Deborah J. Culley, M.D., Editor

Right Ventricular Perfusion

Physiology and Clinical Implications

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ABSTRACT

Regulation of blood flow to the right ventricle differs significantly from that to the left ventricle. The right ventricle develops a lower systolic pressure than the left ventricle, resulting in reduced extravascular compressive forces and myocardial oxygen demand. Right ventricular perfusion has eight major characteristics that distinguish it from left ventricular perfusion: (1) appreciable perfusion throughout the entire cardiac cycle; (2) reduced myocardial oxygen uptake, blood flow, and oxygen extraction; (3) an oxygen extraction reserve that can be recruited to at least partially offset a reduction in coronary blood flow; (4) less effective pressure–flow autoregulation; (5) the ability to downregulate its metabolic demand during coronary hypoperfusion and thereby maintain contractile function and energy stores; (6) a transmurally uniform reduction in myocardial perfusion in the presence of a hemodynamically significant epicardial coronary stenosis; (7) extensive collateral connections from the left coronary circulation; and (8) possible retrograde perfusion from the right ventricular cavity through the Thebesian veins. These differences promote the maintenance of right ventricular oxygen supply–demand balance and provide relative resistance to ischemia-induced contractile dysfunction and infarction, but they may be compromised during acute or chronic increases in right ventricle afterload resulting from pulmonary arterial hypertension. Contractile function of the thin-walled right ventricle is exquisitely sensitive to afterload. Acute increases in pulmonary arterial pressure reduce right ventricular stroke volume and, if sufficiently large and prolonged, result in right ventricular failure. Right ventricular ischemia plays a prominent role in these effects. The risk of right ventricular ischemia is also heightened during chronic elevations in right ventricular afterload because microvascular growth fails to match myocyte hypertrophy and because microvascular dysfunction is present. The right coronary circulation is more sensitive than the left to α-adrenergic–mediated constriction, which may contribute to its greater propensity for coronary vasospasm. This characteristic of the right coronary circulation may increase its vulnerability to coronary vasoconstriction and impaired right ventricular perfusion during administration of α-adrenergic receptor agonists.

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THE right ventricle (RV) was initially viewed as a relatively passive conduit through which systemic venous blood returned to the lungs for reoxygenation, but it is now very apparent that the RV plays a fundamental role in maintaining systemic circulatory homeostasis, as reflected in the many excellent reviews addressing RV function in health and disease.[1–7] However, these articles have paid only cursory attention to the mechanisms governing RV perfusion. A thorough understanding of these mechanisms is essential for the clinical anesthesiologist, because it provides a strong physiologic basis for the use of interventions (*e.g.*, drugs and fluids) to maintain RV oxygen supply commensurate with RV oxygen demand. Studies performed since the early 1900s have provided a detailed picture of the coronary vascular control mechanisms in the left ventricle (LV).[8–11] These observations are often extrapolated to the RV, but this approach is inappropriate because there are distinct differences in the determinants of coronary blood flow to the RV *versus* the LV, including those related to the phasic pattern of blood flow and pressure–flow autoregulation.[12,13] In this article, we review the fundamental mechanisms regulating coronary blood flow in the RV and how these mechanisms differ from those in the LV. We also address how the distinct characteristics of RV perfusion impact the changes in RV contractile function and perioperative care in various clinical settings, including coronary insufficiency, coronary artery spasm, acute normovolemic hemodilution, and acute and chronic pulmonary arterial hypertension (PAH).

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Cardiac Anatomy

In contrast to the thicker-walled, ellipsoidal-shaped LV, which pumps oxygenated blood at high pressure into the systemic arterial tree, the thinner-walled, crescent-shaped RV pumps deoxygenated blood into a substantially lower pressure, more compliant pulmonary arterial bed.[7,14] The mass of the LV is approximately six times that of the RV, reflecting their respective pressure load and stroke work. A high degree of interaction and interdependence exists between the ventricles because of their shared interventricular septum and the restraining influence of the pericardium.[4] This structural design emphasizes that the load on one ventricle may be substantially influenced by the filling and function of the contralateral ventricle.

The left and right coronary arteries (LCA and RCA, respectively) originate from the aorta at the right and left sinuses of Valsalva behind the corresponding aortic valve leaflet (fig. 1).[12] The perfusion territory of the LCA is greater than that of the RCA. The LCA runs distally and to the left of the anterior interventricular groove, between the pulmonary artery and the left atrial appendage, and divides into the left anterior descending artery (LAD) and left circumflex coronary artery. These arteries provide blood flow to most of the anterior and lateral LV walls and the anterior two thirds of the septum. The RCA follows the atrioventricular groove to the right margin of the heart. The coronary artery that supplies blood to the posterior descending coronary artery defines the left or right dominance of the coronary circulation.[14] The RCA is dominant in 85% of the population, which, in addition to supplying blood flow to the RV free wall, supplies the inferior wall of the LV and the posterior third of the septum.[15] In the minority of patients, the RCA is nondominant and supplies only the RV. It is important to recognize that the portion of the flow through a dominant RCA that supplies the LV and septum is subjected to the mechanical forces and metabolic factors associated with the higher developed systolic pressure of the LV. Thus, studies of hemodynamic responses in the human RCA can be ambiguous because of the heterogeneous nature of its perfusion territory in some subjects. In contrast to humans, dogs typically possess a left-dominant coronary circulation, in which the RCA does not contribute to perfusion of the LV wall or septum.[12] Indeed, this anatomic distinction allows the canine model to be exploited for studies of selective right coronary physiology.

Mechanisms of Coronary Blood Flow Regulation

Coronary blood flow is directly related to perfusion pressure and inversely related to vascular resistance, the latter of which is determined by multiple factors. For technical reasons, some of the animal studies of RV perfusion that we discuss were performed with an open pericardium, an experimental model in which reduced ventricular interaction occurs. This factor may have influenced the subsequent findings during which the volume of the RV or LV varies.

Transmural Flow Distribution and Extravascular Compressive Forces

Studies in awake and anesthetized dogs conducted with radioactive tracer microspheres consistently demonstrated that myocardial blood flow is higher in the LV than in the RV and that its distribution is essentially uniform across both ventricular walls at baseline.[16–18] However, phasic measurements of left and right coronary blood flow indicate that the ventricles differ markedly in how the flow varies during the cardiac cycle (fig. 2).[12,19] As early as 1900, Langendorff[20] observed that LV contraction impeded perfusion in isolated mammalian heart preparations. Subsequent measurements of phasic blood flow through the LAD or left circumflex coronary artery provided additional evidence for this effect by demonstrating that flow predominantly occurs during diastole (fig. 2).[9,12,21] The

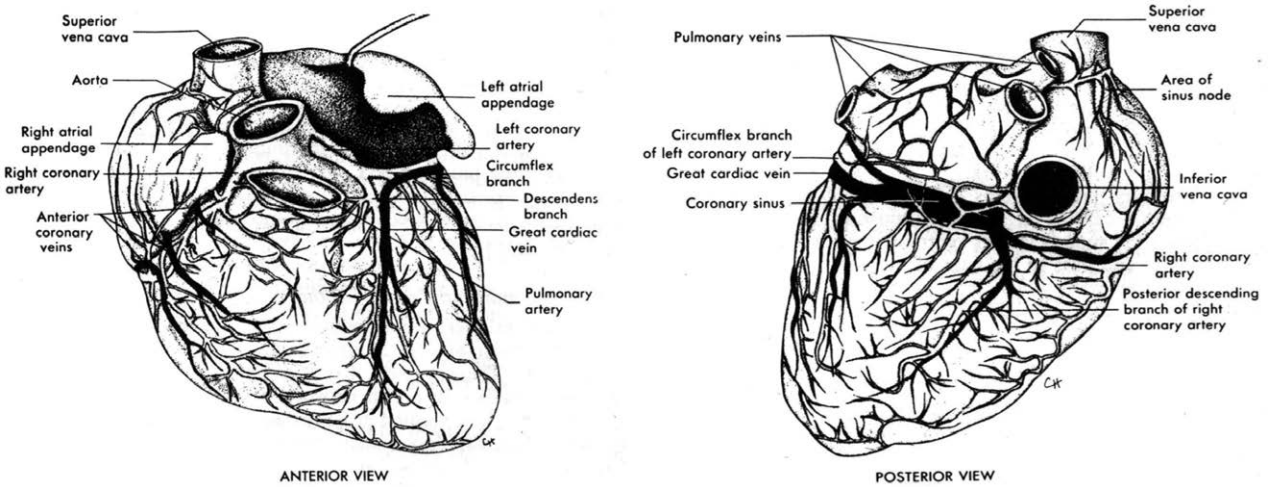

Fig. 1. Anterior and posterior aspects of the heart, illustrating the location and distribution of the major coronary arteries and veins. Published with permission from Koeppen and Stanton.[19]

