MINIREVIEW

Mechanisms of Oxygen Demand/Supply Balance in the Right Ventricle

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Few studies have investigated factors responsible for the O_2 demand/supply balance in the right ventricle. Resting right coronary blood flow is lower than left coronary blood flow, which is consistent with the lesser work of the right ventricle. Because right and left coronary artery perfusion pressures are identical, right coronary conductance is less than left coronary conductance, but the signal relating this conductance to the lower right ventricular O_2 demand has not been defined. At rest, the left ventricle extracts ~75% of the O_2 delivered by coronary blood flow, whereas right ventricular O_2 extraction is only ~50%. As a result, resting right coronary venous PO_2 is ~30 mm Hg, whereas left coronary venous PO_2 is ~20 mm Hg. Right coronary conductance does not sufficiently restrict flow to force the right ventricle to extract the same percentage of O_2 as the left ventricle. Endogenous nitric oxide impacts the right ventricular O_2 demand/supply balance by increasing the right coronary blood flow at rest and during acute pulmonary hypertension, systemic hypoxia, norepinephrine infusion, and coronary hypoperfusion. The substantial right ventricular O_2 extraction reserve is used preferentially during exercise-induced increases in right ventricular myocardial O_2 consumption. An augmented, sympathetic-mediated vasoconstrictor tone blunts metabolically mediated dilator mechanisms during exercise and forces the right ventricle to mobilize its O_2 extraction reserve, but this tone does not limit resting right coronary flow. During exercise, right coronary vasodilation does not occur until right coronary venous PO_2 decreases to ~20 mm Hg. The mechanism responsible for right coronary vasodilation at low PO_2 has not been delineated. In the poorly autoregulating right coronary circulation, reduced coronary pressure unloads the coronary hydraulic skeleton and reduces right ventricular systolic stiffness. Thus, normal right ventricular external work and O_2 demand/supply balance can be maintained during moderate coronary hypoperfusion. Exp Biol Med 230:507–519, 2005

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In a chapter entitled "Differences in the Regulation of Coronary Perfusion to the Right and Left Ventricles," Marcus (1) noted that:

> ...phasic coronary blood flow, autoregulation, and the effects of sudden increases in ventricular pressure on transmural perfusion are very different in vessels that perfuse the right and left ventricles. These basic differences in the regulation of perfusion to the right and left ventricles will affect the responses of their respective vascular beds to a variety of physiological and pathological stimuli. (pp. 339–340)
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> All too often, these differences are ignored by investigators and clinicians. Discrepancies in the regulation of perfusion to the right and left ventricles deserve much more attention than they have been given in the past. (p. 343)

Although Marcus' caveat was published in 1983, relatively few subsequent investigations have specifically addressed right coronary physiology or interactions between right coronary function and right ventricular function. Such investigations have been limited, to some degree, by technical difficulties in manipulating and measuring right coronary hemodynamic variables and in collecting right coronary venous samples to investigate relationships between mechanisms of right coronary vasoregulation and right ventricular metabolism. These technical difficulties have posed significant challenges for investigations in anesthetized, open-chest animal models (2) and have been

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overcome only recently by our laboratory in the instrumented, conscious canine model (3–8).

Assessing Right Coronary Venous PO_2 and Right Ventricular O_2 Extraction

To study the myocardial O_2 demand/supply balance and assess the role of myocardial PO_2 in regulating coronary blood flow, coronary venous blood must be sampled. In the canine heart, the right coronary artery supplies only the central portion of the right ventricular free wall (9). Thus, measurements of right coronary artery flow specifically reflect flow to the right ventricular myocardium and, if venous blood can be collected from this tissue, right ventricular O_2 extraction and O_2 consumption can be readily determined. For this reason, the canine model is ideal for investigations of right coronary physiology and right ventricular metabolism.

Kusachi *et al.* (10) sampled right and left coronary venous blood from anesthetized, open-chest dog hearts and reported that O_2 extraction was lower in the right ventricle (51%) than in the left ventricle (60%). They also reported that mean right ventricular myocardial O_2 consumption was less than half that of the left ventricle (4.0 compared with 8.6 ml O_2/min/100 g). Similar findings of lower resting right coronary flow and lesser right ventricular myocardial O_2 consumption were reported by Saito *et al.* (11–13) and Takeda *et al.* (14). These findings are not surprising, considering the much lower afterload imposed on the right ventricle. We also measured O_2 extraction by right ventricular myocardium of the anesthetized, open-chest dog heart and examined the effects of altering right coronary perfusion pressure on right ventricular O_2 extraction (15–17). With normal right coronary artery perfusion pressure, right ventricular O_2 extraction was ~45%. The extraction of O_2 fell to ~32% as right coronary pressure was elevated to 120 mm Hg and rose to ~56% as right coronary pressure was reduced to 40 mm Hg.

Whereas studies on anesthetized, open-chest dogs have provided information on right ventricular O_2 extraction and O_2 consumption under various conditions (10–17), there has been concern that anesthesia and the acute effects of extensive open-chest surgery may have produced artifacts. Anesthesia reduces right ventricular O_2 demand (3) and may alter right coronary tone (18), so mechanisms of O_2 demand/supply balance might be affected. For example, the extent and ability to recruit flow and O_2 extraction reserves are most likely different in the conscious state. Clearly, a need existed to extend these studies to the intact right coronary circulation of the conscious animal.

The left coronary circulation drains primarily to the coronary sinus, which can be catheterized in humans and in relatively large, anesthetized, or conscious experimental animals (19, 20). In contrast, samples of right coronary venous blood must be collected from small, superficial veins on the surface of the right ventricle. Owing to their small size and fragility, obtaining blood from these veins is difficult, especially in the conscious state. This problem is most likely responsible for our lesser understanding of right ventricular O_2 balance.

A novel procedure developed in this laboratory has enabled us to collect right coronary venous blood from conscious dogs (4). Briefly, a coronary venous catheter is inserted into one branch of a bifurcated superficial right ventricular vein draining the perfusion territory of the right coronary artery. The side holes of this small diameter catheter are positioned in a stream of flowing blood from the other branch of the bifurcation. We found that PO_2 of blood collected from the right coronary venous catheter decreased during partial constriction of the right coronary artery and rose during the reactive hyperemia after release of the constriction (4). These findings, along with observation of the catheter position at autopsy, demonstrated that the catheter remained in place and provided samples of right coronary venous blood.

