$.

RCP was increased to 140 and 180 mmHg, RCV increased 33% and 92%, respectively. Table 4 shows RCV for RCP at 60 mmHg prior to vasopressin infusion and for RCP at 100 and 140 mmHg with vasopressin. RCV did not change as RCP was increased from 60 mmHg to 100 mmHg. This value of RCV with vasopressin was significantly less than that measured at RCP of 100 mmHg without vasopressin (Table 3). When RCP was further increased to 140 mmHg, RCV significantly increased (Table 4), but was significantly less than that measured at RCP of 140 without vasopressin (Table 3).

Right coronary blood flow (RCF)

Individual values for RCF without vasopressin are shown in Fig. 2. RCF linearly increased as RCP was increased ($P < 0.0001$). RCF data are summarized in Table 3. Mean RCF was 0.79 ± 0.07 (ml/min/g) at the baseline level (RCP = 100 mmHg). RCF fell 43% as RCP was reduced to 60 mmHg. RCF increased 73% as RCP was increased to 140 mmHg, and 186% as RCP was increased further to 180 mmHg. Table 4 shows values of RCF for RCP at 60 mmHg prior to vasopressin infusion and for RCP at 100 and 140 mmHg with vasopressin. When RCP was increased from 60 mmHg to 100 mmHg, RCF did not change significantly. This value of RCF at RCP of 100 mmHg with vasopressin was significantly less than that measured at RCP of 100 mmHg without vasopressin (Table 3). When RCP was increased further to 140 mmHg, RCF significantly increased (Table 4), but was significantly less than that measured at RCP of 140 mmHg without vasopressin. Figure 4 illustrates relationship between RCF and RCV without vasopressin.

Table 3. Coronary vascular volume, coronary blood flow, and MVO_2 (without vasopressin)

	RCP (60 mmHg) (n = 15)	RCP (100 mmHg) (n = 15)	RCP (140 mmHg) (n = 15)	RCP (180 mmHg) (n = 6)	ANOVA
RCV (ml/100 g)	6.1 ± 0.6	8.8 ± 0.7	11.7 ± 0.9	16.9 ± 1.0	$P < 0.05$
RCF (ml/min/g)	0.45 ± 0.04	0.79 ± 0.07	1.37 ± 0.14	2.26 ± 0.41	$P < 0.05$
	(n = 9)	(n = 9)	(n = 9)	(n = 0)	ANOVA
MVO_2 (ml/min/100 g)	3.7 ± 0.5	4.4 ± 0.6	5.1 ± 0.6	NM	$P < 0.05$
	(n = 6)	(n = 6)	(n = 6)	(n = 0)	ANOVA
Lactate (mmol/l) *arterial*	1.97 ± 0.34	1.83 ± 0.34	1.83 ± 0.40	NM	$P > 0.05$
venous	1.60 ± 0.28	1.52 ± 0.30	1.71 ± 0.35	NM	$P > 0.05$
extraction	0.38 ± 0.20	0.31 ± 0.17	0.11 ± 0.08	NM	$P > 0.05$
Lactate Uptake (μmol/min./100 g)	10.76 ± 7.48	13.69 ± 6.11	7.43 ± 5.95	NM	$P > 0.05$

Values are means ± SE; n = no. of dogs; RCP = coronary perfusion pressure; RCF = right coronary blood flow; RCV = coronary vascular volume; NM = not measured; MVO_2 = myocardial oxygen consumption.

Table 4. Coronary vascular volume, coronary blood flow, and MVO_2 (with vasopressin)

	RCP (60 mmHg) (n = 7)	RCP (with vp) (100 mmHg) (n = 7)	RCP (with vp) (140 mmHg) (n = 7)
RCV (ml/100 g)	5.4 ± 0.8	5.1 ± 0.8†	9.0 ± 1.1*†‡
RCF (ml/min/g)	0.37 ± 0.04	0.40 ± 0.04†	0.91 ± 0.08*†‡
MVO_2 (ml/min/100 g)	3.7 ± 0.7 (n = 6)	2.9 ± 0.4† (n = 6)	3.2 ± 0.4† (n = 6)
Lactate (mmol/l) *arterial*	1.97 ± 0.34	2.13 ± 0.36	2.48 ± 0.48*†
venous	1.60 ± 0.28	1.92 ± 0.24	2.13 ± 0.41*
extraction	0.38 ± 0.20	0.21 ± 0.19	0.35 ± 0.12†
Lactate Uptake (μmol/min/100 g)	10.76 ± 7.48	5.16 ± 6.61†	30.28 ± 11.60†‡

Values are means ± SE; n = no. of dogs; RCP = coronary perfusion pressure; RCF = right coronary blood flow; RCV = coronary vascular volume; MVO_2 = myocardial oxygen consumption; vp = vasopressin; * $P < 0.05$ vs RCP = 60 mmHg; † $P < 0.05$ vs values without vp at constant RCP (Table 3); ‡ $P < 0.05$ vs RCP = 100 with vp.