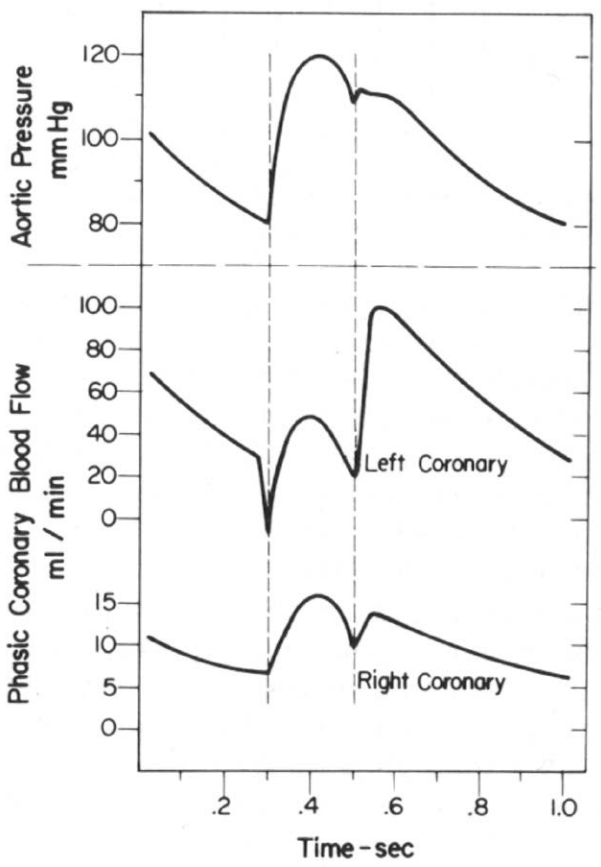

Fig. 2. Difference in phasic blood flow in the left coronary (LC) and right coronary (RC) arteries. LC blood flow is impeded by extravascular compressive forces generated by systolic LV contraction. These forces are so high that LC blood flow is briefly reversed. LC blood flow increases to a maximum early in diastole and then falls gradually following the decline in aortic pressure during the remainder of diastole. Because of a lower developed pressure in the RV, there is no systolic inhibition of RC blood flow; RC blood flow follows the shape of the aortic pressure curve and remains appreciable throughout the entire cardiac cycle. The *left vertical line* indicates the onset of systole, whereas the *right vertical line* indicates the onset of diastole. Published with permission from Koeppen and Stanton.[19]

inhibition of left coronary blood flow during systole results from extravascular compressive forces exerted on intramural vessels located predominantly in the subendocardium.[9,12] Conversely, preferential subendocardial flow occurs during diastole and compensates for this inhibition of systolic blood flow, thereby preserving transmurally uniform LV perfusion. The primary mechanism for this response is a metabolically mediated adjustment in vasomotor tone.[22] Transmurally uniform perfusion across the LV wall was also observed after coronary vasomotor tone was abolished pharmacologically.[23] These results demonstrate that a second mechanism, namely a gradient of vascularity favoring the subendocardium, also compensates for the systolic flow limitation. Tachycardia increases the relative percentage of time spent during systole (shortening of diastole) and consequently the duration of restricted LV perfusion. In contrast to the LV, systolic intramyocardial pressure is low in the RV and thus does not produce compressive forces that impede blood flow.[12] Indeed, blood flow to the RV is appreciable throughout the entire cardiac cycle, essentially following the shape of the aortic pressure curve (fig. 2).[19,21,24,25] Measurements of phasic coronary flow velocity obtained in patients with a doppler probe indicated that the ratio of systolic to diastolic flow velocity in RV branches of the RCA was three times that in the LAD.[21] Acute and chronic PAH are accompanied by increases in RV tissue pressure such that RV perfusion becomes more diastole dominant, as observed in the LV.

Comment. In contrast to the LV, which is perfused predominantly during diastole, the RV receives appreciable blood flow throughout the entire cardiac cycle. This characteristic of RV perfusion is advantageous in maintaining adequate myocardial oxygen delivery. However, in the presence of acute or chronic PAH, RV systolic pressure is elevated, resulting in a phasic distribution of blood flow similar to that of the LV.

Metabolic Regulation: Maintenance of Myocardial Oxygen Supply–Demand Balance

The heart is a continuously active organ that depends almost exclusively on aerobic metabolism to fulfill its energy demands. In the absence of ischemia, more than 95% of adenosine triphosphate (ATP) formation in the heart is derived from oxidative phosphorylation in the mitochondria.[26] Free fatty acids, glucose, and lactate are principal substrates of aerobic metabolism. When oxygen availability is limited, the cardiomyocyte uses the anaerobic glycolytic pathway, namely the conversion of glucose to lactate in the cytosol, for energy production.[26] Thus, an elevated lactate concentration in the coronary venous effluent is a marker for myocardial ischemia.[27] Anaerobic glycolysis has a very limited ability to fulfill the energy requirements of the myocardium, because myocardial contraction ceases within 10 to 15 s after coronary blood flow is interrupted.[12]

The primary determinants of myocardial oxygen demand are wall stress (according to the law of Laplace, a direct function of peak developed pressure and chamber radius and an inverse function of wall thickness), heart rate, and contractility.[28] Myocardial oxygen uptake reflects myocardial oxygen demand when oxygen supply is not limited. Under steady-state conditions, the Fick equation can be used to calculate myocardial oxygen uptake (MVO_2), such that $MVO_2 = MBF \times (CaO_2 - CvO_2)$, where MBF is myocardial blood flow and $(CaO_2 - CvO_2)$ is the coronary arteriovenous oxygen content difference. Myocardial oxygen extraction (MEO_2), as a percentage, is calculated from measurements of CaO_2 and CvO_2: $MEO_2 = [(CaO_2 - CvO_2)/CaO_2] \times 100$.

The common venous drainage of the LV to the readily accessible and easily catheterized coronary sinus facilitates measurements of myocardial oxygen uptake in that chamber (fig. 1). However, the small size and delicate nature of the

superficial veins that drain the RV make these measurements much more challenging in the RV. Despite this technical difficulty, several laboratories were successful in obtaining measurements of RV oxygen uptake in dogs, and a few, including our own, were able to obtain measurements of myocardial oxygen uptake in both chambers simultaneously. These studies demonstrated that baseline values for myocardial oxygen uptake are much smaller in the RV compared with the LV (table 1).[29–33] The reduced oxygen uptake in the RV occurs as a result of lower values for blood flow and oxygen extraction and is consistent with the RV's lower peak developed systolic pressure and thus wall stress. Indeed, blood flow (per 100 g tissue) in the RV is approximately two thirds of that in the LV (table 1).[29,30,33] Baseline coronary vascular resistance is substantially greater in the RV compared with the LV, thus reflecting this blood flow difference. The noncylindrical geometry and nonuniform radius of the RV result in a heterogeneous stress within its free wall. Regional variation in RV oxygen uptake and blood flow would be expected under these circumstances, but this hypothesis has not as yet been confirmed experimentally.

Coronary flow reserve is the ratio of maximum coronary blood flow to baseline coronary blood flow. A reduced coronary flow reserve renders the myocardium more susceptible to ischemia during an increase in myocardial oxygen demand.[34,35] Indeed, this principle provides the utility of exercise or dobutamine-induced stress testing for the diagnosis for coronary artery disease. Coronary flow reserve can be estimated by analysis of the reactive hyperemic response or by using an intracoronary or intravenous infusion of a vasodilator such as adenosine or dipyridamole.[36] Reactive hyperemia is the increase in blood flow that follows a brief period of ischemia. The time course of the reactive hyperemic response reflects the action of metabolites produced in the ischemic tissue that initially dilate the resistance vessels and subsequently wash out during reperfusion (fig. 3). The normal RV and LV each have appreciable (approximately 400 to 500%) coronary flow reserves.[21,29,30,37] Coronary flow reserve is reduced in a variety of conditions, including pressure-overload ventricular hypertrophy, hemodilution, hypoxemia, hypercapnic acidosis, and an atherosclerotic epicardial stenosis (fig. 3).[12,30,38–40] For example, a 90% epicardial stenosis is associated with complete exhaustion of the coronary flow reserve.[38] A reduced coronary flow reserve may also result from microvascular dysfunction without a distinct epicardial stenosis, as occurs most frequently in the coronary circulation of postmenopausal women or patients with diabetes mellitus.[40,41]

Two mechanisms are potentially available to meet an elevated myocardial oxygen demand, an increase in coronary blood flow and a greater oxygen extraction. Oxygen extraction in the LV is nearly maximal (70 to 80%) under baseline conditions; thus, an increase in LV oxygen uptake is essentially dependent on a proportional increase in blood flow.[30,42,43] The tight metabolic coupling of LV blood flow and oxygen uptake is reflected in a nearly constant value for coronary sinus oxygen tension that remains approximately 20 mmHg under most circumstances. The smaller baseline oxygen extraction of RV indicates that blood flow is high relative to oxygen uptake. This overperfusion of the RV has been attributed to a blunting of right coronary vasoconstriction by nitric oxide, a coronary vasodilator, released tonically from the vascular endothelium.[13] Indeed, antagonism of nitric oxide synthesis caused a reduction in resting right coronary blood flow,[44] but this intervention had no effect on resting left coronary blood flow.[45,46] The sustained basal release of nitric oxide in the right coronary circulation may be due to a greater vascular resistance, flow velocity, and