It is essential that samples of right coronary venous blood do indeed originate in the right ventricle and not be contaminated by blood from other sources. Two possible sources of contamination are blood retrogradely drawn from the right atrium and blood originating from tissue supplied by arteries other than the right coronary artery. In our initial study, the PO_2 of the sampled blood averaged 27.7 ± 1.0 mm Hg during resting conditions. Although this value is higher than that measured in coronary sinus blood (19, 20), it is consistent with data from anesthetized dogs (15, 17, 21). Furthermore, this value is much less than the PO_2 of mixed venous blood in the right atrium, which indicates little or no contamination of the sample with atrial blood. To further investigate whether there was contamination from right atrial blood, radioactive microspheres were infused iv in three instrumented, conscious dogs and one anesthetized dog (5) while blood samples were collected from the right atrium and the right coronary vein. Because circulating microspheres were trapped in the pulmonary circulation, any radioactivity within the right coronary venous samples would have come from right atrial contamination. Radioactivity detected in the right coronary venous blood samples was less than 0.1% of that in atrial blood. These data demonstrated that right atrial blood was not withdrawn into the venous samples.

The possibility of contamination by blood from sources other than the right coronary artery was explored in an earlier canine study in our laboratory by Murakami *et al.* (16). They infused Evans blue dye (Sigma Chemical, St. Louis, MO) intravenously while perfusing the right coronary artery with dye-free blood from a reservoir that was isolated from the systemic circulation. Blood samples were collected from the systemic circulation and from a right coronary vein with right coronary perfusion pressure reduced to 80 mm Hg and normal systemic arterial pressure. Analysis of optical density of the right coronary venous plasma and that of the systemic plasma indicated that the left coronary contribution

to right coronary venous drainage was 1.2%. Under normal conditions, there would be no disparity between right and left coronary perfusion pressures, so these data show that contamination of right coronary venous samples with blood from other coronary sources would be negligible. This new technique for collecting right coronary venous blood from the conscious dog has been used by our laboratory to examine factors responsible for right ventricular O_2 balance under a number of conditions, as described next.

Resting Right Coronary Blood Flow and Vascular Conductance

As for the left ventricle, right coronary flow is an important determinant of right ventricular O_2 supply. Resting right coronary flow is less than generally reported for left coronary flow (1, 3, 5–8, 10–16, 21–44), and this lower right coronary flow is consistent with the lesser work and myocardial O_2 consumption of the right ventricle (1, 5–8). Because left and right coronary artery perfusion pressures are normally identical, right coronary conductance is much less than left coronary conductance. The mechanism that couples the lower O_2 demand of the right ventricle with lesser conductance of the right coronary circulation is an important physiologic issue and is poorly understood at present.

Consistent with a much lesser right ventricular systolic pressure, right coronary flow, unlike left coronary flow, is not impeded by systolic contraction (1, 26). As a consequence, right coronary flow is sustained throughout the cardiac cycle (23), and the subendocardial region of the right ventricle is not as dependent on diastolic flow (26) as the left ventricular subendocardium (26). However, because significant right coronary perfusion occurs in systole, diastolic right coronary conductance must be correspondingly reduced to lessen excessive right ventricular perfusion.

The lesser resting conductance of the right coronary circulation might be due, at least in part, to accentuated sympathetic-mediated constriction of the right coronary vasculature. However, Zong *et al.* (7) recently demonstrated that this mechanism is not an important determinant of resting right coronary tone because blockade of α-adrenergic receptors with phentolamine produced no significant increases in resting right coronary flow or conductance. This new finding for the right coronary circulation is consistent with prior reports that sympathetic vasoconstrictor tone does not restrict resting left coronary flow (45–48).

Although the lower flow in the right ventricular myocardium is consistent with its lower O_2 demand, the metabolic regulation of right coronary flow has not been delineated. Furthermore, there are interesting differences in the metabolic regulation of the right and left coronary flow at rest. For example, right coronary venous PO_2 is appreciably higher than left coronary venous PO_2 at rest (4–8, 46, 49), so metabolic control mechanisms must not be regulating flow to achieve the same myocardial PO_2, assuming that coronary venous PO_2 is a valid index of tissue PO_2. In any case, the lower resting right coronary conductance does not sufficiently restrict flow to force the right ventricle to extract the same percentage of O_2 as the left ventricle.

Because right coronary venous PO_2 is higher than for the left ventricle and right coronary conductance is lower than for the left ventricle, it is tempting to suggest that coronary conductance is directly or indirectly controlled by tissue PO_2. However, this seems to not be the case for the right coronary circulation, at least at high PO_2 values. Experiments in our laboratory demonstrated that right coronary venous PO_2 can fall from 30 mm Hg to 20 mm Hg with no change in right coronary conductance as the right coronary O_2 extraction reserve is mobilized during exercise (5). However, when right coronary venous PO_2 reached ~20 mm Hg, further declines were closely associated with increased right coronary conductance. In this lower range of PO_2 values, both right and left coronary conductances were similarly sensitive to changes in venous PO_2 (Fig. 1; Refs. 5–7, 20, 46, 50).

Because resting conductance is less in the right coronary circulation than in the left coronary circulation, arteriolar constriction would be greater, which would result in a greater flow velocity in these regulatory vessels. Therefore, greater vascular shear stress–mediated release of nitric oxide would be expected in the right coronary circulation. Zong *et al.* (6) and Martinez *et al.* (8) reported that the inhibition of nitric oxide synthesis reduced not only resting right coronary flow in conscious dogs, but also the regression intercept when right coronary conductance and right coronary venous PO_2 were plotted as functions of right ventricular myocardial O_2 consumption. These findings are consistent with results of earlier studies in anesthetized and conscious animals showing that the inhibition of nitric oxide synthesis reduced resting right coronary blood flow (21, 42, 51–54). In contrast, previous investigations reported little or no effect of nitric oxide synthesis inhibition on left coronary flow (42, 49, 54–59). Thus, it appears that nitric oxide is a significant factor in preventing right coronary conductance at rest from falling sufficiently to force right ventricular O_2 extraction to be as high as that of the left ventricle.