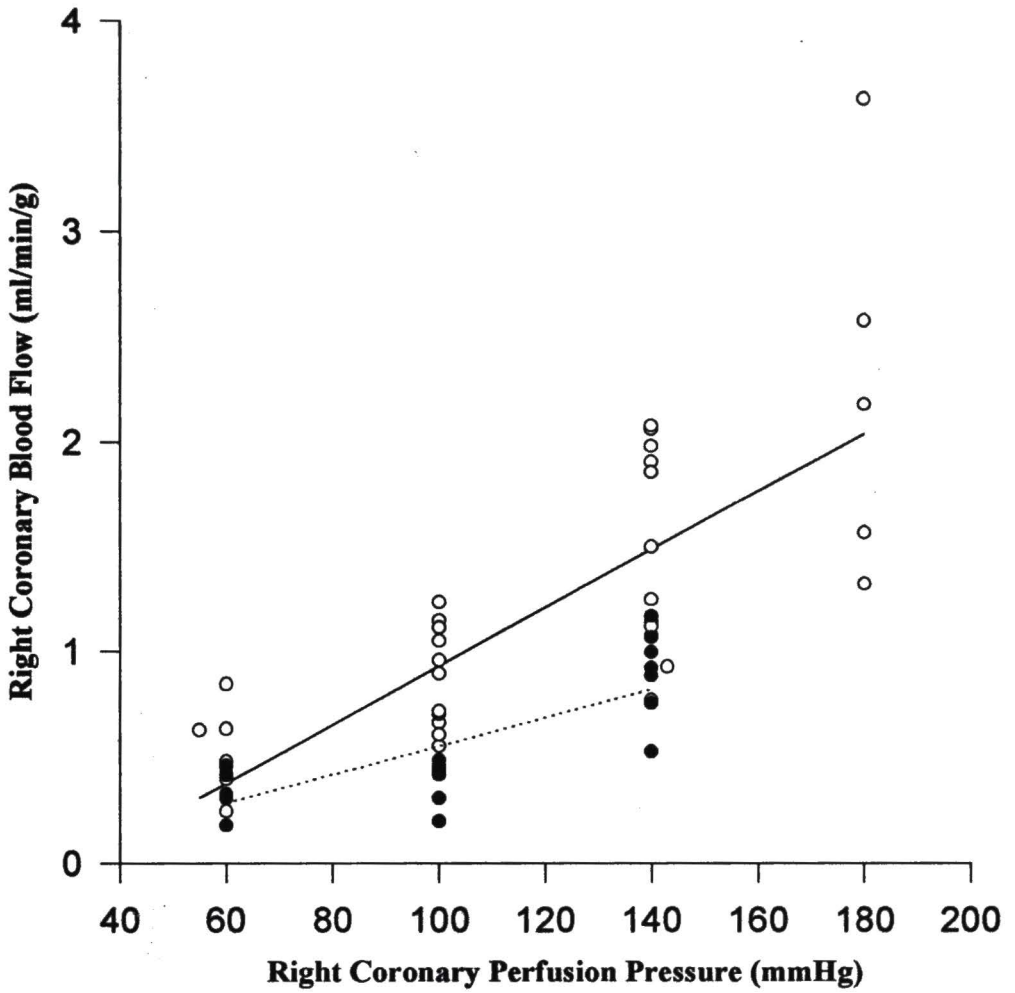

Fig. 2. Relationship between right coronary perfusion pressure (X) and right coronary blood flow (Y) with (n = 7) and without vasopressin (n = 15). Open circles represent right coronary blood flow without vasopressin. Filled circles represent right coronary blood flow with vasopressin. The straight line illustrates the equation: $Y = -0.467 + 0.0137 \bullet X$; $R^2 = 0.610$; $P < 0.0001$. The dotted line illustrates the equation: $Y = -0.12 + 0.00676 \bullet X$.