Table 1. Right and Left Ventricular Oxygen Uptake and Associated Variables during Inotropic Stimulation (Isoproterenol, 0.1 μg · kg^{-1} · min^{-1} intravenously) in Anesthetized, Open-chest Dogs

	Right Ventricle		Left Ventricle	
	Baseline	Isoproterenol	Baseline	Isoproterenol
MVO_2, ml · min^{-1} · 100 g^{-1}	4.8 ± 1.3	8.2 ± 1.6*	10.6 ± 0.9	14.2 ± 1.8*
MBF, ml · min^{-1} · 100 g^{-1}	59 ± 12	73 ± 12*	84 ± 16	104 ± 14*
A-V O_2 diff, ml O_2/100 ml blood	9.1 ± 1.1	11.4 ± 1.0*	13.5 ± 0.8	14.3 ± 0.8
O_2 extraction, %	42 ± 5	51 ± 3*	63 ± 4	64 ± 3
Lactate extraction, %	56 ± 11	50 ± 11	60 ± 8	51 ± 10
Systemic variables				
CI, ml · min^{-1} · kg^{-1}	65 ± 6	89 ± 9*		
MAP, mmHg	111 ± 99	99 ± 5*		
RVSP, mmHg	27 ± 1	29 ± 1		
PCWP, mmHg	5.0 ± 1.0	3.7 ± 1.5*		
HR, beats/min	104 ± 12	153 ± 18*		

Isoproterenol caused increases in oxygen uptake in both ventricles but only the right ventricle satisfied this, in part, by recruitment of an oxygen extraction reserve. Values are mean ± SE. Adapted from Crystal *et al*.[30]

*$P < 0.05$ *versus* baseline.

A-V O_2 diff = coronary arteriovenous oxygen content difference; CI = cardiac index; HR = heart rate; MAP = mean aortic pressure; MBF = myocardial blood flow; MVO_2 = myocardial oxygen uptake; PCWP = pulmonary capillary wedge pressure; RVSP = right ventricular systolic pressure.

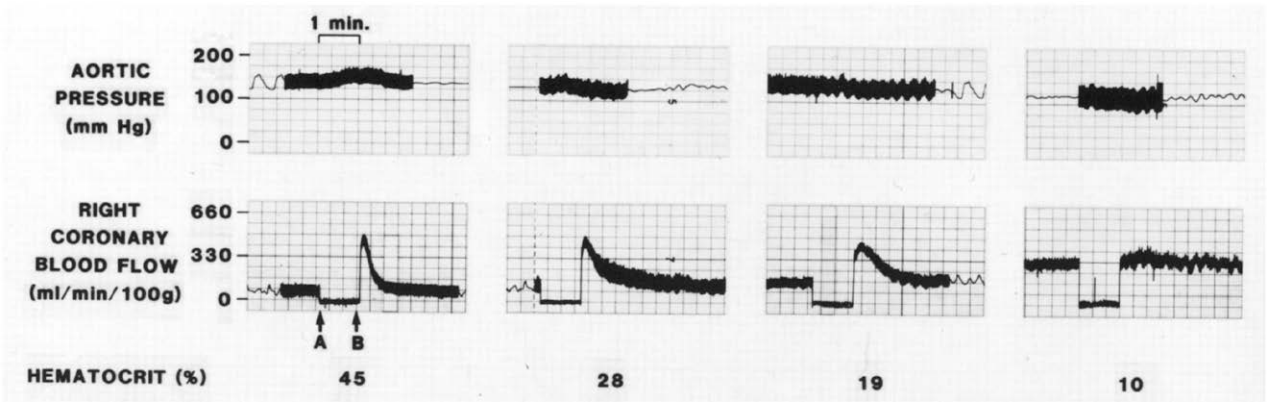

Fig. 3. Original tracing demonstrating effect of graded acute normovolemic hemodilution on the reactive hyperemic response after a 60-s occlusion of the right coronary artery of a dog. *A*, Right coronary artery was occluded; *B*, occlusion was released. The reactive hyperemic response (and thus the coronary flow reserve) decreased progressively as hematocrit was reduced and was essentially exhausted at a hematocrit of 10%. Published with permission from Crystal *et al.*[30]

shear stress.[13,44] The lower baseline oxygen extraction of the RV compared with the LV provides it with a substantial oxygen extraction reserve. This oxygen extraction reserve, along with increases in blood flow, allows the RV to meet increases in oxygen demand (table 1).[29–33] The relative importance of oxygen extraction in the RV *versus* the LV is consistent with their respective capillary reserves, as measured by stop-motion microcinematography in rat hearts *in situ*.[47] These experiments demonstrated that the RV has a smaller number of open capillaries at baseline and a greater total capillary density than the LV, indicative of a greater capillary reserve. Indeed, the capillary reserve of the RV is approximately twice that of the LV.

Insight into the interplay between increases in RV blood flow and oxygen extraction was obtained in a study of chronically instrumented dogs undergoing graded treadmill exercise.[31] The findings demonstrated that the RV relies preferentially on increases in oxygen extraction at low levels of exercise, whereas the contribution of blood flow becomes prominent during more intense exercise when the coronary venous oxygen tension falls to approximately 20 mmHg. These observations in the RV, and those described above for the LV, support the contention that a coronary venous oxygen tension of 20 mmHg is the critical value for activation of a metabolically linked coronary vasodilator response.

The metabolic mechanisms responsible for linking coronary blood flow and myocardial oxygen demand are similar in the RV and LV. The action of locally produced metabolites dilate the intramural arterioles (less than 100 μm in diameter) to increase coronary blood flow. The arterioles are the site of the most pronounced drop in perfusion pressure and thus are termed the *resistance vessels*.[48] The intramural arterioles in both ventricles normally have a high resting tone and a substantial dilator reserve. These microvessels are highly responsive not only to vasoactive metabolites produced by the myocardium but also to exogenous vasoactive drugs. A current theory of metabolic control of coronary blood flow proposes a feed-forward mechanism whereby vasodilating metabolites are produced by the myocardium in proportion to the level of cardiac work (fig. 4).[10] The primary metabolites for these effects are carbon dioxide generated in the citric acid cycle (Kreb's cycle) reactions and superoxide anion, produced by the mitochondrial respiratory chain in proportion to the rate of myocardial oxygen uptake and converted to hydrogen peroxide in the cytosol.[10] A number of secondary downstream mechanisms, including the ATP-sensitive potassium and the voltage-gated potassium channels, mediate the flow response initiated by these metabolites. Endogenous adenosine was traditionally thought to be the most important metabolite coupling coronary blood flow to myocardial oxygen demand, but the role of adenosine in flow–metabolism coupling is primarily limited to conditions in which the main stimulus for its production, that is, low tissue oxygen tension, is present.[10] Both the right and left coronary circulations dilate in direct response to hypoxemia and hypercapnic acidosis.[11,49–51]

Comment. The RV has a smaller developed systolic pressure and thus oxygen demand than the LV. This feature of the RV lessens its vulnerability to myocardial ischemia. Metabolic regulation of coronary blood flow is a principal mechanism in both the RV and LV for maintaining myocardial oxygen balance. A diminished coronary flow reserve, such as occurs in the hypertrophied RV, impairs the efficacy of this mechanism. The RV but not the LV possesses an oxygen extraction reserve, which functions as an additional defense mechanism against myocardial ischemia.