Contributions of Flow Reserve and O_2 Extraction Reserve to Right Ventricular O_2 Supply When Right Ventricular O_2 Consumption Is Increased

Myocardial O_2 demand and supply must be balanced to avoid ischemia or excessive perfusion. Myocardial O_2 demand is determined primarily by (i) heart rate; (ii) afterload; and (iii) contractility. To a lesser extent, preload and coronary perfusion pressure also influence myocardial O_2 demand. As long as myocardial O_2 supply is adequate and ischemia is avoided, myocardial O_2 demand is reflected by the rate of myocardial O_2 consumption. There are two

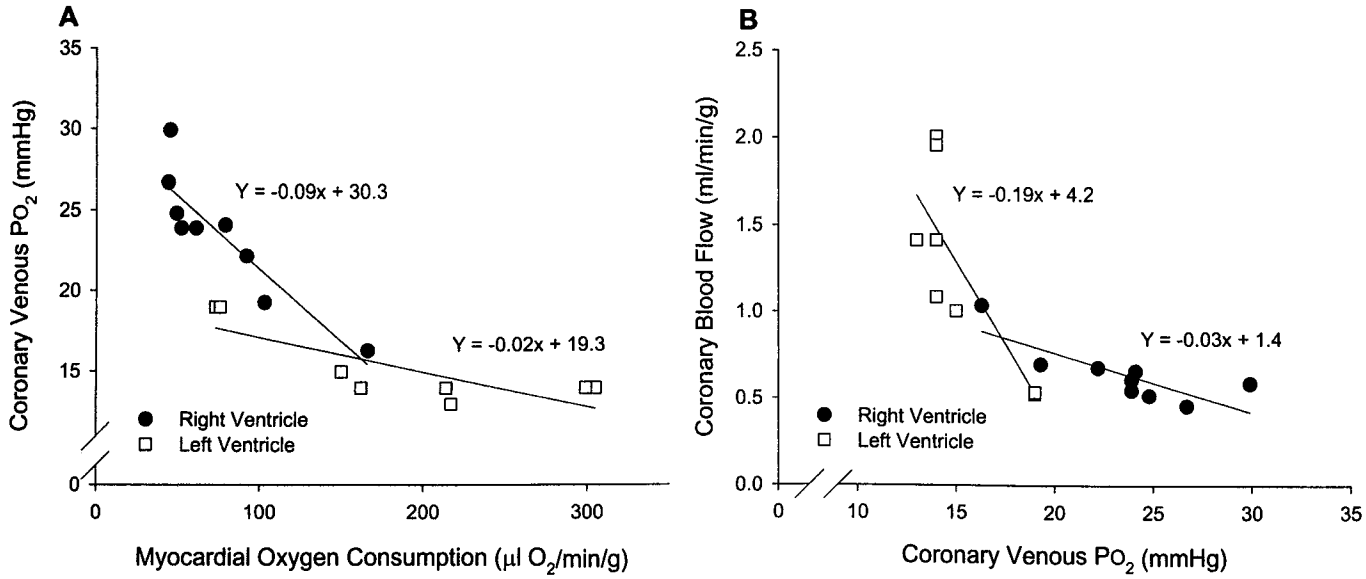

Figure 1. Relationships between myocardial oxygen consumption, coronary blood flow, and coronary venous oxygen tension during exercise for canine right and left ventricles. (A) Oxygen consumption is lower in the right ventricle than in the left, and this is associated with higher coronary venous oxygen tensions. (B) As right ventricular oxygen consumption increases during exercise, the initial response is increased oxygen extraction (i.e., decreased venous oxygen tension) with little increase in flow. However, there is an inflection point between oxygen tensions of 15 mm Hg and 20 mm Hg at which flow increases sharply with decreasing venous oxygen tension. Resting left ventricular venous oxygen tension is ~18 mm Hg and sits near this inflection point. These results suggest that the left and right ventricles may share common flow control mechanisms and that a powerful vasodilator mechanism is recruited when coronary venous oxygen tension falls below 15 mm Hg–20 mm Hg. (Reproduced from Ref. 20 with permission from the American Physiological Society.)

options to balance increasing myocardial demand for O_2. One is to use the coronary flow reserve; the other is to make use of the myocardial O_2 extraction reserve. Coronary flow reserve is the difference between maximal possible flow and the existing flow at a given perfusion pressure. Myocardial O_2 extraction reserve is the difference between 100% and the existing percentage of O_2 extraction. Thus, myocardial O_2 consumption, coronary blood flow, and O_2 extraction are the key variables used to evaluate O_2 demand/supply relationships.

Exercise increases myocardial O_2 demand, and the effect of exercise on right coronary blood flow has been studied in several animal species (22, 30, 37, 42). In dogs, Ball *et al.* (22) found that myocardial blood flow in the right ventricle increased linearly with heart rate during graded treadmill exercise and remained uniformly distributed across the right ventricular free wall. Bauman *et al.* (38) also examined exercise-induced increases in canine right coronary flow and found similar left and right coronary flow reserves during exercise. In ponies, Manohar (30) and Parks and Manohar (28) found that maximal exercise produced large increases in right coronary blood flow that were uniformly distributed across the right ventricular free wall. As a percentage, the increase in right coronary flow (921%) exceeded the increase in left coronary flow (419%), but these values largely reflected the lesser resting right coronary flow (30). At maximal exercise, flow values were similar in right and left ventricular free walls. Similar findings were later reported in horses (37). In swine, Duncker *et al.* (42) also found that exercise produced a greater percentage increase in right coronary blood flow (307%) than in left coronary blood flow (172%) which, as in ponies, reflected a lesser resting right coronary flow as well as a slightly larger flow during exercise.

In ponies, horses, and swine, exercise causes large increases in pulmonary artery pressure (30, 37, 42), which elevates right ventricular work and requirements for right coronary blood flow (24, 25). In contrast, the effects of exercise on human and canine pulmonary artery and right ventricular systolic pressures are much less pronounced (5, 60, 61). None of the earlier studies of right coronary blood flow during exercise sampled right coronary venous blood to compute right ventricular myocardial O_2 consumption, so these studies could not relate changes in right coronary flow and conductance to changes in right ventricular myocardial O_2 consumption. Also, these earlier studies could not determine the relative contributions of increased right coronary blood flow and right ventricular O_2 extraction in meeting elevated right ventricular O_2 requirements during exercise.

Under conscious resting conditions, the left ventricle extracts ~75% of the O_2 delivered by coronary arterial blood, so left ventricular O_2 extraction reserve is quite limited (20, 62, 63). Thus, increases in left ventricular O_2 demand, as occur during exercise, must be met primarily by increasing left coronary flow (20, 22, 58, 59, 62–66). With both a large flow reserve and a large O_2 extraction reserve, the right ventricle has two options to increase its O_2 supply when O_2 demand increases. Hart *et al.* (5) measured, for the first time, right ventricular myocardial O_2 consumption and

its determinants, right ventricular O_2 extraction, and right coronary flow during exercise. They then evaluated the respective roles of the right coronary flow reserve and the right ventricular O_2 extraction reserve in balancing right ventricular O_2 demand and supply. Initially, the right ventricular O_2 extraction reserve was preferentially used (Fig. 2). During the first level of exercise (4 mi/hr), the increase in O_2 extraction provided 82% of the incremental increase in O_2 supply. An increase in right coronary blood flow provided only 18%. Right coronary conductance did not increase until the right ventricular O_2 extraction had increased to ~75%. In this process, right coronary venous PO_2 decreased to ~20 mm Hg without concomitant right coronary vasodilation.