Myocardial oxygen consumption (MVO_2)

Figure 3 illustrates mean values of MVO_2 without vasopressin at RCP of 60 mmHg, 100 mmHg, and 140 mmHg. MVO_2 data are shown in Table 3. MVO_2 was 4.4 ± 0.6 (ml/min/100 g) at RCP of 100 mmHg. MVO_2 fell 16% as RCP was reduced to 60 mmHg, and MVO_2 increased 16% as RCP was increased to 140 mmHg. Table 4 shows values of MVO_2 for RCP at 60 mmHg prior to vasopressin infusion and for RCP at 100 and 140 mmHg with vasopressin. MVO_2 did not change significantly when RCP was increased from 60 mmHg to 100 mmHg and further to 140 mmHg (Table 4). MVO_2 at RCP of 100 and 140 mmHg with vasopressin (Table 4) was significantly less than that measured at RCP of 100 and 140 mmHg without vasopressin (Table 3).

Blood lactate

Lactate extraction was measured in six dogs at RCP of 60 mmHg, 100 mmHg, and 140 mmHg without vasopressin, and RCP of 100 and 140 mmHg with vasopressin. Values of arterial lactate concentration, venous lactate concentration, and lactate extraction are shown in Table 3 (without vasopressin) and Table 4 (with vasopressin). Lactate release was not evident under any conditions, i.e., RCP was reduced to 60 mmHg, and vasopressin was given through the RC perfusion line at RCP of 100 and 140 mmHg. Without vasopressin, lactate extraction did not change significantly as RCP was increased from 60 to 100 mmHg, but decreased significantly as RCP was increased further to 140 mmHg. Lactate extraction at RCP of 100 mmHg with

vasopressin (Table 4) was not significantly different from that measured at RCP of 100 mmHg without vasopressin (Table 3). When RCP was increased further to 140 mmHg, lactate extraction increased significantly compared to that observed at this pressure without vasopressin (Table 3). With vasopressin, lactate uptake dicreased significantly at RCP of 100 mmHg and increased significantly at RCP of 140 mmHg comparded to that observed at these pressures without vasopressin (Table 3 and 4).

