Coronary vasoregulation in health and disease

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The present article reviews pertinent contributions from the Coronary Physiology Research Group at the Quebec Heart Institute to the understanding of coronary physiology in health and disease. Mechanisms that contribute to regulation of coronary blood flow and its distribution across the ventricular wall are discussed. Data from animal studies of ischemia-reperfusion injury are also presented and discussed in the context of current concepts regarding postischemic myocardial protection strategies. Future research directions regarding the cardiac nervous system and its importance in the regulation of coronary blood flow, cardiac function and myocyte injury during acute myocardial infarction are also discussed.

Key Words: *Autoregulation; Cardiac nervous system; Ischemia-reperfusion injury; Ischemic preconditioning; Myocardial blood flow; Vasoregulation*

Early interests of clinical researchers at the Quebec Heart Institute focused on various aspects of cardiac physiology, biochemistry (ie, metabolism) and pathology. In the late 1970s, the Quebec Heart Institute recruited Dr Jacques Rouleau, a cardiologist whose primary research interests focused on biophysical mechanisms that regulate the distribution of blood flow across the ventricular wall. The later addition to this laboratory of Dr John Kingma, whose research focused on mechanisms involved in myocardial protection following ischemia-reperfusion injury, created a basic science-clinical research collaboration that continues today.

The principal function of the heart is to supply the different organs in the body with blood containing essential nutrients and oxygen required for their proper functioning. In addition, the heart is essential for the transport of metabolic waste products, the accumulation of which would influence organ function. Mechanical work necessary to pump blood is performed by the myocardium. Proper functioning of the myocardium depends on blood flow in the coronary circulation, which comprises large epicardial conductance vessels originating from the coronary ostia. These large vessels branch into smaller vessels that supply the capillary network responsible for the transport of oxygen and nutrients to the myocytes. Comprehension of mechanisms responsible for regulation of the coronary circulation requires the interpretation of information from several disciplines, including cardiology, physiology, biochemistry and physics; this list is far from exclusive because new information regarding interactions of molecular and mechanical signals is consistently being added to the equation. The present review summarizes several achievements resulting from this research collaboration over the past two decades.

Régulation coronarienne du coeur sain et malade

Cet article résume diverses contributions du Groupe de recherche en physiologie coronarienne de l'Institut de cardiologie de Québec qui permettent de mieux comprendre l'importance de la régulation coronarienne du coeur sain et malade. Les mécanismes qui contribuent au contrôle du débit sanguin coronarien et de sa distribution à travers les parois ventriculaires sont discutés. Les données expérimentales d'ischémie-reperfusion chez l'animal sont aussi présentées dans le contexte actuel de protection du myocarde post-ischémie. Les directions futures de la recherche impliquant le système nerveux cardiaque et son rôle dans le contrôle de la perfusion coronarienne, de la fonction cardiaque et de la protection cellulaire durant l'infarctus aigu du myocarde sont aussi discutées.

REGULATION OF THE DISTRIBUTION OF MYOCARDIAL BLOOD FLOW

Control of the coronary circulation involves a host of interactions among mechanical factors, such as arterial pressure, blood flow, ventricular contraction and myocardial wall tension. Suffice it to say that coronary blood flow is never constant but rather adaptive in relation to the metabolic and oxygen requirements of the myocardium; approximately 70% of oxygen transported is extracted from blood flowing in arterial vessels. This intrinsic capacity of arterial vessels to adjust in calibre and maintain constant perfusion over a range of arterial pressures is referred to as 'coronary autoregulation' (Figure 1). Principal mechanisms involved in the control of coronary blood flow include metabolic mediator(s) between myocytes and vascular cells, myogenic tone (induced by stretch) and neurogenic stimulation. However, studies on flow control mechanisms in the coronary circulation are limited because function of intramyocardial resistance vessels cannot be investigated with the currently available techniques. Exercise-induced increases in myocardial oxygen demand are accommodated by increases in coronary blood flow, the latter being controlled by local regulatory processes that fine-tune the oxygen supply to myocardial metabolic demands. Assessments of the relation between coronary perfusion pressure and blood flow allow us to better understand in situ mechanisms that control coronary circulation under physiological or pathophysiological conditions.