Neural Regulation

The coronary circulation possesses rich sympathetic and parasympathetic innervation, expressing both α- and β-adrenergic receptors and cholinergic–muscarinic receptors (table 2).[52] Stimulation of α-adrenergic receptors mediates coronary vasoconstriction, whereas stimulation of β-adrenergic receptors mediates coronary vasodilation. The α_1-adrenergic receptors predominate in small coronary arteries, but the α_2-adrenergic receptors are prevalent in the

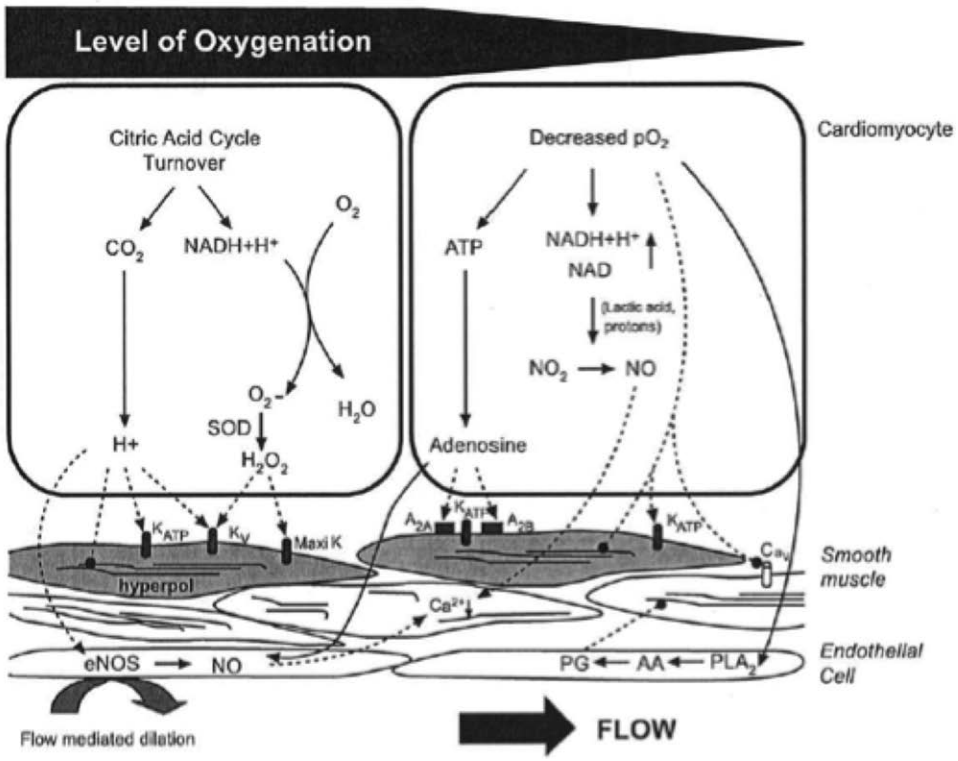

Fig. 4. Current concepts of metabolic regulation of coronary blood flow. The concepts are separated for physiologic conditions (unchanged level of myocardial oxygenation, *left side of the diagram*) and pathologic conditions (decreased myocardial oxygenation, *right side*), such as coronary insufficiency. Biochemical reactions and metabolic interaction are indicated by *solid arrows*, and links to effectors are indicated by *broken arrows*. *Pointed ends* indicate activation, and *rounded ends* inhibition. Carbon dioxide (CO_2), produced in the citric acid cycle, and superoxide anion (O_2^-), produced in the mitochondria and converted to hydrogen peroxide (H_2O_2) in the cytosol, act in a feed-forward manner to match coronary blood flow to an increased cardiac work when tissue oxygenation is adequate. Downstream mediators in coronary vasodilation include the release of nitric oxide (NO) from the vascular endothelium and an opening of the ATP-sensitive (K_{ATP}) and voltage-dependent (K_V) potassium channels. When tissue oxygenation is reduced (*e.g.*, coronary stenosis), other mediators, most notably adenosine, also contribute to dilation of the coronary resistance vessels. AA = arachidonic acid; A_{2A} and A_{2B} = adenosine subtype 2A and 2B receptors, respectively; Ca_V = voltage-gated calcium channels; eNOS = endothelial nitric oxide synthase; PG = prostaglandins; PLA_2 = phospholipase A_2; SOD = superoxide dismutase. Published with permission from Deussen *et al.*[10]

Table 2. Major Adrenergic and Muscarinic Receptor Subtypes: Effect of Activation in Coronary Circulation

Receptor	Effector	Effector Response	Vascular Effect
Adrenergic			
α_1	Small artery vascular smooth muscle	Contraction	Constriction
α_2	Arteriolar vascular smooth muscle	Contraction	Constriction
β_1	Cardiac myocyte	Increased rate and force of contraction resulting in increased oxygen demand	Dilation
β_2	Arteriolar vascular smooth muscle	Relaxation	Dilation
Muscarinic			
M_3	Arteriolar vascular smooth muscle	Contraction	Constriction
M_3	Arteriolar vascular endothelium	Release of nitric oxide	Dilation

These autonomic receptors are present in both the right and left ventricles, although in some cases (*e.g.*, the arteriolar α_2 receptors) their influence differs, as described in text.

coronary arterioles, where an impact on coronary blood flow regulation is exerted.[53] Indeed, intracoronary injections of a selective α_1-adrenergic receptor agonist, methoxamine, had no effect on coronary blood flow, but those of a selective α_2-adrenergic receptor agonist, BHT933, caused dose-dependent decreases in coronary blood flow in patients with normal coronary arteries.[54] The effect was enhanced in the atherosclerotic coronary circulation, presumably because of an impaired background release of nitric oxide from the vascular endothelium.[54] The distribution of α-adrenergic

receptor subtypes within the coronary vascular tree explains why an intravenous infusion of phenylephrine (a selective α_1-adrenergic receptor agonist) does not produce a significant coronary vasoconstrictor response in either the RV or LV.[18] β_1-Adrenergic receptors are prominent in the myocardium where they mediate positive inotropic, chronotropic, dromotropic, and lusitropic effects, and β_1-adrenergic receptors also outnumber the β_2-adrenergic receptors in large coronary arteries. However, only β_2-adrenergic receptors are present in small arterioles, where their activation mediates coronary vasodilation and increases in coronary blood flow.[55,56] M_3 muscarinic receptors are present in both the coronary vascular smooth muscle and coronary vascular endothelium.[57] In the normal coronary circulation, the predominant action of a muscarinic receptor agonist (*e.g.*, acetylcholine) is vasodilation mediated by production and release of nitric oxide from the vascular endothelium in response to activation of its M_3 receptors.[57,58] The endothelial dysfunction associated with atherosclerosis unmasks a vasoconstrictor effect of a muscarinic agonist due to stimulation of the M_3 receptors in the vascular smooth muscle.[57,59]

Activation of the cardiac sympathetic nerves, whether through direct stimulation of the stellate ganglion or indirectly by a reflex-mediated unloading of the carotid baroreceptors during hypotension, has differential effects on LV and RV blood flow.[9,12,60,61] Sympathetic nervous stimulation causes an increase in coronary blood flow in the LV because local metabolic vasodilation occurs in response to a pronounced increase in myocardial oxygen demand (positive chronotropic and inotropic effects mediated by the myocardial β_1-adrenergic receptors), thus overriding the direct influence of α-adrenergic receptor–mediated vasoconstriction.[9,12] Indeed, pretreatment with a β_1-adrenergic receptor antagonist and its consequent attenuation of the increases in myocardial oxygen uptake are required to demonstrate coronary vasoconstriction during sympathetic nerve stimulation. In contrast, an activation of the cardiac sympathetic nerves causes relatively small changes in RV oxygen demand. As a result, coronary vasoconstriction and a decrease in blood flow to the RV are typically observed when sympathetic nervous system activity is augmented.[32,60,61] This effect is similar before and after administration of propranolol, which emphasizes the lack of influence of a β-adrenergic–mediated inotropic effect and its subsequent effect on metabolic regulation on blood flow in the RV.[60,61] These findings clearly demonstrate that blood vessels supplying the RV are more susceptible to neurogenic, α-adrenergic receptor–mediated vasoconstriction than those perfusing the LV.

Studies using an α-adrenergic receptor antagonist indicated that an activation of these receptors, presumably through an arterial baroreceptor–sympathetic nerve mechanism, limits the increases in right coronary blood flow in exercising dogs.[32] Nevertheless, adequate oxygenation in the RV is maintained through recruitment of its oxygen extraction reserve. Notably, the flow-limiting activation of the cardiac sympathetic nerves during exercise is much less pronounced in the LV.[32] The greater manifestation of sympathetically mediated vasoconstriction in the RV *versus* the LV during exercise is probably because the increase in oxygen uptake in the RV is less than that in the LV, with the result that the competing influence of metabolic vasodilators is reduced.

In contrast to the right coronary vasoconstriction and decreases in coronary blood flow observed during activation of the cardiac sympathetic nerves, selective intracoronary infusions of exogenous norepinephrine (dose range from 0.05 to 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) increase right coronary blood flow, RV oxygen uptake, and RV contractility in canine hearts.[62] These responses demonstrate a dominance of metabolic vasodilation over α-adrenergic receptor–mediated vasoconstriction. Moreover, they suggest that the net change in coronary blood flow in the RV during adrenergic stimulation depends on the balance between these two mechanisms, which can vary under differing circumstances, such as changes in agonist concentration. Thus, the dose, the relative α- and β-adrenergic receptor potency, and the preexisting inotropic and coronary vasodilator reserve will determine whether right coronary vasodilation or vasoconstriction occurs when an adrenergic agonist is administered.

Parasympathetic (vagal) efferent stimulation causes bradycardia, which reduces myocardial oxygen uptake, leading to a decrease in coronary blood flow through local metabolic mechanisms. If the heart is paced during vagal stimulation (or if acetylcholine is infused selectively into an RCA or LCA), an increase in coronary blood flow occurs secondary to coronary vasodilation through the endothelium-dependent, nitric oxide/cyclic guanosine monophosphate pathway.[46,58] To our knowledge, there are no data suggesting that parasympathetic control of blood flow differs for the RV *versus* the LV.