Interestingly, left coronary venous PO_2 is ~20 mm Hg at rest (20, 58, 62, 63). In contrast to findings in the right ventricle, increases in left ventricular myocardial O_2 consumption during exercise produce decreases in left coronary venous PO_2 (Fig. 1) and, concomitantly, large increases in coronary blood flow (Fig. 3; Refs. 20, 22, 58, 59, 62–66). The fact that conductance increases in both right and left coronary circulations when coronary venous PO_2 falls below 20 mm Hg suggests that this is a critical value for the activation of a powerful vasodilator mechanism (Fig. 1). Despite much research, mostly applied to the left coronary circulation, this mechanism has not been delineated.

When right ventricular myocardial O_2 consumption is

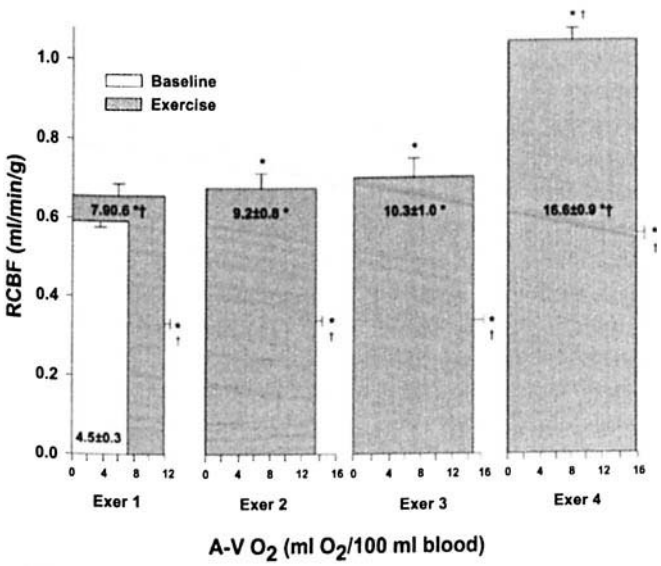

Figure 2. Right ventricular oxygen supply and consumption at rest and during exercise. The area within each rectangle is right ventricular myocardial oxygen consumption (MVO_2; ml $O_2 \cdot min^{-1} \cdot 100$ g $tissue^{-1}$) calculated from the product of arteriovenous O_2 content difference ($A\text{-}V\Delta O_2$; x axis) multiplied by the normalized right coronary blood flow (RCBF; y axis). The MVO_2 values for each condition are shown within the respective rectangle. Exercise data are shown by shaded rectangles and resting data are shown by the white area within the exercise 1 rectangle. *, different from resting baseline condition ($P < 0.05$). †, different from prior, less strenuous condition ($P < 0.05$). (Reproduced from Ref. 5 with permission from the American Physiological Society.)

increased by acute pulmonary hypertension, right coronary flow increases as myocardial O_2 consumption is elevated, with no apparent venous PO_2 threshold for right coronary dilation (6, 27). Zong *et al.* (6) examined the relative contributions of right coronary flow and right ventricular O_2 extraction required to sustain increased right ventricular myocardial O_2 consumption during pulmonary hypertension in conscious dogs. In this study, right ventricular myocardial O_2 consumption increased 39% as pulmonary artery pressure was elevated to ~50 mm Hg, and right coronary blood flow increased 33%. Because aortic pressure was unchanged during pulmonary hypertension, the increase in right coronary flow resulted from dilation of the right coronary resistance vessels. This increase in right coronary flow provided 82% of the increase in right ventricular myocardial O_2 consumption, and little use was made of the right ventricular O_2 extraction reserve under this condition.

The mechanism responsible for increased right coronary flow during pulmonary hypertension was further explored by analysis of O_2 supply variables as functions of right ventricular myocardial O_2 consumption before and after nitric oxide synthesis blockade with N^{ω}-nitro-L-arginine. After nitric oxide synthesis blockade, the right coronary flow and conductance responses to changes in right ventricular myocardial O_2 consumption were 21% and 50% less, respectively. This attenuated right coronary flow response to pulmonary hypertension forced the right ventricle to use its O_2 extraction reserve, as reflected by the reductions in right coronary venous PO_2 at any measured right ventricular myocardial O_2 consumption. Thus, nitric oxide is required for the right coronary hyperemic response to acute pulmonary hypertension, as well as for regulating resting right coronary blood flow.

To reconcile the different findings of relative contributions of right coronary flow and O_2 extraction to right ventricular O_2 supply during exercise and pulmonary hypertension, Zong *et al.* (6, 7) suggested that an augmented, sympathetic-mediated vasoconstrictor tone blunts metabolically mediated dilator mechanisms during exercise and forces the right ventricle to mobilize its O_2 extraction reserve. During acute pulmonary hypertension experiments, arterial pressure did not fall (6). Therefore, in the absence of an error signal, it seems unlikely that sympathetic-mediated vasoconstrictor tone was increased.

To further investigate control of right coronary blood flow during exercise, Zong *et al.* (7) examined right ventricular O_2 balance during graded treadmill exercise before and during α-adrenergic blockade with phentolamine. During exercise, α-adrenergic blockade increased right coronary flow and conductance responses to increased right ventricular myocardial O_2 consumption by 25% and 60%, respectively. Before α-adrenergic blockade, hyperemia provided 39%–66% of the additional O_2 consumed by the right ventricle during graded exercise. After α-adrenergic blockade, hyperemia contributed 74%–85%. In contrast, smaller increases in left coronary flow have been