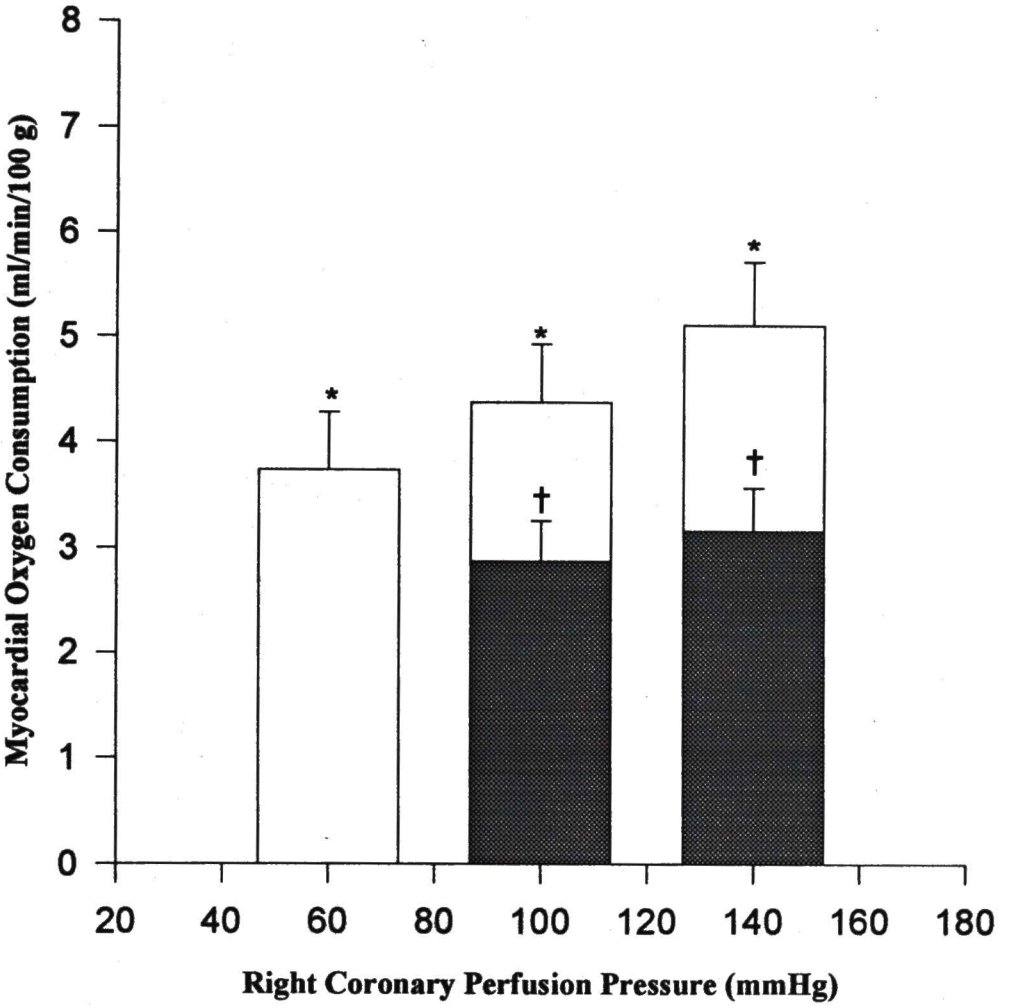

Fig. 3. Myocardial oxygen consumption as a function of right coronary perfusion pressure with (n = 7) and without vasopressin (n = 9). Open bars represent myocardial oxygen consumption without vasopressin. Filled bars represent myocardial oxygen consumption with vasopressin. * $P < 0.05$ vs values at other perfusion pressures; † $P < 0.05$ vs values without vasopressin at constant right coronary perfusion pressure.

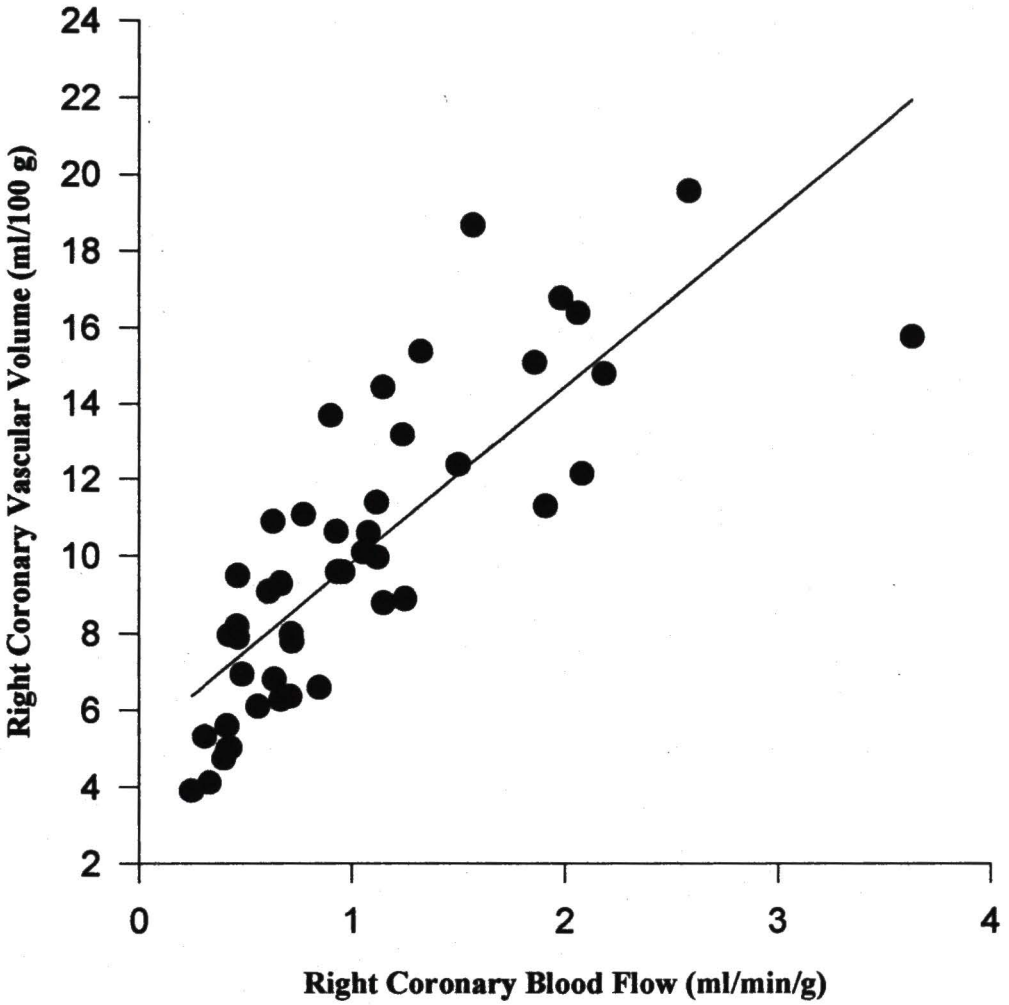

Fig. 4. Relationship between right coronary blood flow (X) and right coronary vascular volume (Y) without vasopressin (n = 15). The straight line illustrates the equation: Y = 4.70 + 4.92 • X; $R^2 = 0.667$; $P < 0.0001$.

