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Review article

Regulation of coronary resistance vessel tone in response to exercise

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ABSTRACT

Exercise is a primary stimulus for increased myocardial oxygen demand. The ~6-fold increase in oxygen demand of the left ventricle during heavy exercise is met principally by augmenting coronary blood flow (~5-fold), as hemoglobin concentration and oxygen extraction (which is already ~70% at rest) increase only modestly in most species. As a result, coronary blood flow is tightly coupled to myocardial oxygen consumption over a wide range of physical activity. This tight coupling has been proposed to depend on periarteriolar oxygen tension, signals released from cardiomyocytes and the endothelium as well as neurohumoral influences, but the contribution of each of these regulatory pathways, and their interactions, to exercise hyperemia in the heart remain incompletely understood. In humans, nitric oxide, adenosine and K_{ATP} channels each appear to contribute to resting coronary resistance vessel tone, but evidence for a critical contribution to exercise hyperemia is lacking. In dogs K_{ATP}-channel activation together with adenosine and nitric oxide contribute to exercise hyperemia in a non-linear redundant fashion. In contrast, in swine nitric oxide, adenosine and K_{ATP} channels contribute to resting coronary resistance vessel tone control in a linear additive manner, but do not appear to be mandatory for exercise hyperemia. Rather, exercise hyperemia in swine appears to involve β-adrenergic activation in conjunction with exercise-induced blunting of an endothelin-mediated vasoconstrictor influence. In view of these remarkable species differences in coronary vasomotor control during exercise, future studies are required to determine the system of vasodilator components that mediate exercise hyperemia in humans. This article is part of a Special Issue entitled "Coronary Blood Flow".

Contents

1. Introduction

Cardiac function is critically dependent on adequate oxygenation of the myocardium since oxidative phosphorylation is the most important source of energy production, with less than 5% of ATP production resulting from glycolytic metabolism [1]. As the heart pumps continuously throughout life, at a rate of at least 60 beats per minute, myocardial energy requirements are high. The heart has therefore been equipped with a very efficient system of oxygen utilization: 60–80% of the arterially delivered oxygen is actually utilized for energy production [2,3] which is achievable due to the high capillary density of 3000–4000 per mm^2 in the myocardium [4].

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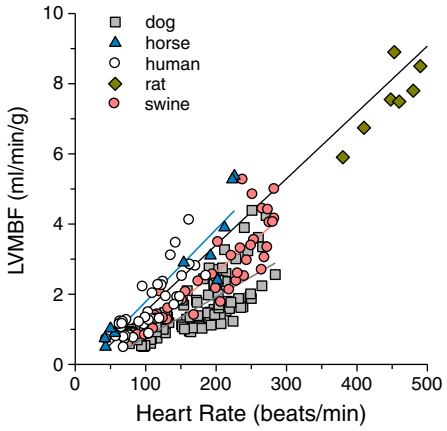

Fig. 1. Relations between heart rate and left ventricular myocardial blood flow (LVMBF) at rest and during treadmill exercise in dogs [9,21,33–61], horses [14,28,62,63], humans [7,22,23,65–76], and swine [17,29,30,32,77–87]. Data from humans were obtained principally from young healthy male subjects performing upright bicycle exercise. Data from rats [88–90] have been added to illustrate that the high LVMBF values in this species are the result of the high heart rates, so that the rat data fall close to the regression line for the human data. Modified from [27] with permission of the American Physiological Society.