Comment. The coronary vessels in the RV have a distinctive sensitivity to α-adrenergic receptor–mediated vasoconstriction. This effect may be manifested during arterial baroreceptor reflex–mediated activation of the sympathetic system secondary to arterial hypotension or during exercise. Under conditions of a diminished RV vasodilator reserve (*e.g.*, RV hypertrophy or coronary atherosclerotic disease) or when the RV inotropic reserve is compromised, the administration of an adrenergic agonist, such as norepinephrine, for circulatory support may result in coronary vasoconstriction, a reduction in coronary blood flow, and an initiation or exacerbation of myocardial ischemia in the RV.[63]

Pressure–Flow Autoregulation

Pressure–flow autoregulation defines the ability of a vascular bed to maintain relatively constant blood flow over a wide range of perfusion pressures through adjustments in vasomotor tone. Thus, vasodilation occurs in response to a decrease in perfusion pressure, whereas vasoconstriction is observed in response to an increase in perfusion pressure.[64]

This phenomenon is intrinsic to the coronary circulation and not dependent on the autonomic nervous system or humoral factors. H. Fred Downey's laboratory systematically evaluated pressure–flow autoregulation in the right and left coronary circulations of the open-chest anesthetized dog using an extracorporeal controlled–pressure blood reservoir or a screw clamp to simulate the drop in arterial pressure beyond a stenosis.[65,66] Pressure–flow autoregulation was attenuated in the right compared with the left coronary circulation; coronary blood flow was relatively constant across the pressure range of 70 to 120 mmHg in the left coronary circulation, whereas coronary blood flow varied essentially as a function of perfusion pressure in the right coronary circulation (fig. 5). The studies demonstrated further that, when reductions in blood flow occurred, they were preferentially subendocardial in the LV but transmurally uniform in the RV. The relative hypoperfusion of the subendocardium in the LV is related to its higher tissue pressures and in part explains why this region is most vulnerable to ischemia and infarction.[12] Finally, the findings showed that RV oxygen uptake decreased in parallel with the decline in coronary blood flow as perfusion pressure was reduced. There are two possible explanations for the parallel reductions in right coronary blood flow and RV oxygen uptake at reduced perfusion pressures: either myocardial oxygen uptake decreased because of inadequate oxygen delivery (blood flow; indicative of ischemia), or metabolic vasoconstriction resulting from reduced myocardial oxygen demand occurred. Indeed, additional findings from Downey's group supported the latter mechanism.[13,67,68] The absence of myocardial ischemia was demonstrated from the following observations. First, regional wall motion (percentage of segmental shortening measured using sonomicrometry) in the right coronary perfusion territory did not change during reductions in perfusion pressure. Second, lactate uptake and not production was observed. Third, myocardial biopsies revealed that high energy phosphate concentrations remained at normal levels. Thus, the ability to maintain constant external work associated with contraction despite a decline in oxygen uptake indicated that the RV myocardium had downregulated its metabolic demand and increased its oxygen utilization efficiency when perfusion pressure was reduced. Evidence of reduced myocardial stiffness, caused by a decreased coronary turgor, was proposed as a potential mechanism for the increased RV oxygen utilization efficiency.[68] This concept refers to the ability of a reduction in transmural distending pressure within the coronary vascular bed and the concomitant decrease in vascular volume to reduce RV stiffness and cardiac internal work (*i.e.*, the work performed before the ejection of blood during the phase of isovolumic contraction) and thereby to increase the efficiency of myocardial oxygen use. This effect most likely occurs in the RV but not the LV because of the lower transmural pressure and thinner wall of the former chamber. A downregulation of RV oxygen demand during hypoperfusion maintains tissue viability in the face of restricted oxygen supply: this phenomenon is termed *hibernation*.[13,69,70] The ability of the positive inotropic drug dobutamine to markedly increase contractile function in the hypoperfused RV myocardium provides direct evidence for the existence of this hibernating state.[69]

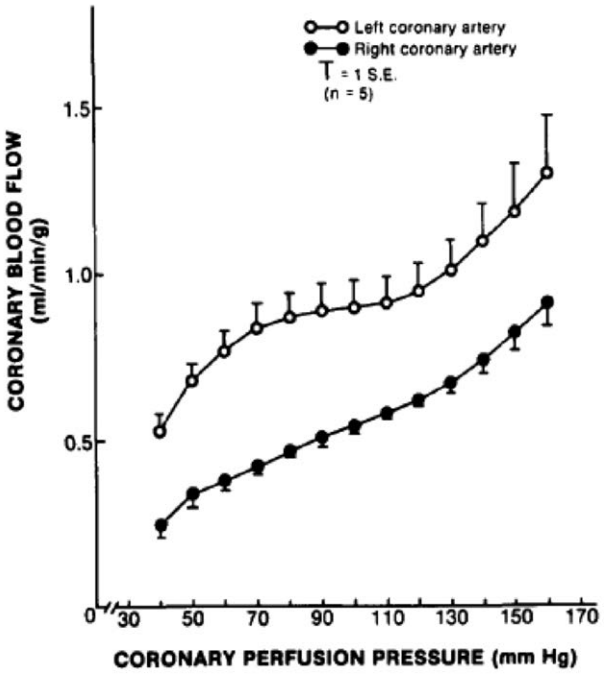

Fig. 5. Pressure–flow relations in a left coronary artery (*open circles*) and right coronary artery (*closed circles*) obtained simultaneously in same canine hearts. Effective autoregulation was demonstrated in the left coronary circulation between perfusion pressures of 70 and 120 mmHg, whereas, in the right coronary circulation, blood flow essentially varied as a function of perfusion pressure. Published with permission from Yonekura *et al.*[65]

Comment. The right coronary circulation has a relatively poor autoregulatory capability. Thus, a reduction in right coronary perfusion pressure, which occurs as a consequence of an epicardial coronary stenosis, is accompanied by a nearly proportional decrease in coronary blood flow. However, because of the relatively thin RV wall, a concomitant decrease in wall stiffness occurs, resulting in a reduction in internal work and oxygen demand and an increased oxygen utilization efficiency, thus preserving oxygen supply–demand balance. This mechanism is important in providing protection to the RV against ischemia-induced dysfunction and injury.

Clinical Implications

Vulnerability to Myocardial Ischemia

In 1930, Sanders[71] provided the first description of the clinical syndrome of RV myocardial infarction when he described the triad of hypotension, increased jugular venous pressure, and clear lung fields in a patient who had postmortem findings of extensive RV necrosis concomitant with

minimal LV involvement. RV infarction was not considered an important clinical entity in the subsequent four decades, in part because animal studies demonstrated that there was no impact on overall cardiac performance when the RV was deliberately rendered dysfunctional.[72] Such studies were later criticized because they were performed with an open pericardium and thus did not take into account the role of ventricular interaction.[4] Indeed, a critical role for the RV in the maintenance of systemic circulatory homeostasis is now well recognized.[1–7]

In 1979, Cohn[73] published a classic report in which RV myocardial infarction was described as a distinct entity. Nevertheless, isolated RV myocardial infarction is a relatively uncommon occurrence, accounting for less than 3% of all cases of myocardial infarction.[74] Moreover, a small fraction of inferior wall LV infarctions resulting from occlusion of the proximal RCA are accompanied by RV dysfunction or evidence of RV necrosis.[74,75] Finally, RV ejection fraction increases during the recovery period in survivors of right ventricular myocardial infarction independent of subsequent coronary artery surgery.[76] A number of factors may contribute to this relative resistance of the RV to ischemic dysfunction and injury, the first four of which were discussed in detail previously: (1) appreciable coronary blood flow throughout the entire cardiac cycle; (2) lower baseline oxygen uptake with a physiologically significant oxygen extraction reserve that is capable of at least partially offsetting reductions in coronary blood flow; (3) ability to downregulate oxygen demand during reduced perfusion, thus preserving high energy phosphates stores; (4) when blood flow is reduced by a hemodynamically significant epicardial coronary stenosis, the decrease in blood flow in the RV is transmurally uniform, whereas it is disproportionally subendocardial in the LV; and (5) extensive collateral connections, particularly those originating from the moderator band artery, a branch of the LAD.[75] Furthermore, it has been suggested, but not definitely established, that retrograde perfusion from the RV cavity through the Thebesian veins may protect against RV ischemia when coronary blood flow is impaired.[2] Notably, an increased incidence of right ventricular myocardial infarction is found in cases of RV hypertrophy associated with PAH.[77] This finding may be attributable to an impaired RV oxygen supply due to several factors, including reductions in systolic perfusion, coronary vasodilator reserve, collateral blood flow, and oxygen extraction capability, in the presence of an increased oxygen demand in the hypertrophied RV.[77–79]

Coronary Artery Spasm. In 1959, Prinzmetal *et al.*[80] described variant angina as a condition characterized by a decrease in myocardial oxygen supply at rest. This form of angina is unrelated to the increase in myocardial oxygen demand during exercise in the presence of a fixed atherosclerotic obstruction to coronary blood flow that characterizes classical angina. Subsequent angiographic studies convincingly demonstrated a role for coronary artery spasm, that is, a sudden intense constriction of a large epicardial coronary artery, in the pathogenesis of variant angina.[81,82] The RCA and its branches demonstrate the highest incidence of vasospasm.[83] Variant angina may severely impair myocardial perfusion and oxygenation, thereby predisposing to the development of malignant cardiac arrhythmias or acute myocardial infarction independent of atherosclerotic disease. Based on the intrinsic defense mechanisms present in the RV against the development of myocardial ischemia, it seems probable that coronary spasm may have less impact on RV *versus* LV function. Coronary vasospasm has been attributed to endothelial dysfunction combined with a hyperactivity of coronary vascular smooth muscle to vasoconstrictor stimuli, including sympathetic nerve stimulation, abnormal platelet activation causing release of thromboxane A_2 and serotonin, endothelin-1, and hypocapnia.[11,84] The relative susceptibility of the RCA to vasospasm may be related to the observation that these blood vessels have a greater sensitivity to sympathetic vasoconstriction mediated through α-adrenergic receptors.