Early research projects by the Coronary Physiology Research Group at the Quebec Heart Institute focused primarily on extravascular factors that could affect coronary blood flow regulation. The Group investigated whether muscular

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Figure 1) Relation between diastolic coronary pressure and blood flow (upper panel) during autoregulation (filled circles) and maximal coronary vasodilation (dotted line). Lower panel The subendocardial to subepicardial tissue blood flow ratio (endo/epi ratio). With normal tone, coronary blood flow and endo/epi ratio are constant over the autoregulatory range. During maximal coronary vasodilation, the relation between coronary pressure and both coronary blood flow and endo/epi ratio is linear. The lower pressure limit (LPL) of autoregulation can be modulated to higher (rightward shift) or lower (leftward shift) diastolic coronary pressures in response to myocardial oxygen demand, in the presence of cardiovascular disease and during therapeutic interventions. Adapted from data from reference 82

coronary artery overbridging could induce myocardial ischemia in a canine model and documented that transient systolic compression (ie, simulates myocardial bridging) of the left coronary circumflex artery results in a diastolic lag time that is necessary to repressurize the distal coronary bed (1). Diastolic lag time may be an important limiting factor for myocardial perfusion, particularly during tachycardia and coronary vasodilation. In patients with myocardial bridging, medical, interventional or surgical therapy markedly improves patient status and relieves angina and ischemia (2).

Modulation of coronary sinus outflow pressure in normal canine hearts affects intramyocardial tissue pressure and has been shown to reduce blood flow in the subepicardial tissue layer independently of coronary artery pressure (3,4). This is of clinical relevance following the Fontan operation, in which right atrial and coronary sinus pressures are often elevated (5). Similarly, when the effect of acute tamponade was examined in dogs, it was found that increased venous outflow pressure contributed to reduced myocardial perfusion (6).

When diastolic coronary perfusion pressure drops below the lower limit of autoregulation, myocardial ischemia ensues; this situation is exacerbated in diseased coronary vessels. In hypertensive patients, lowering of diastolic perfusion pressure by treatment with antihypertensive drugs has been shown to reduce cardiovascular morbidity and mortality (7,8). In men with systolic hypertension, a J-shaped curve has been reported between cardiovascular mortality and diastolic blood pressure (9,10); however, the existence of a J effect remains controversial. In patients with underlying ischemic heart disease, coronary vessels may be particularly sensitive to minor decreases in diastolic coronary pressure. In the International Verapamil SR-Trandolapril (INVEST) study, a J effect with a nadir at a diastolic blood pressure of 84 mmHg (systolic blood pressure of 119 mmHg) for all-cause mortality was reported (11,12). Berl et al (12) recently concluded that blood pressures less than 120/85 mmHg were associated with an increase in cardiovascular events in patients with diabetic nephropathy. Adverse cardiovascular events occur when the coronary vascular reserve is exhausted; to further understand the underlying mechanisms that may be responsible, coronary autoregulation was assessed in a canine experimental model of left ventricular hypertrophy. Acute treatment with an angiotensin-converting enzyme inhibitor significantly lowered the coronary autoregulatory break point; however, the distribution of blood flow across the left ventricular wall was preserved and the subendocardial vascular reserve was also maintained (13). On the basis of these findings, it was concluded that the beneficial effects of treatment with angiotensin-inhibiting drugs in hypertensive patients with left ventricular hypertrophy may be due to preserved autoregulatory capacity and may explain the beneficial outcome with these pharmacological agents in patients with hypertension and left ventricular hypertrophy.