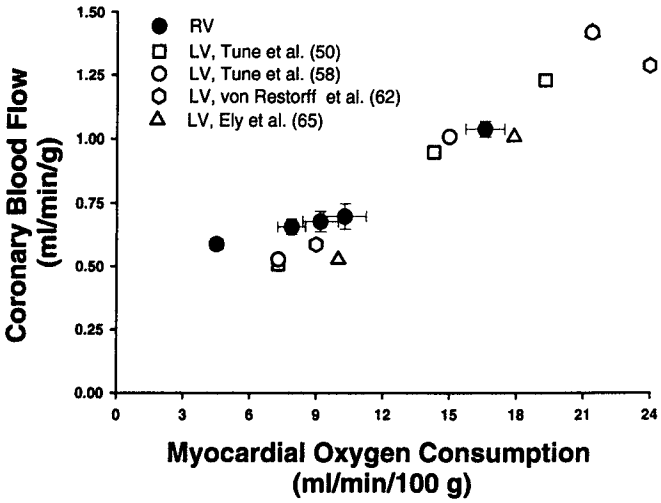

Figure 3. Coronary blood flow is plotted as a function of MVO_2. Filled circles show right ventricular data from this investigation. Open symbols show comparable, published left ventricular data. (Reproduced from Ref. 5 with permission from the American Physiological Society.)

reported by Gorman *et al.* (22%; Ref. 46), Heyndrickx *et al.* (14%; Ref. 48), Huang and Feigl (6%; Ref. 67), Strader *et al.* (21%; Ref. 68), and Bache *et al.* (16%; Ref. 69).

The impact of exercise-induced sympathetic vasoconstriction on O_2 balance in the right and left coronary circulations can be compared by plotting right and left coronary venous PO_2 as functions of myocardial O_2 consumption (7). Figure 4A shows that the right coronary vasodilation caused by α-adrenergic blockade significantly elevated venous PO_2 at any exercise-induced increase in right ventricular O_2 consumption. This effect of α-adrenergic blockade on venous PO_2 was much less in the left coronary circulation (Fig. 4B). To further investigate the role of adrenergic mechanisms in regulating right coronary flow, additional experiments were conducted on anesthetized, open-chest dogs with constant right coronary perfusion pressure and β-adrenergic blockade. The right coronary flow response to intracoronary norepinephrine was shifted to the left compared with that measured in the left coronary circulation, which is consistent with observations in the conscious, exercising dogs (7). Thus, it is evident that during exercise, physiologic modulation of coronary conductance by sympathetic vasoconstrictor tone and its effect on O_2 delivery by the coronary circulation is more pronounced in the right ventricle. However, right ventricular O_2 balance can still be maintained by using the large right ventricular O_2 extraction reserve.

During systemic hypoxia, right ventricular O_2 consumption increases due to elevated heart rate and right ventricular systolic pressure and contractility, which results from increased sympathetic activation. Hypoxia-induced pulmonary vasoconstriction also contributes to the rise in right ventricular systolic pressure. However, in the face of this increased right ventricular O_2 consumption, arterial O_2 content falls during hypoxia. Martinez *et al.* (8) recently reported that increases in right ventricular O_2 demand during graded hypoxia are met by increased right coronary blood flow with no increase in O_2 extraction. They also demonstrated that nitric oxide is an important factor in this hypoxia-induced right coronary vasodilation (8). However, when nitric oxide synthesis was blocked and the hypoxia-induced coronary hyperemia was blunted, the large right ventricular O_2 extraction reserve was mobilized to compensate for reduced vasodilation and right ventricular ischemia was avoided (8).

Besides the role of nitric oxide in regulating right coronary blood flow under various conditions, the effect of nitric oxide on right ventricular metabolism was also investigated (21, 43, 44). Setty *et al.* (43) demonstrated in anesthetized dogs that nitric oxide has a depressive effect on right ventricular O_2 demand when changes in right coronary flow are avoided by maximal dilation with adenosine. During norepinephrine-induced increases in right ventricular mechanical performance and right ventricular O_2 consumption, nitric oxide acts to lessen myocardial O_2 demand and, thus, contributes to the right ventricular O_2 demand/supply balance by increasing right ventricular O_2 utilization efficiency (21). In another study, Setty *et al.* (44) found that nitric oxide improved right ventricular O_2 utilization efficiency in hypoperfused myocardium.

Transmural Distribution of Right Coronary Blood Flow

At rest and during exercise, right coronary blood flow is preferentially distributed to the right ventricular subendocardium (7, 26, 27, 31, 70), as has been noted in the left ventricle (7, 26, 67). Huang and Feigl (67) reported that α-adrenergic blockade in the left circumflex region of the left ventricle decreased the ratio of subendocardial to subepicardial flow during exercise. They concluded that enhanced α-adrenergic coronary vasoconstriction is beneficial by redistributing left coronary flow toward the subendocardium, the region of the left ventricular wall most vulnerable to underperfusion. Morita *et al.* (71) demonstrated that α-adrenergic–mediated left coronary vasoconstriction reduced systolic retrograde coronary flow. Thus, reduction of to-and-fro flow oscillations in arterial vessels that penetrate the left ventricular wall might result in more flow to the subendocardium during exercise. However, in anesthetized dogs, Baumgart *et al.* (72) could detect this effect only when the coronary vasculature had been previously dilated maximally and the cardiac sympathetic nerves were stimulated. Also, Dodd-o and Gwirtz (73) reported that α-adrenergic coronary vasoconstriction does not affect left ventricular transmural blood flow distribution during exercise.

Whether sympathetic vasoconstriction is important for maintaining flow to the subendocardium of the right ventricle was tested by Zong *et al.* (7). They concluded that adequate right ventricular subendocardial flow is not