Acute Normovolemic Hemodilution. Acute normovolemic hemodilution (ANH) is a blood conservation technique in which a patient's blood volume is partially replaced with a crystalloid or colloid solution to reduce subsequent loss and the need for allogeneic blood transfusions. The routine use of ANH for blood conservation remains controversial,[85] but its efficacy in cardiac surgery is well established.[86] Furthermore, virtually all of the patients undergoing cardiopulmonary bypass during cardiac surgery become hemodiluted because cell-free solutions are used to prime the bypass circuit. Studies performed in our laboratory[30] compared the ANH-induced changes in myocardial oxygen uptake and related variables, including myocardial blood flow measured with radioactive microspheres, in the RV and LV of anesthetized dogs. The responses in RV and LV were similar. Graded reductions in hematocrit from 40 to 10% caused increases in blood flow to both ventricles in proportion to the declines in arterial oxygen content and the local arteriovenous oxygen content difference. These compensatory responses served to maintain myocardial oxygen delivery, oxygen uptake, and oxygen extraction at baseline values (fig. 6). Lactate uptake was also well preserved in the RV and LV, suggesting that tissue oxygenation was adequate and that anaerobic metabolism did not occur (fig. 6). Right coronary flow reserve (assessed using reactive hyperemic responses) decreased progressively as oxygen carrying capacity was reduced and became essentially exhausted at a hematocrit of 10% (fig. 3). These findings implied that the increases in blood flow through the RCA were dependent on a recruitment of the coronary vasodilator reserve by local metabolic mechanisms and that reduced blood viscosity played a minor role, if any. A progressive diminution in the reactive hyperemic response also occurs in the left coronary circulation during graded ANH.[37]

Notably, the RV did not recruit its oxygen extraction reserve during ANH in contrast to the observations during increases in oxygen demand when hematocrit was in the

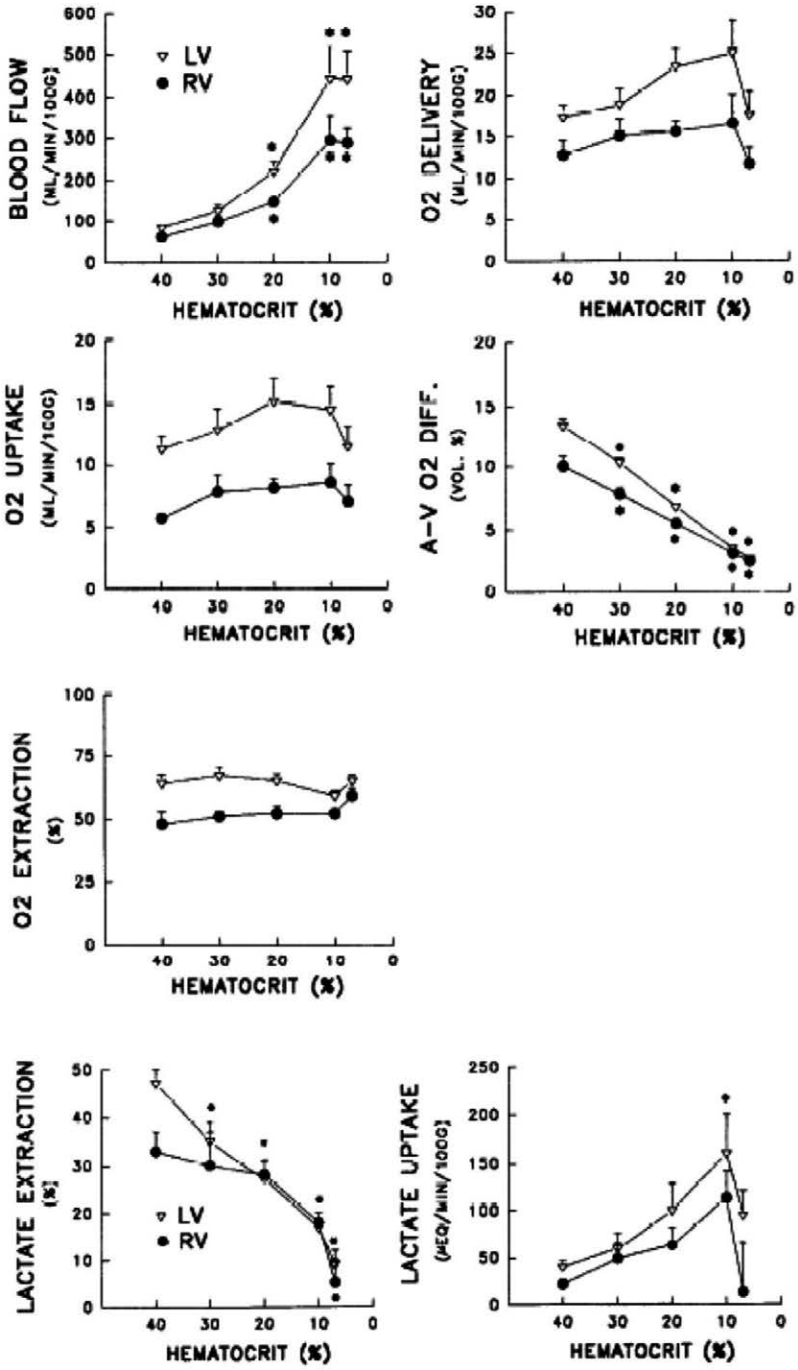

Fig. 6. Comparison of effect of graded acute normovolemic hemodilution (ANH) on myocardial oxygen (O_2) delivery and uptake and related variables in the right and left ventricles (RV and LV, respectively) of anesthetized dogs. Increases in myocardial blood flow to both the RV and LV were sufficient to maintain myocardial O_2 delivery and O_2 uptake over the hematocrit range 40 to 10%. Although percentage of lactate extraction decreased in both ventricles during ANH (presumably secondary to an increased blood flow rate), myocardial lactate uptake was well maintained if hematocrit was 10% or greater. AVO_2 diff = arteriovenous O_2 difference. *$P < 0.05$ from value at hematocrit of 40. Published with permission from Crystal *et al.*[30]

normal range. Impaired release of oxygen from the diluted red blood cells[87,88] may be responsible for this finding, but this explanation seems unlikely, because inotropic stimulation (isoproterenol) increased RV oxygen uptake during ANH in part through a greater oxygen extraction.[30] It appears more probable that the lack of mobilization of the oxygen extraction reserve in the RV during ANH was because of an insufficient metabolic stimulus for capillary recruitment.

The experimental findings suggest that a patient with normal RV and LV function should be able to readily tolerate a hematocrit as low as 20% during ANH from the perspective of myocardial oxygen delivery. This capability of

the RV and LV is compatible with the current recommendation that a restrictive transfusion trigger using a hemoglobin concentration of 7 to 8 g/dl be adopted in hemodynamically stable patients.[89] However, the dependence on compensatory increases in coronary blood flow to maintain myocardial oxygen delivery implies that even moderate ANH may be unsafe when coronary vasodilator reserve is limited, for example, in the presence of atherosclerotic disease or pressure–overload ventricular hypertrophy.[37,39,89]

Acute PAH

The RV and LV differ profoundly in their ability to tolerate increases in afterload.[90,91] The more muscular LV is capable of maintaining stroke volume over a wide range of afterloads. In contrast, the thin-walled RV is very sensitive to acute increases in afterload. These increases in RV afterload may result from a wide variety of conditions, including lung reperfusion injury, LV failure, pulmonary embolism, external compression of the pulmonary artery by a mediastinal mass, hypoxemia, hypercapnia, acidosis, or intrinsic pulmonary disease.[92–94] The Frank–Starling mechanism and sympathetically mediated increases in myocardial contractility are physiologic mechanisms that compensate for impairment to RV function during acute increases in RV afterload.[95]

Acute increases of RV systolic pressure of 30 to 40% are accompanied by simultaneous increases in RV blood flow and oxygen uptake.[29,44] RV lactate uptake is maintained, indicating absence of anaerobic metabolism and myocardial ischemia. Systemic hemodynamics, such as arterial pressure and heart rate, remain generally stable in the presence of normal RV function, and global cardiac performance does not deteriorate. The increase in right coronary blood flow during an acute increase in pulmonary arterial pressure occurs primarily during diastole because of the impeding influence of higher systolic RV intramural pressure.[96] Thus, the phasic pattern of RV perfusion becomes more akin to that observed in the LV where diastolic flow predominates (left ventricularization of the RV).