Risk of cardiovascular events and mortality (14,15) is also increased in the setting of renal failure. Indeed, many factors that influence cardiovascular function, including direct hemodynamic effects, neurogenic reflexes and circulating hormones (16,17), are modulated in these patients. To further understand cardiorenal interactions on coronary vasoregulation, a canine model of acute renal failure was developed. Experimental findings showed a reduction in coronary vasodilatory reserve, vascular reactivity and a shift of the autoregulatory break point to higher diastolic coronary pressures (18). Each of these factors contributes to increase the risk of an adverse coronary event in these patients, particularly when elevations in myocardial oxygen demand are not met due to a limited coronary vascular reserve.

The role of the central nervous system in the regulation of cardiac function and the coronary circulation is emerging as an important area of research. Postganglionic neurons that have been identified within discrete fat pads on the surface of the heart have been shown to modulate cardiac function in mammalian species (19). Exposure of these neurons to various chemicals can either activate or suppress information processing by the intrinsic cardiac nervous system. In canine models of acute and chronic cardiac decentralization, it has been observed that intrinsic cardiac neurons can contribute to coronary autoregulatory control and distribution of myocardial blood flow. In addition, in the chronic decentralized dog, angiotensin-converting enzyme inhibition allows the heart to work at lower coronary perfusion pressures while at the same time preserving distribution of myocardial blood flow (20). A

mismatch between the myocardial oxygen supply and the oxygen demand was also observed in decentralized hearts and it is believed that when cardiovascular nervous system connections are ablated, small increases in myocardial oxygen demand result in the maldistribution of blood flow with attendant reductions in systemic oxygen transport. This leads to subendocardial ischemia and left ventricular contractile dysfunction (work capacity), which would probably be exacerbated with the presence of progressive vascular disease. Reductions in coronary flow reserve and the onset of subendocardial ischemia during myocardial stress in the decentralized heart may therefore contribute to progressive cardiovascular dysfunction as observed in cardiac transplant patients (21).

Progressive loss of coronary autoregulation in diseased coronary vessels provides an important substrate for myocardial ischemia and subsequent infarction. To limit myocardial injury induced by acute coronary occlusion, numerous interventions (ie, pharmacological and nonpharmacological) aimed at protecting the ischemic heart have been examined. Some of the findings obtained from these studies, mostly conducted in large animal experimental preparations, are discussed below.

MYOCARDIAL PROTECTION

Considerable fundamental, epidemiological and interventional research efforts have contributed to the development of pharmacological and interventional treatment strategies to limit morbidity and mortality caused by an acute coronary event.

Ischemia causes vascular injury with attendant dysfunction in conductance and resistance vessels (22-24); resultant vascular incompetence impairs the ability of the heart to respond to recurrent ischemic episodes (25,26). Animal studies (27-30) have shown both antinecrosis and antiarrhythmic effects with a host of pharmacological agents that modulate different intra- and extracellular mechanisms. Indeed, Kingma et al (27,28), Denniss et al (29) and Werns et al (30) have documented significant reductions of infarct size in animal preparations of chronic coronary artery occlusion in the absence of restoration of blood flow. Acute myocardial infarction significantly lowers vasoregulatory capacity, which probably contributes to reducing contractile dysfunction; however, postischemic deficits in cardiac contractile function (ie, myocardial stunning/hibernation) are dependent on the duration or severity of the ischemic insult and on the adequacy of return of blood flow to reversibly injured myocardium (31,32). Improvement of blood flow at the microvascular level may speed healing and reduce the degree of infarct expansion and myocardial remodelling (33). However, it is possible that restoration of blood flow to previously ischemic but reversibly injured myocardium could provoke further cellular damage (34-36). Precise causes of this so-called 'reperfusion injury' have not been established, and the mechanisms involved remain controversial (37,38).