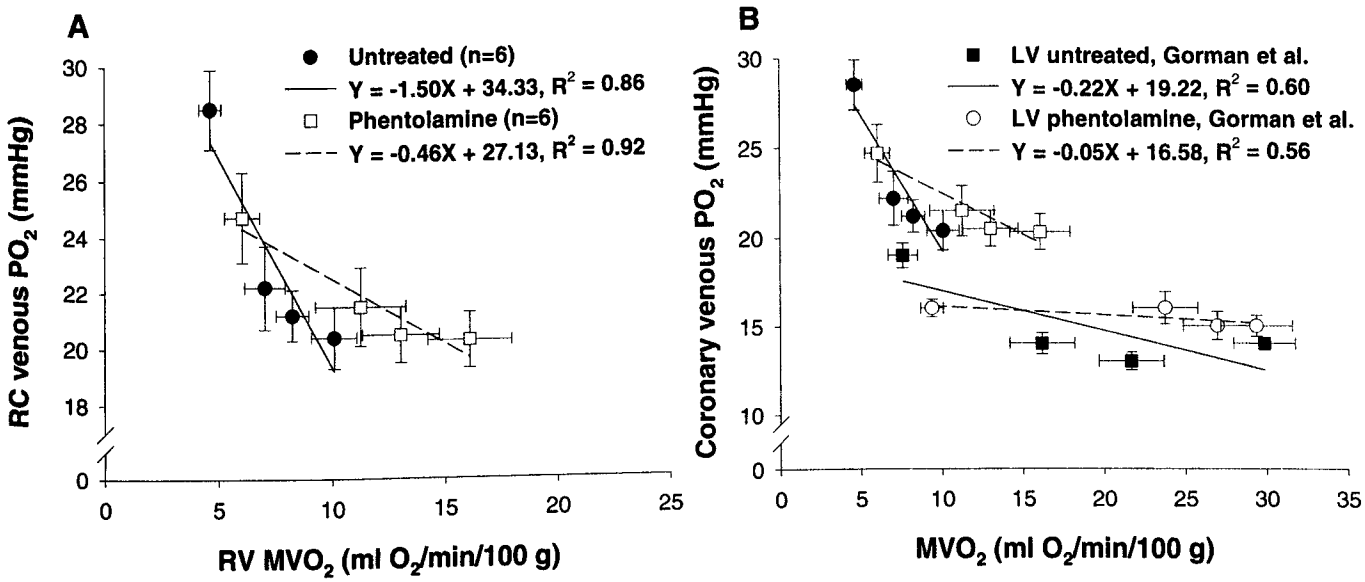

Figure 4. (Panel A) Right coronary venous PO_2 is plotted as a function of right ventricular MVO_2 at rest and during graded treadmill exercise for the untreated condition, after α-adrenergic blockade (phentolamine 1 mg/kg iv; $n = 6$). (Panel B) Effects of α-adrenergic blockade on right and left coronary venous PO_2 as functions of MVO_2 are compared. In panel B, right coronary venous PO_2 is replotted as a function of right ventricular MVO_2 (same symbols as in panel A, but with a change of scale) at rest and during graded treadmill exercise before and after α-adrenergic blockade. Also plotted is left coronary venous PO_2 as a function of left ventricular MVO_2 at rest and during graded treadmill exercise before and after α-adrenergic blockade with phentolamine, as reported by Gorman *et al.* (Ref. 46; data are replotted with permission from Ref. 46). In the untreated state, the decline in the relationship between venous PO_2 and MVO_2 was significantly greater for the right ventricle. Phentolamine made the slope of this relationship significantly less negative for both ventricles. (Reproduced from Ref. 7 with permission from the Society for Experimental Biology and Medicine.)

dependent on sympathetic vasoconstrictor tone because α-adrenergic blockade did not alter the transmural distribution of right coronary blood flow either at rest or during exercise (7). Because the right ventricular wall is much thinner than the left ventricular wall, and the right coronary circulation is subjected to lesser myocardial tissue pressures than the left coronary circulation, to-and-fro flow oscillations of right coronary flow would likely be minimal, so vasoconstrictor tone might not be required to direct adequate blood flow to the right ventricular subendocardium.

In the left ventricular free wall, flow to subendocardium is reduced to a greater extent than is flow to subepicardium during severe coronary hypotension (74–77), while the coronary flow reserve in that region also falls (77). In contrast to the left coronary circulation, as right coronary artery perfusion pressure was decreased from 100 mm Hg to 40 mm Hg, subepicardial and subendocardial flows were similarly reduced (31). This finding is consistent with differences in the left and right coronary artery phasic flow patterns (1, 23) because right ventricular subendocardial perfusion is much less dependent on diastolic flow.

Right Coronary Autoregulation

Murray and Vatner (78) reported that a 34% increase in mean aortic pressure due to aortic constriction in normal conscious dogs was accompanied by a 55% increase in right coronary blood flow. This finding suggests that the right coronary circulation poorly autoregulates its flow (i.e., it lacks the capability of maintaining constant flow in the face of changing right coronary artery perfusion pressure). Likewise, Urabe *et al.* (29) reported a linear decline in right coronary flow as perfusion pressure was reduced from 125 mm Hg to 25 mm Hg. Subsequent studies in our laboratory confirmed poor autoregulatory ability of the right coronary circulation (3, 15, 16, 31, 36).

The absence of effective autoregulation in the right coronary circulation contrasts markedly with the potent autoregulation often found in the left coronary circulation (15, 77, 79–86). Most studies of coronary autoregulation have been conducted in anesthetized dogs. However, Bian *et al.* (3) evaluated right coronary autoregulation in conscious dogs that were chronically instrumented to measure right coronary flow and right coronary pressure as a hydraulic occluder on the right coronary artery was inflated. These dogs were then anesthetized and right coronary autoregulation was again assessed. In the conscious state, right coronary autoregulatory closed loop gain (G_c) was 0.59–0.27 ($G_c = 1$ if changes in pressure have no effect on flow) as right coronary pressure was reduced from 100 mm Hg to 40 mm Hg. In the anesthetized state, G_c was not significantly less than in the conscious state at right coronary pressure >50 mm Hg, so previously reported poor right coronary autoregulation was not an artifact due to anesthesia.

In contrast to the reports of absence or weak autoregulation by the right coronary artery as previously described, Guth *et al.* (34) reported a marked autoregulatory capacity within the right coronary artery perfusion territory of anesthetized swine. In this study, the pressure-flow

relationship of the right ventricle showed nearly perfect autoregulation down to a right coronary pressure of 30 mm Hg, with a significant decrease in blood flow observed only at 20 mm Hg. Regional contractile function of the right ventricle was well maintained until right coronary pressure was reduced below 30 mm Hg. Interestingly, autoregulation was poor in the right atrium.

The potent right coronary autoregulation observed by Guth *et al.* (34) in swine may reflect a species difference. Another explanation for this potent right coronary autoregulation is elevated sympathetic stimulation of the right coronary circulation. In their experiments, the right coronary artery was perfused by an extracorporeal circuit that withdrew blood from a carotid artery. The other carotid artery was also catheterized to measure arterial blood pressure. Bilateral ligation of the carotid arteries would have unloaded the carotid baroreceptors, resulting in a reflex increase in sympathetic drive to the right ventricle (2). This may have enhanced baseline right coronary vasoconstriction in this animal model and blunted the potency of the metabolic vasodilators released under conditions of reduced right coronary perfusion pressure. Interestingly, an earlier study by Jones *et al.* (87) showed that sympathetic-mediated coronary vasoconstriction increased the efficiency of left coronary blood flow autoregulation. Increased sympathetic activity may have also helped sustain right ventricular contractile function as perfusion pressure was reduced.