In contrast to the findings during a mild-to-moderate increase in pulmonary arterial pressure, marked increases in pulmonary arterial pressure have the potential to completely overwhelm the adaptive capability of the RV to an increased afterload and cause RV failure.[5,97] In 1936, Fineberg and Wiggers[98] postulated that "circulatory failure following obstruction of the pulmonary circuit had no other cause than fatigue of the right ventricle." Subsequent studies provided additional details about the mechanisms responsible for RV failure during severe acute PAH.[1,7,91] A rapid and large increase in pulmonary arterial pressure (*e.g.*, those that accompany a massive pulmonary thromboembolism) damages the RV contractile apparatus as a result of excessive chamber distension and lengthening of individual sarcomeres beyond their optimal interactive capacity. The resultant decrease in RV stroke volume initiates a vicious cycle by producing further distension that may become irreversible.[1] An integral component of this progressive deterioration is the inability of blood flow to the RV to increase sufficiently to meet an increased oxygen demand, resulting in myocardial ischemia.[96,99–101] The mechanisms by which RV blood flow is compromised during severe acute PAH are multifactorial (fig. 7). A decrease in aortic pressure because of impaired LV filling (LV preload) caused by the interventricular septum impinging on the LV combined with a decreased pulmonary venous blood flow produces a reduction in coronary perfusion pressure. The pressure gradient for RV blood flow is reduced further by increases in RV systolic and diastolic tissue pressures. A canine

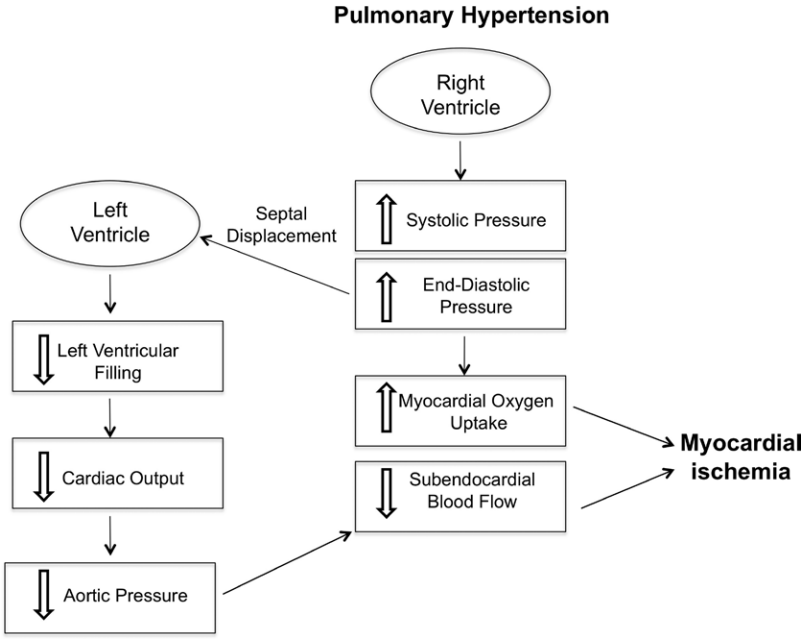

Fig. 7. Mechanisms underlying right ventricular ischemia during severe acute pulmonary hypertension.

study demonstrated that RV failure during acute severe PAH (RV systolic pressure increased by 100%) was associated with an exhausted vasodilator reserve, as indicated by absence of a reactive hyperemic response to a brief coronary occlusion, a nonuniform transmural distribution of myocardial blood flow (decrease in endocardium/epicardium blood flow ratio), and adverse changes in biochemical indices of myocardial oxygenation (*e.g.*, reduced tissue concentrations of ATP and creatine phosphate and an increase in the ratio of lactate to pyruvate) consistent with ischemia.[99]

Interestingly, administration of phenylephrine reversed the adverse effects of acute severe PAH on RV perfusion and oxidative metabolism simply by raising coronary perfusion pressure, despite the ability of α_1-adrenergic agonists to further increase vasomotor tone in the pulmonary circulation.[102] Other canine studies showed a similar salutary effect of increased coronary perfusion pressure during acute PAH.[96,103,104] These findings underscore that the adverse impact of an increased afterload on RV systolic function is more complex than an overstretching of the sarcomeres and that an imbalance between myocardial oxygen supply and demand also plays an important role in determining RV contractility in the presence of acute severe PAH.

The current recommended approach for treating acute PAH is the use of positive inotropic drugs with pulmonary vasodilating characteristics (*e.g.*, milrinone) and selective pulmonary vasodilators (*e.g.*, inhaled nitric oxide and prostaglandin E_1), although in some centers, including ours, these strategies are used in combination with systemic vasoconstrictors (*e.g.*, norepinephrine, phenylephrine, or vasopressin) to increase coronary perfusion pressure.[5,7,105]

Norepinephrine is currently recommended for α_1-receptor–mediated systemic vasoconstriction during PAH because, as a mixed adrenergic receptor agonist, it also has positive inotropic and chronotropic capabilities through activation of the myocardial β_1-adrenergic receptors.[106,107] The resultant metabolic vasodilation offsets, at least in part, the α_2-adrenergic receptor–mediated coronary vasoconstriction in the RV caused by norepinephrine. Another advantage of norepinephrine is that α_2- and β_2-adrenergic vasodilation in the pulmonary circulation moderates the pulmonary vasoconstrictor effect of α_1-adrenergic receptor activation. Norepinephrine has been demonstrated to improve RV perfusion, RV contractility, and cardiac output in animal models of acute RV dysfunction caused by PAH.[108–110] The selective α_1-receptor agonist phenylephrine is essentially devoid of a direct coronary vasoconstricting action, but its ability to cause unopposed pulmonary vasoconstriction may further increase RV afterload and worsen RV systolic function during PAH.[106] Phenylephrine may also produce reflex bradycardia, which may further compromise RV output in the presence of reduced RV stroke volume. Vasopressin is a potent dose-dependent vasoconstrictor in the systemic circulation (through activation of the V1 receptors in vascular smooth muscle), but it has a different pharmacologic profile in the pulmonary circulation.[106,107,111] The dose–response curve for vasopressin in the pulmonary circulation is biphasic, such that vasodilation occurs at low concentrations (through the release of nitric oxide from the vascular endothelium and activation of the V2 receptors in vascular smooth muscle), and vasoconstriction occurs at high concentrations (through activation of the vascular smooth muscle V1 receptors).[106,107,112,113] The pulmonary vasodilator effect of low-dose vasopressin is an advantage during acute PAH. However, a potential problem when vasopressin is used during acute PAH is its dose-dependent coronary vasoconstrictor effect, which may produce or exacerbate RV ischemia and contribute to contractile dysfunction.[106,114–116] Vasopressin at low doses (0.03 to 0.07 U/min) has been demonstrated to be safe and effective in patients with acute PAH and RV failure.[106] However, the use of a higher dose of vasopressin (0.2 U/min) in a canine model of acute PAH caused an increase in pulmonary vascular resistance and a decrease in RV contractility, reflecting its pulmonary and coronary vasoconstrictor effects.[117] Vasopressin use during PAH should be limited to a low-dose infusion in patients with catecholamine-resistant shock due to peripheral vasodilation according to current recommendations.[106]

Chronic PAH: Right Ventricular Hypertrophy

Chronic PAH occurs as a consequence of many disease states, the classification, etiology, diagnosis, and treatment of which are beyond the scope of the current review and are addressed in detail elsewhere.[118–121] The increase in RV wall stress due to chronically elevated intraluminal RV pressure can be blunted by an increase in wall thickness or a reduction in internal radius (law of Laplace). The RV adapts to chronic PAH by increasing muscle mass (concentric hypertrophy) similar to the response of LV to chronic elevations in afterload (pressure–overload hypertrophy).[3,122] These compensatory changes serve to maintain stroke volume. The increased wall stress raises the oxygen demand of the hypertrophied RV. The loss of the RV oxygen extraction reserve[78] and an impairment to RV perfusion[79] provide obstacles for satisfying this increased oxygen demand. Several factors are responsible for the limitation of RV perfusion in chronic PAH. First, coronary microvascular growth by angiogenesis fails to match myocyte growth in the hypertrophied RV, resulting in a reduction in myocardial blood flow per gram of tissue and a decline in coronary flow reserve, most prominently within the subendocardium (fig. 8).[39,79,122,123] Second, right coronary blood flow becomes strongly biphasic, with the systolic/diastolic flow ratio declining in proportion to the magnitude of the increase in RV systolic pressure (figs. 8 and 9).[79] Third, chronic PAH is accompanied by microvascular dysfunction in the RV, including impaired coronary vascular endothelial reactivity.[3,122] Finally, arterial hypotension accompanies chronic PAH, in part because of ventricular interdependence, which, in turn, further reduces the pressure gradient for RV perfusion because of elevated RV intramural