Interestingly, the myocardium can adapt to potentially lethal exogenous stresses without pharmacological or medical interventions. Murry et al (39) initially showed that myocardium subjected to brief, repeated episodes of sublethal ischemia becomes highly tolerant to the consequences of subsequent lethal ischemia. This endogenous cellular adaptation, more commonly referred to as ischemic preconditioning (IPC), has been documented in many mammalian species, including humans (40-42), and is not necessarily exclusive to the heart. IPC-mediated cytoprotection is biphasic: an early phase develops within minutes of the initial ischemic event and lasts 2 h to

3 h (39), while the delayed phase is initiated within 12 h and lasts three to four days (43,44). Early IPC is probably triggered via stimulation of different receptor subtypes and/or upregulation of signal transduction pathways (45-48). The most salient effect of IPC is protection of myocytes against ischemic injury. Few studies have shown a positive influence of IPC on restoration of cardiac contractile function (49). Protection against vascular dysfunction by IPC also remains controversial (50-53), but several studies have shown that preconditioning pretreatment protects blood vessels and possibly the microcirculation against vascular stunning (54,55). The mechanisms that are responsible for cytoprotection against infarction and contractile or vascular stunning are not the same, and many of these mechanisms are believed to be shared. An in-depth investigation of myocardial distribution of blood flow post-IPC has not been performed but merits consideration because restoration of blood flow plays an important role in myocardial remodelling after acute myocardial infarction. It is imperative to understand that restoration of blood flow in the larger conductance vessels does not automatically reflect restoration of blood flow in the microvasculature, particularly at the level of the subendocardial tissue layers. Delayed IPC, more commonly referred to as the 'second window of protection', is somewhat less cardioprotective than that observed with early IPC; the transcription of proto-oncogenes, stress proteins and antioxidant proteins have been proposed as potential mechanisms (56-58). Preconditioning studies by Boudriau et al (59) targeted different proteins that comprise the cardiac cytoskeleton; alteration of proteins that link the cytoskeleton and sarcolemma and their causal relation to cellular adaptation postischemia remain to be determined. Changes in the organization of cytoskeletal proteins are reported to be involved in gap junction assembly and migration (60). In studies by Daleau et al (61), a spatial reorganization of the gap junction complex was documented that may contribute to IPC-mediated limitations in cardiac arrhythmias. Kingma (58) reported the rapid induction of cytoprotective genes that are part of the stress protein family and nuclear proto-oncogenes following IPC in rabbit hearts. Although definite progress has been made to define cellular mechanisms involved in the IPC phenomenon, mostly in animal models, this nonpharmacological approach to confer resistance to ischemia-induced injury may be difficult to harness as a clinical tool due, in part, to logistical and ethical difficulties. Some of the potential mechanisms for IPC-induced attenuation of angina symptoms have also been examined in clinical studies at the Quebec Heart Institute (62,63). Briefly, patients with ischemic heart disease underwent successive treadmill exercise tests (ie, Naughton protocol) separated by brief rest periods. Attenuation of myocardial ischemia in these patients could not be explained by downregulation of myocardial contractility, improved myocardial perfusion (assessed by Tl-201 single photon emission computed tomography imaging), or blockade of adenosine receptors or potassium ATP channels. Interestingly, 'warm-up' or 'walk-through' angina (ie, symptoms provoked by initial exertion are attenuated or disappear if exertion is momentarily diminished or stopped before resumption of exertion) is frequently described in patients with chronic ischemic heart disease and may be somewhat analogous to the experimental phenomenon of IPC.

While it is conceivable that direct induction of ischemia could be used to precondition vital organs via angioplasty, coronary bypass surgery or cardiac transplantation, other safer

interventions should be explored. Indeed, pharmacological stimulation of opioid receptors has been documented to confer cardioprotection in various animal models (64) and may be used in the clinical setting. While the mechanisms responsible for opioid-induced cardioprotection are not clear, it is possible that activation of opioid receptors within the central nervous system may contribute either directly or indirectly to cardioprotection. Recent studies also document cellular protection of the heart by postconditioning (ie, repetitive ischemia-reperfusion episodes after reopening the infarct-related artery) (65) and remote IPC, in which protection appears to be transduced from one organ to another (66,67) via humoral factors (68,69) or activation of the autonomic nervous system (70).