CHAPTER IV

DISCUSSION

The important findings of this investigation are 1) pressure-induced changes in coronary blood flow in the canine RV are associated with marked changes in coronary vascular volume; and 2) MVO_2 increases with increases in RCF and RCV induced by coronary perfusion pressure. The results of this investigation were further compared with data from a previous study in which LV coronary circulation was poorly autoregulated in some of the experiments (4) (Figure 5). We found 1) pressure-induced changes in coronary vascular volume in RV are similar to that in LV of hearts with ineffective autoregulation; and 2) RCV is smaller than left coronary vascular volume. Another important finding of this study was that increases in perfusion pressure had no significant effect on MVO_2, when RCF and RCV were kept constant by intracoronary infusion of vasopressin (Figure 3). This is the first report which describes changes in RCV in response to changes in RCP. Also described here for the first time is the effect of RCF and RCV on RV MVO_2.

Relationship between coronary perfusion pressure and MVO_2. Following the recognition of the "Gregg phenomenon" (11), the effects of coronary perfusion pressure on oxygen consumption and cardiac performance have been studied extensively. Arnold and co-workers (2) demonstrated that changes in coronary

perfusion pressure resulted in changes in coronary flow and MVO_2, and they proposed the "garden hose theory" to explain this "Gregg phenomenon." In this theory, increased coronary perfusion pressure causes increased coronary vascular volume, and the resulting lengthening of myocardial fibers enhances myocardial contractile strength, according to the Frank-Starling mechanism, and thus increases oxygen consumption. Farsang et al. (8) found that increased coronary blood flow had no significant effect on MVO_2 at constant perfusion pressure in the isolated fibrillating canine heart and concluded that perfusion pressure rather than coronary blood flow affected oxygen consumption. Farsang et al. suggested that pressure-induced changes in MVO_2 may be attributed to increased myocardial fiber length, although they did not present any evidence which could show changes in the geometry of the heart, i.e., changes in myocardial segment length or changes in intracoronary vascular volume. In agreement with the "garden hose theory", we found that MVO_2 increased as RCP was increased in the absence of vasopressin (Fig. 3). However, these increases in MVO_2 were associated also with increased RCF.

The effects of RCP on RCV. In an early study, Salisbury et al. (20) found a linear relationship between coronary perfusion pressure and coronary vascular volume of isolated canine hearts. They also found a similar relationship between coronary blood flow and coronary vascular volume. Morgenstern et al. (17) also reported that increased coronary perfusion pressure caused a significant increase in intracoronary vascular volume in working, *in situ* canine left ventricle. In addition, they suggested

that pressure-induced changes in intracoronary vascular volume contribute to changes in heart work by altering the geometry of the LV. Their findings support the "garden hose theory", but they did not measure MVO_2. In this investigation, we have shown that coronary vascular volume increased with increased coronary perfusion pressure (Fig.1) and with increased coronary blood flow (Fig. 4) in working, *in situ* canine RV.

Previously, our laboratory (4) studied the effects of coronary perfusion pressure on coronary vascular volume in the canine LV, and demonstrated that pressure-induced changes in left coronary vascular volume and MVO_2 were associated with poor autoregulation. However, LV and RV differ in work performance, coronary blood flow, and oxygen consumption (15), so findings in LV may not be applicable to RV. The pattern of changes in RCV with changes in RCP were similar to these we found in LV of hearts with ineffective autoregulation (Fig. 5). Interestingly, RCV was smaller than reported values of left coronary vascular volume. This difference in left and right coronary vascular volume has not been described previously. The coronary vascular volume we measured is total RCV that includes arteries, microcirculation elements, and veins. A preliminary study in our laboratory has shown no significant difference in the small vascular volume between RV and LV (personal communication from S. Setty). Thus, that differences in large vessel volume, i.e., arteries and veins, between RV and LV must contribute to the difference in total left and right vascular volume.