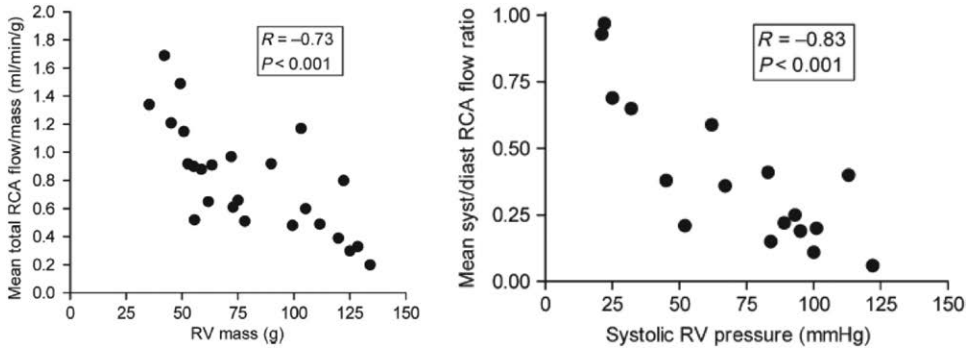

Fig. 8. *Left*, Inverse correlation between right ventricular (RV) mass and mean blood flow in the right coronary artery (RCA) per gram of myocardial mass in patients with chronic pulmonary hypertension. *Right*, Inverse correlation between systolic RV pressure and mean systolic/diastolic flow ratio in RCA in patients with chronic pulmonary hypertension. Published with permission from van Wolferen *et al*.[79]

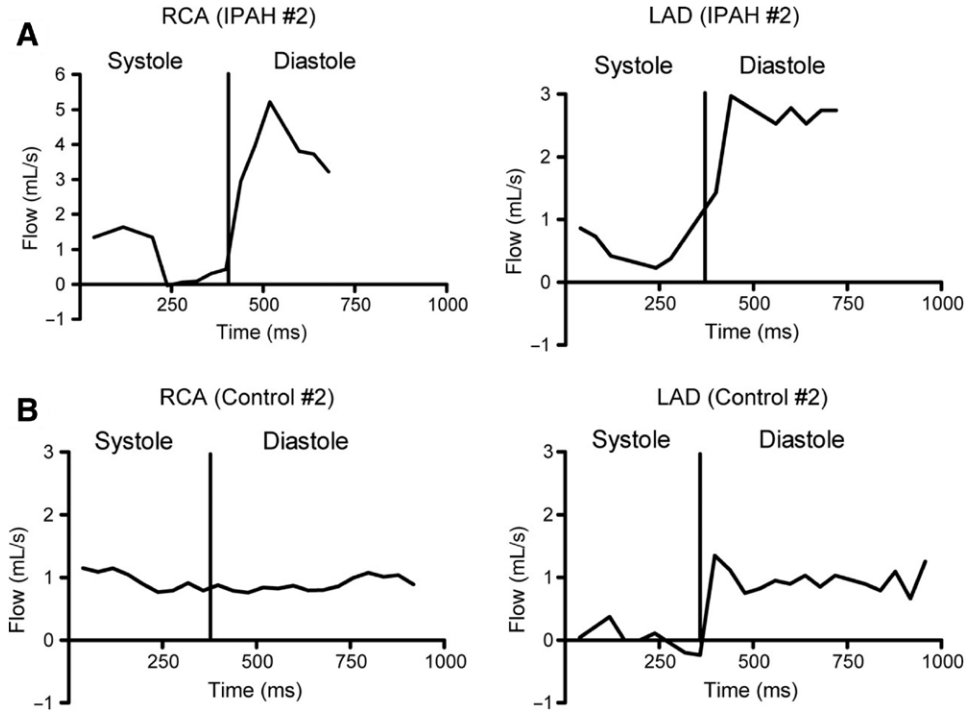

Fig. 9. Representative tracings of phasic blood flow in the right coronary artery and left anterior descending coronary artery in a patient with chronic pulmonary artery hypertension (*top*) and a healthy control (*bottom*). Of note is that right coronary blood flow is relatively constant across the cardiac cycle in the normal patient but nearly limited exclusively to diastole in the patient with chronic pulmonary hypertension, essentially mimicking the phasic distribution of coronary blood flow in the normal left coronary circulation. Published with permission from van Wolferen *et al*.[79]

pressure.[123] Evidence of RV ischemia has been detected in patients with chronic severe PAH using myocardial scintigraphy and is directly correlated with the development of RV systolic dysfunction.[124] The ability of increased wall stress resulting from eventual RV dilation to increase myocardial oxygen demand while simultaneously decreasing myocardial oxygen supply is the basis of a vicious cycle of additional RV dysfunction and dilation leading to overt RV failure.[122]

A recent pilot study using stereologic techniques demonstrated a strong correlation between total vascular length and myocyte volume in RV specimens obtained postmortem from four patients with advanced PAH and three control patients.[125] These interesting findings suggest that capillary growth by angiogenesis may limit oxygen diffusion distances in the hypertrophied RV thus helping to maintain myocardial oxygen delivery. Their importance awaits confirmation with a larger number of specimens.

Patients with chronic severe PAH with RV hypertrophy present a special challenge for the anesthesiologist. Maximizing RV oxygen supply while minimizing RV oxygen demand is an important goal in management of these patients. Maintenance of RCA perfusion pressure and a reduction in RV

Table 3. Compared to the Left Ventricle, the Right Ventricle Has Distinctive Characteristics (Listed Below) Relative to Its Regulation of Blood Flow and Maintenance of Oxygen Supply–Demand Balance

Lack of mechanical inhibition to perfusion during ventricular contraction; blood flow well maintained throughout entire cardiac cycle
Lower baseline oxygen demand because of lower developed systolic pressure and less wall stress
Release of nitric oxide from vascular endothelium causing modest coronary vasodilation at baseline
Lower baseline values for both blood flow and oxygen extraction; the latter results in oxygen extraction reserve, which can be recruited to offset decreases in blood flow or to help satisfy increases in oxygen demand during inotropic stimulation
Less effective pressure–flow autoregulation
Transmurally uniform reduction in blood flow beyond hemodynamically significant epicardial coronary stenosis
Enhanced myocardial oxygen utilization efficiency during reduced perfusion pressure, *i.e.*, upstream coronary stenosis, allowing avoidance of myocardial ischemia and maintained contractile function despite reduced blood flow
Pronounced responsiveness to α-adrenergic vasoconstriction

afterload (*e.g.*, milrinone or inhaled selective pulmonary vasodilators) are often essential to achieve these objectives.

CONCLUSIONS

The principles and limitations of right coronary blood flow described in the current review have been primarily defined in canine models. With the exceptions already outlined, there is no reason to suspect that these basic principles of right coronary physiology are not applicable to humans. Nevertheless, caution should be exercised in applying them to patients with or without heart disease, advanced age, coexisting diseases (*e.g.*, diabetes mellitus), or those receiving anesthetics or other vasoactive medications with independent effects on the RV vasculature. For example, the evidence is convincing that the volatile anesthetics cause coronary vasodilation in the LV.[126–128] Although this action has not been as definitely demonstrated in the RV, its occurrence is likely. With these caveats in mind, the following general conclusions can be drawn. The determinants and regulatory mechanisms governing coronary blood flow in the RV differ substantially from those in the LV, as summarized in table 3. These differences include the lack of a systolic mechanical impediment to perfusion, the existence of an oxygen extraction reserve, and the ability to downregulate the myocardial oxygen requirement during hypoperfusion. These factors favor the maintenance of RV oxygen supply–demand balance and thus provide protection against ischemia-induced contractile dysfunction and injury. However, the mechanisms are compromised during acute or chronic increases in RV afterload resulting from PAH. Indeed, impaired right coronary blood flow has been shown to play a major role in the RV dysfunction in the presence of severe PAH. The right coronary circulation is susceptible to α-adrenergic receptor vasoconstriction when norepinephrine is administered to treat systemic hypotension, especially in the presence of reduced inotropic reserve or coronary atherosclerosis.

Future research in RV hemodynamics should include studies in human subjects. Such research may be facilitated by recent advances in nuclear imaging, allowing an assessment of RV perfusion, metabolism, morphology, and contractile function in a single test session.[129] While having diagnostic and prognostic value, this emerging technology also provides an opportunity for confirming previous findings in animal models and for clarifying the role of impaired perfusion in RV disease.

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Competing Interests

The authors declare no competing interests.

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