As indicated earlier in the present overview, an interest has developed in understanding the role of the central nervous system in the regulation of cardiac physiology. As such, studies have been initiated to examine whether the cardiac nervous system influences the development of cellular injury in various models of ischemia-reperfusion injury. Beneficial actions of either beta-blockers or angiotensin-converting enzyme inhibitors for the clinical management of cardiac pathology probably occur via direct actions of these drugs on cardiomyocytes, or by indirect actions that include modulation of intrinsic cardiac neurons of the cardiac nervous system (71,72). Numerous intracardiac ganglia with independent functions are found in fat pads on the surface of the heart (73). Direct involvement of these intracardiac neurons on IPC-mediated cardioprotection has not been examined; however, autonomic ganglion blockers (ie, trimetaphan and hexamethonium) have been reported to block IPC-mediated protection (66,74,75). These drugs are known to produce significant systemic effects that may affect other cellular adaptive pathways. Local triggers, such as nitric oxide, bradykinin and adenosine, are considered important mediators of IPC-induced protection (76,77). However, these compounds have also been shown to directly activate the autonomic nervous system (70,74). Pre-emptive neuromodulation therapy by spinal cord stimulation is now being used in patients with chronic angina that is refractory to standard treatment strategies (ie, medication or revascularization procedures) (78), and this approach has recently been reported to reduce infarct size in rabbits (79). This cardioprotection may involve the participation of cardiac adrenergic neurons. A study by Kingma et al (80) in dog hearts subjected to brief (ie, 5 min) coronary occlusion-reperfusion showed that spinal cord stimulation had little effect on ventricular dynamics or distribution of blood flow across the ventricular wall; however, these studies were done in healthy dogs with no detectable myocardial necrosis. More recent studies (preliminary unpublished results) examined infarct size in innervated and denervated canine hearts subjected to the classical IPC protocol (39) followed by 90 min of regional coronary occlusion and 180 min of reperfusion. These results support earlier observations of smaller infarcts (approximately 28% smaller than controls) in denervated hearts (81). In innervated and denervated hearts pretreated by IPC, infarct size was approximately 31% and 36% smaller, respectively, than the corresponding non-IPC control hearts. As such, the presence of larger infarcts in normally innervated hearts is probably related to cardiac stresses originating from activation of sympathetic or parasympathetic pathways following the onset of acute myocardial infarction.

CONCLUSIONS

The present report summarizes some of the experimental findings of the Coronary Physiology Research Group over the past two decades. The Group has been particularly interested in examining different intrinsic factors that are responsible for modulating tone at the level of the microvessels and that can influence heterogeneity of blood flow distribution across the myocardial wall in relation to oxygen supply and demand requirements. The majority of the Group's studies used animal models (ie, canine, porcine and ovine) with no underlying cardiac pathology. However, more recent research efforts have attempted to simulate pathological conditions, including left ventricular hypertrophy, acute renal failure and cardiac decentralization. Knowledge gained from these research endeavours may contribute to improved treatment strategies targeted at factors that influence heart rate, arterial blood pressure and, ultimately, distribution of blood flow to target organs.

The present paper has also summarized some of the research findings regarding the development of tolerance to cellular injury after acute disruption of coronary blood flow. Cardioprotection provided by different pharmacological and nonpharmacological interventions has been shown to delay the development of transmural infarcts; however, in accordance with numerous published findings, myocardial protection is not permanent, and neither vascular nor ventricular contractile function is preserved. A possible explanation for these results is that research efforts have mostly targeted the myocyte component of the heart with little consideration for the cardiac nervous system. Novel attention is currently being devoted to cardiac neural mechanisms, which have been shown to be involved in cardiac dynamics, vasoregulation and regulation of contractile function. Further basic science studies are needed before these findings can be translated into a clinical reality that would benefit patients with coronary artery disease.

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