Tani *et al.* (33) used a canine model in which the right and left circumflex coronary arteries were perfused from a single pressure reservoir. They also found significant autoregulatory capacity in the right coronary circulation, and the pressure at the lower end of the autoregulatory range was lower in the right than in the left circumflex coronary artery. However, different size cannulae were likely required to perfuse the left and right coronary circulations. This factor and the differences in left and right coronary artery flows would have made it impossible for a common reservoir to simultaneously perfuse these arteries at identical pressures. If more pressure were dissipated in a smaller diameter right coronary cannula, any change in the reservoir pressure would have altered right coronary perfusion pressure less than left coronary perfusion pressure. Under these circumstances, right coronary flow would have changed less than left coronary flow, leading the investigators to conclude that right coronary autoregulatory capability exceeded left coronary autoregulatory capability.

Smolich *et al.* (32, 35) reduced aortic pressure and, thus, right coronary artery perfusion pressure, with a large arteriovenous shunt and found potent right coronary autoregulation. This reduction in systemic arterial pressure would have activated the baroreflex, which may have enhanced right coronary autoregulation as in the experiments of Guth *et al.* (34). Furthermore, opening an arteriovenous shunt increases both right ventricular venous return and right ventricular O_2 demand. Thus, when right coronary perfusion pressure was reduced by opening the shunt, an increase in right ventricular myocardial O_2 consumption would sustain right coronary flow and make right coronary autoregulation appear to be potent. This was confirmed by Gaugl *et al.* (36) who observed augmented right ventricular myocardial O_2 consumption at lower right coronary perfusion pressure when an arteriovenous shunt was opened. In the same dogs, selective changes in right coronary perfusion pressure produced corresponding changes in coronary blood flow (i.e., right coronary autoregulation was ineffective).

As previously mentioned, implicit in the definition of autoregulation is the assumption that changes in coronary perfusion pressure do not produce changes in O_2 demand. For the right coronary circulation, this prerequisite of constant myocardial O_2 consumption was absent over the entire range of pressures (i.e., 40 mm Hg–160 mm Hg) examined by Yonekura *et al.* (15). Furthermore, when autoregulation was abolished in the maximally dilated right coronary circulation, graded increases in coronary perfusion pressure increased both right coronary blood flow and right ventricular myocardial O_2 consumption (43). Because changes in perfusion pressure have a marked effect on right ventricular myocardial O_2 consumption (15, 16, 43), the corresponding changes in right coronary flow may reflect appropriate metabolic autoregulation, although pressure-flow autoregulation is attenuated. In fact, when the change in right ventricular myocardial O_2 consumption was taken into account, a "corrected" right coronary autoregulatory gain could be computed, which agreed well with left coronary autoregulatory gain (15). In contrast, left coronary circulations with potent autoregulation had essentially constant myocardial O_2 consumption as left coronary perfusion pressure was varied (83, 85, 86).

Right Ventricular Systolic Stiffness and Right Ventricular Function

The tendency for coronary pressure to independently affect ventricular myocardial O_2 consumption was first noted by Gregg (88, 89) and is known as the Gregg phenomenon. The cause of the pronounced Gregg phenomenon in the right ventricle has not been delineated. We have argued that ventricular systolic stiffness varies with coronary vascular volume and that this affects myocardial O_2 consumption in hearts with poorly autoregulating coronary circulations (86, 90). The greater sensitivity of right ventricular myocardial O_2 consumption to altered perfusion pressure probably results from more readily distensible vessels exposed to lesser intramural pressures of the right ventricular free wall (1). Furthermore, the pressure-induced increase in O_2 demand may be more readily apparent in the right ventricle because of its lower resting O_2 consumption.

Systolic stiffness is an important determinant of ventricular internal work, so changes in systolic stiffness affect the internal to external work ratio and impact on

ventricular O_2 utilization efficiency (17, 86, 91, 92). Systolic stiffness can be estimated from the ratio of isometric force (ΔF) and nearby segment shortening (ΔSL) during ventricular ejection (39, 93). Bian and Downey (39) estimated changes in systolic ventricular stiffness during decreased right coronary pressure in intact, ejecting canine hearts. The ΔF decreased as right coronary pressure was decreased from baseline, although the ΔSL was unchanged. Thus, right ventricular systolic stiffness ($\Delta F/\Delta SL$) fell. This may account for the remarkable ability of the right ventricle to maintain external work and cytosolic energetics in the face of moderately reduced coronary blood flow and also reduced right ventricular myocardial O_2 consumption (17). In contrast, there is a tight relationship between left coronary flow and left ventricular mechanical function as left coronary flow is reduced (92, 94, 95).

Reduced systolic stiffness at low coronary perfusion pressure would improve the ratio of external to total work. This would decrease myocardial O_2 demand as O_2 supply is reduced, so the ventricular O_2 demand/supply balance could be maintained. Maintenance of this balance was evident from the absence of lactate production (39, 40, 44). We have observed marked changes in right coronary vascular volume that correlated with right ventricular myocardial O_2 consumption (96), as we have reported for left coronary circulations with impaired autoregulation (86). Thus, we propose that in the poorly autoregulating right coronary circulation, reduced coronary pressure unloads the coronary hydraulic skeleton and reduces right ventricular systolic stiffness.

A comparison of the data from both ventricles shows that right ventricular systolic stiffness is much less than left ventricular stiffness (39, 90), as is consistent with the thinner right ventricular wall. Because baseline right ventricular systolic stiffness is so low, changes in coronary pressure produce proportionally greater changes in right ventricular stiffness compared with the left ventricle. This may explain why changes in coronary perfusion pressure produce more marked changes in myocardial O_2 consumption in the right ventricle than in the left ventricle.

Left ventricular mechanical function is very sensitive to reductions in left coronary blood flow (94, 95). However, global right ventricular function is much less sensitive to changes in right coronary flow. Because the canine right coronary artery does not supply the interventricular septum (97), it is not surprising that complete occlusion of the right coronary artery has been reported to have little effect on right ventricular systolic pressure of dogs (98). However, in swine, as in humans, the right coronary artery supplies portions of the left and right ventricles (1). Thus, proximal right coronary artery occlusion will have a greater effect on cardiac function in these species. Clearly, evaluation of the relationship between right coronary flow and right ventricular function relation requires direct assessment of function in the right ventricular perfusion territory of the right coronary artery, as by measuring regional right ventricular segment shortening.