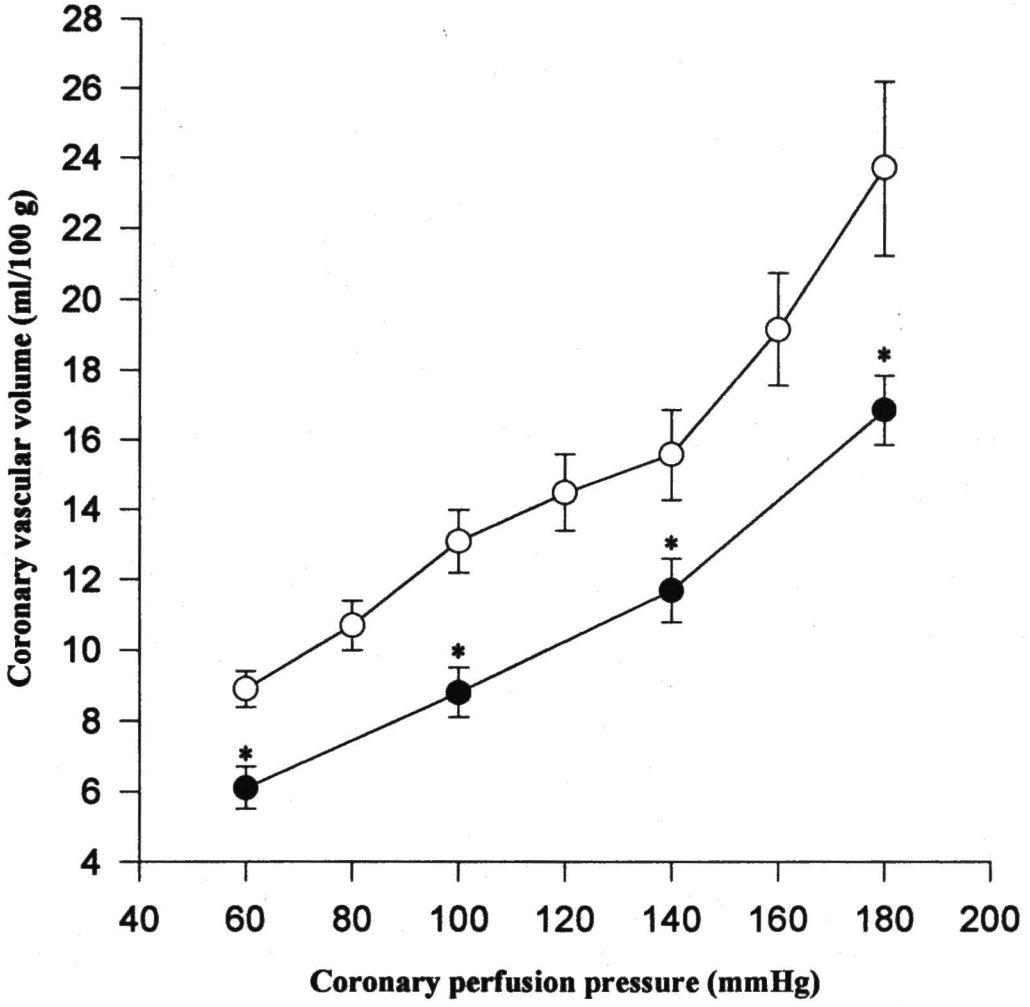

Fig. 5. Comparison between right coronary vascular volume (n = 15) and left coronary vascular volume (n = 12) in the presence of changes in coronary perfusion pressure. Filled circles represent right coronary vascular volume and open circles represent left coronary vascular volume. * $P < 0.05$ vs values of left coronary vascular volume at the same coronary perfusion pressure.

Relationship of RCF and RCV to MVO_2. In a search for a possible explanation for the "Gregg phenomenon", controversial conclusions have been made about its mechanism. In contrast to the findings of Farsang et al., our laboratory (12) studied the effects of increased coronary blood flow with or without increased coronary perfusion pressure on myocardial contractile force and MVO_2 in working, *in situ* canine hearts, and found that myocardial contractile force and MVO_2 of LV increased with increased coronary blood flow even in the absence of changes in coronary perfusion pressure. These data indicate that changes in myocardial contractile force and systolic ventricular stiffness could be caused by coronary blood flow as well as by changes in coronary perfusion pressure. These effects are probably responsible for coronary perfusion related changes in MVO_2 (12). Weisfeldt et al. (22) studied the effects of coronary perfusion pressure on coronary blood flow and MVO_2 in nonworking Langendorff perfused rat hearts. Their results suggest that the increase in coronary blood flow accompanying perfusion pressure is importantly related to the mechanism responsible for the increase in MVO_2 (11).