Bian *et al.* (3) and Bian and Downey (39) implanted a pair of piezoelectric crystals in the midmyocardium of the right coronary artery perfusion territory to measure myocardial segment lengths. They found that right ventricular function was unchanged until right coronary pressure was reduced to <50 mm Hg in both conscious and anesthetized dogs (Fig. 5). Consistent with ineffective right coronary autoregulation, right coronary flow fell with right coronary pressure. However, right ventricular function did not fall until right coronary flow fell by ~34% in conscious dogs and ~56% in anesthetized dogs. Because the right ventricle has much greater O_2 extraction reserve compared with the left ventricle (5–8, 10, 13, 14, 16, 49, 58, 62, 63), it is tempting to attribute the maintenance of right ventricular function with reduced flow to mobilization of this O_2 extraction reserve. However, we previously found that right ventricular O_2 extraction increased only from 44% to 55% as right coronary pressure was reduced from 80 mm Hg to 40 mm Hg (16), although right ventricular myocardial O_2 consumption significantly fell. Faced with a moderate decrease in right coronary pressure and a corresponding decrease in right coronary flow, the right ventricle decreases its O_2 demand with little or no decrement in right ventricular function. This theory is further supported by another report from our laboratory that right ventricular function and high-energy phosphates were well maintained as right coronary pressure was reduced to 60 mm Hg, although right coronary flow fell 45% (17). These findings are consistent with our view that ventricular systolic stiffness decreases as coronary pressure is reduced and that this reduction in internal cardiac work permits maintenance of normal cardiac external work and cytosolic energetics during moderate coronary hypoperfusion (39, 90, 99).

In a recent, further study of right coronary hypoperfusion in anesthetized dogs, Setty *et al.* (44) found that right ventricular function, as indexed by the triple product (i.e., heart rate × right ventricular peak systolic pressure × right ventricular dP/dt_{max}), was not significantly altered when right coronary perfusion pressure was reduced from 80 mm Hg to 40 mm Hg. In this process, right ventricular myocardial O_2 consumption fell, reflecting an increase in O_2 utilization efficiency (i.e., triple product/myocardial O_2 consumption). Setty *et al.* (44) also found that nitric oxide contributed to this adaptation to right coronary hypoperfusion by restraining myocardial O_2 consumption and promoting coronary vasodilation. Therefore, nitric oxide released during hypoperfusion makes the moderately ischemic right ventricle more efficient. Blockade of nitric oxide synthesis during hypoperfusion increased right ventricular myocardial O_2 consumption, but did not significantly affect right ventricular mechanical function. In contrast, Heusch *et al.* (55) reported that external left ventricular work and left ventricular myocardial O_2 consumption decrease during moderate ischemia, leaving

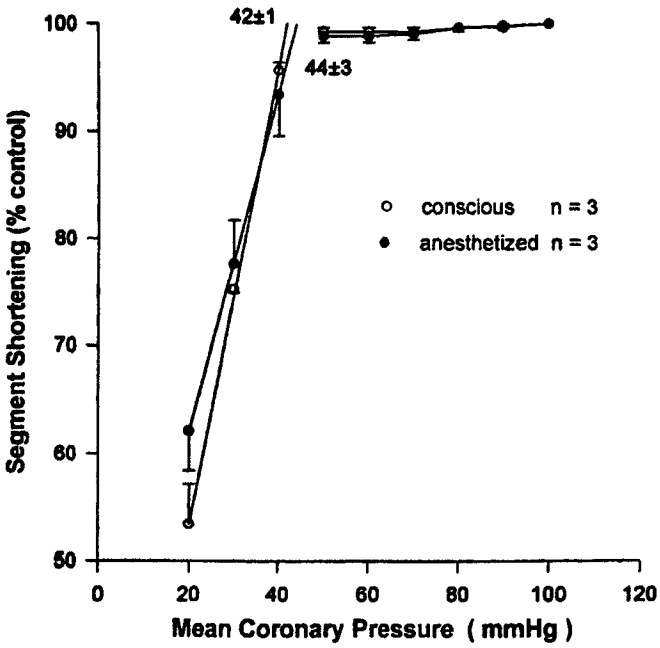

Figure 5. The relationship between right coronary pressure and right ventricular segment shortening for conscious and anesthetized states. Segment shortening fell abruptly when right coronary pressure reached 42 ± 1 mm Hg in the conscious state and 44 ± 3 mm Hg in the anesthetized state. Below these critical pressures, reductions in segment shortening were linearly related to right coronary pressure. Values are means ± SE. (Reproduced from Ref. 3 with permission from the American Physiological Society.)

left ventricular efficiency virtually unaltered. In this study, the mechanical function of the hypoperfused left ventricle was further depressed after blockade of nitric oxide synthesis, whereas myocardial O_2 consumption was unchanged.

Although the right ventricle can sustain its contractile function during brief periods of right coronary hypoperfusion, Yi *et al.* (41) noted both reduced right ventricular function and O_2 consumption by 15 mins of hypoperfusion at a right coronary pressure of 40 mm Hg. A reduction in O_2 demand of the underperfused right ventricular myocardium might allow it to remain viable despite limited O_2 supply, as has been described for hibernating left ventricular myocardium (100). Yi *et al.* (41) also found that low-dose dobutamine significantly increased contractile function and O_2 utilization efficiency of the hypoperfused right ventricle. Thus, the decrease in right ventricular function during hypoperfusion was an adaptation to reduced right coronary flow and not the direct effect of ischemia.

Conclusions

Compared with the left ventricular O_2 demand/supply balance, the right ventricle has the following distinctive features:

1. Lower systolic pressure and less wall stress
2. Lower O_2 requirements at rest and during exercise
3. Lower resting coronary blood flow and conductance
4. Systole increases rather than decreases coronary flow
5. Ineffective pressure-flow autoregulation
6. Greater effect of flow and pressure on O_2 demand
7. Less coupling between flow and contractile function
8. Greater O_2 extraction reserve
9. Use of different strategies to meet increases in O_2 demand during pulmonary hypertension, exercise, and hypoxia
10. Nitric oxide is a regulator of resting right coronary blood flow
11. Pronounced α-adrenergic vasoconstriction during exercise, with no effect on transmural right coronary flow distribution
12. Increased efficiency during moderate ischemia
13. Similar reduction in subepicardial and subendocardial flows during hypoperfusion

Considering these important differences in factors impacting the myocardial O_2 demand/supply balance, generalizations about right coronary physiology should not be made from left ventricular observations. The physiology of the right ventricle and its coronary circulation merit much further investigation.

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