In contrast, Bache et al. (3) found that increasing coronary blood flow by infusion of adenosine had no significant effect on MVO_2 in unanesthetized dogs. They did not relate their findings to the "Gregg phenomenon". Braunwald and co-workers (5) found that the relationship between coronary blood flow and MVO_2 was affected by changes in hemodynamic factors, i.e. aortic pressure and cardiac output. This might suggest that cannulation of the coronary artery is required to study the relationship

between coronary blood flow and MVO_2, so that coronary blood flow can be varied by changing coronary perfusion pressure while aortic pressure and cardiac output remain constant.

Since coronary blood flow generally changes with coronary perfusion pressure, previous investigations have not been able to differentiate the role between these factors in the Gregg phenomenon. We attempted to resolve this dilemma by using vasopressin to blunt the effect of coronary perfusion pressure on coronary blood flow. Vasopressin is a potent coronary vasoconstrictor and at constant perfusion pressure can reduce coronary blood flow (13). Lamping et al. (14) examined the site of constriction to vasopressin in the coronary microcirculation, and found that vasopressin constricted arterioles less than 90 μm in anesthetized *in situ* working cat hearts. In this study, we were able to keep RCF constant as perfusion pressure was increased from 60 to 100 mmHg by intracoronary infusion of vasopressin. Under this condition, RCV did not change. Nor did MVO_2 change significantly. These results indicate that MVO_2 is more responsive to changes in coronary blood flow or coronary vascular volume than changes in coronary perfusion pressure.

The ability of vasopressin to decrease HR and dP/dt_{max} has been reported by Cartheuser and Komarek (6). They found these effects of vasopressin resulted in decreased MVO_2. By reducing coronary blood flow, vasopressin may cause myocardial ischemia resulting in depressed cardiac performance (13). In this study, we did not find changes in RV performance during infusion of vasopressin when RCP was increased

from 60 mmHg to 100 mmHg. In addition, anaerobic metabolism indicative of myocardial ischemia was not evident in our experimental preparations, since no lactate release was found in our preparations. Thus, the constant MVO_2 we measured in this study was not due to changes in heart performance and myocardial ischemia produced by vasopressin as RCP was increased from 60 to 100 mmHg.

CHAPTER V

CONCLUSIONS

In the working, in situ canine RV, changes in RCP produced corresponding changes in RCF, RCV, and MVO_2. These findings are consistent with Gregg's hypothesis that changes in coronary perfusion pressure cause changes in MVO_2, and are consistent with the idea that changes in coronary vascular volume mediate pressure-induced changes in MVO_2. RCV was smaller than reported values of left coronary vascular volume. Vasopressin was used to blunt pressure-induced changes in RCF. Under this condition, changes in RCP had no significant effect on RCV and MVO_2. This indicates that changes in coronary blood flow or coronary vascular volume is required for changes in MVO_2 caused by changes in coronary perfusion pressure.

REFERENCES

1. **Abel, R. M., and R. L. Reis.** Effects of coronary blood flow and perfusion pressure on left ventricular contractility in dogs. *Circ. Res.* 27: 961-971, 1970.

2. **Arnold, G., F. Kosche, E. Miessner, A. Neitzert, and W. Lochner.** The importance of the perfusion pressure in the coronary arteries for the contractility and the oxygen consumption of the heart. *Pfluegers Arch.* 299: 339-356, 1968.

3. **Bache, R. J., F. R. Cobb, and J. C. Greenfield, JR.** Effects of increased myocardial oxygen consumption on coronary reactive hyperemia in the awake dog. *Circ. Res.* 33: 588-596,1973.

4. **Bai, X.-J., T. Iwamoto, A. G. Williams, JR., W.-L. Fan, and H. F. Downey.** Coronary pressure-flow autoregulation protects myocardium from pressure-induced changes in oxygen consumption. *Am. J. Physiol.* 266 (*Heart Circ. Physiol.* 35): H2359-H2368, 1994.

5. **Braunwald, E., S. J. Sarnoff, R. B. Case, W. N. Stainsby, and G. H. Welch, JR.** Hemodynamic determinants of coronary flow: effect of changes in aortic pressure and cardiac output on the relationship between myocardial oxygen consumption and

coronary flow. *Am. J. Physiol.* 192: 157-163, 1958.

6. **Cartheuser, C. F. and J. Komarek.** Effects of vasopressin on the circulation, myocardial dynamics, and left ventricular oxygen consumption in the anesthetized dog. *Basic Res. Cardiol.* 75: 668-682, 1980.

7. **Chen, S. and M. L. Gregersen.** Determination of body fluid volumes. In: *Physical Techniques in Biological Research,* edited by W. L. Nastuk. New York: Academic, 1962, vol. 4, p. 36-41.

8. **Farsang, G., A. Kerenyi, and L. Takacs.** Regulation of myocardial oxygen consumption by perfusion pressure in isolated fibrillating canine heart. *Pfluegers Arch.* 388: 211-213, 1979.

9. **Feigl, E. O.** Coronary physiology. *Physiol. Rev.* 63: 1-205, 1983.

10. **Gaugl, J. F., A. G. Williams, and H. F. Downey.** Arteriovenous shunt-mediated increase in venous return cause apparent right coronary arterial autoregulation. *Cardiovasc. Res.* 27: 748-752, 1993.

11. **Gregg, D. E.** Effect of coronary perfusion pressure or coronary flow on oxygen

usage of the myocardium. *Circ. Res.* 13: 497-500, 1963.

12. **Iwamoto, T., X.-J. Bai, and H. F. Downey.** Coronary perfusion related changes in myocardial contractile force and systolic ventricular stiffness. *Cardiovasc. Res.* 28: 1331-1336, 1994.

13. **Khayyal, M. A., C. Eng, D. Franzen, J. A. Breall, and E. S. Kirk.** Effects of vasopressin on the coronary circulation: reserve and regulation during ischemia. *Am. J. Physiol.* 248 (*Heart Circ. Physiol.* 17): H516-H522, 1985.

14. **Lamping, K. G., H. Kanatsuka, C. L. Eastham, W. M. Chilian, and M. L. Marcus.** Nonuniform vasomotor responses of the coronary microcirculation to serotonin and vasopressin. *Circ. Res.* 65: 343-351, 1989.

15. **Marcus, M. L.** Differences in the regulation of coronary perfusion to the right and left ventricles. In: *The Coronary Circulation in Health and Disease.* New York: McGraw-Hill Book Co., 1983, p. 337-347.

16. **Miller, W. P., N. Shimamoto, S. H. Nellis, and A. J. Liedtke.** Coronary hyperperfusion and myocardial metabolism in isolated and intact hearts. *Am. J. Physiol.* 253 (*Heart Circ. Physiol.* 22): H1271-H1278),1987.

17. **Morgenstern, C., U. Holjes, G. Arnold, and W. Lochner.** The influence of coronary pressure and coronary flow on intracoronary blood volume and geometry of the left ventricle. *Pflugers Arch.* 340: 101-111, 1973.

18. **Mosher, P., J. Ross, Jr., P. A. McFate, and R. F. Shaw.** Control of coronary blood flow by an autoregulation mechanism. *Circ. Res.* 41: 250-259, 1964.

19. **Murakami, H., S.-J. Kim, and H. F. Downey.** Persistent right coronary flow reserve at low perfusion pressure. *Am. J. Physiol.* 256 (*Heart Circ. Physiol.* 25): H1176-H1184, 1989.

20. **Salisbury, P. F., C. E. Cross, and P. A. Rieben.** Physiological factors influencing coronary blood volume in isolated dog hearts. *Am. J. Physiol.* 200 (3): 633-636, 1961.

21. **Vergroesen, I., M. I. M. Noble, P. A. Wieringa, and J. A, E. Spaan.** Quantification of O_2 consumption and arterial pressure as independent determinants of coronary flow. *Am. J. Physiol.* 252 (*Heart Circ. Physiol.* 21): H545-H553, 1987.

22. **Weisfeldt, M. L. and N. W. Shock.** Effect of perfusion pressure on coronary

flow and oxygen usage of nonworking heart. *Am. J. Physiol.* 218: 95-101,1970.

23. **Yonekura, S., N. Watanabe, and H. F. Downey.** Transmural variation in autoregulation of right ventricular blood flow. *Circ. Res.* 62: 776-781, 1988.

24. **Yonekura, S., N. Watanabe, J. L. Caffrey, J. F. Gaugl, and H. F. Downey.** Mechanism of attenuated pressure-flow autoregulation in right coronary circulation of dogs. *Circ. Res.* 60: 133-141, 1987.