In view of the high resting levels of myocardial oxygen extraction, increasing oxygen extraction during exercise [5–10] is insufficient to meet the increased oxygen demand produced by exercise (increasing up to 6-fold during maximal exercise). Hence, the increased myocardial oxygen demands during exercise are met principally by augmenting oxygen delivery, and hence by increasing coronary blood flow (CBF). Moreover, in dogs [11,12], horses [13,14] and sheep [15], oxygen delivery during exercise is further facilitated by increases in hemoglobin of up to 30–50%, while hemoglobin concentrations increase by only 10–15% in swine [16–18] and in humans [19,20]. The increase in CBF results from a combination of coronary vasodilation, with a decrease of coronary vascular resistance during heavy exercise to 20–30% of the resting level, and a 20–40% increase in mean arterial pressure [7–11,14,21–23]. Despite intense research efforts over the past decades, the pathways involved in exercise-induced coronary vasodilation remain incompletely understood. In this review, we provide an update of previous reviews on regulation of CBF during exercise [2,3,24–27]. Although the majority of studies reviewed in this article have been performed in animal species, we have included data from human studies where available which, unless otherwise stated, were performed in healthy volunteers.

2. Coronary blood flow

Dynamic exercise increases CBF in proportion to the increase in heart rate, with peak CBF values during maximal exercise typically 3 to 5 times the resting level [9,14,28–32]. The strong correlation between coronary flow and heart rate occurs because heart rate is a common multiplier for the other determinants of myocardial oxygen demand (contractility and cardiac work), which are computed per beat. Regression analysis of published left ventricular myocardial blood flow data against heart rate demonstrates remarkably similar relationships between canine [9,21,33–61], equine [14,28,62,63], human [7,22,23,65–76], porcine [17,29,30,32,77–87] and rodent [88–90] data during dynamic exercise, although the slope of the regression line is slightly lower in dogs (Fig. 1).

3. Myocardial oxygen extraction

In many species, the increased oxygen demand during exercise is met in part by an increased myocardial oxygen extraction, with widening of the arterio-venous O_2 difference and a decrease in coronary venous oxygen content [9–11,22,33,68,71,91–93]. Thus, in dogs [9,33] and horses [10], myocardial oxygen extraction increases progressively with increasing exercise intensity. In humans, myocardial oxygen extraction increases during heavy exercise [22,68, 71], but lower exercise loads (<70% of maximum heart rate) do not result in increased oxygen extraction or decreased coronary venous oxygen content [6,23,94–97]. In contrast, in swine oxygen extraction remains principally unaltered during treadmill exercise, even at levels of up to 80–90% of maximum heart rate [18,79,81,98–103].

The increase in oxygen extraction during intense exercise in dogs and horses is not the result of exhaustion of coronary vasodilator reserve during exercise, since a further increase in CBF can be elicited with a pharmacologic [14,28,30,32,36,78] or ischemic [9,32] vasodilator stimulus. The presence of significant vasodilator reserve during exercise is corroborated by lack of metabolic evidence that ischemia occurs in the normal heart even during heavy exercise, as several studies demonstrated continued lactate consumption even during heavy exercise [6,22,68,93].

4. Regulation of coronary resistance vessel tone during exercise

During exercise the increase in aortic pressure only slightly exceeds the increase in effective back pressure, so that the effective perfusion pressure increases by no more than 20–30% [10,104]. Consequently, the exercise-induced 4 to 6-fold increase in CBF is mediated principally by a decrease in coronary vascular resistance. Indeed, maximal exercise is associated with decreases in calculated coronary vascular resistance to 20–30% of basal resting values in dogs [8], horses [14,28], humans [22,68], and swine [78].

Regulation of coronary vascular resistance is the result of a balance between a myriad of vasodilator and vasoconstrictor signals exerted by metabolic signals from the myocardium, the endothelium, and neurohormonal influences. These signals enable the heart to match the coronary blood supply to the need for oxygen and nutrients, while maintaining a consistently high level of oxygen extraction. The ability of coronary resistance vessels to dilate in response to increments in myocardial oxygen demand, as illustrated by the tight correlation between myocardial oxygen consumption and CBF, is critical for maintaining an adequate supply of oxygen to the heart.

To investigate the mechanisms involved in vasodilation or vasoconstriction in response to various stimuli, including supernatant of isolated cardiac myocytes that were electrically stimulated at

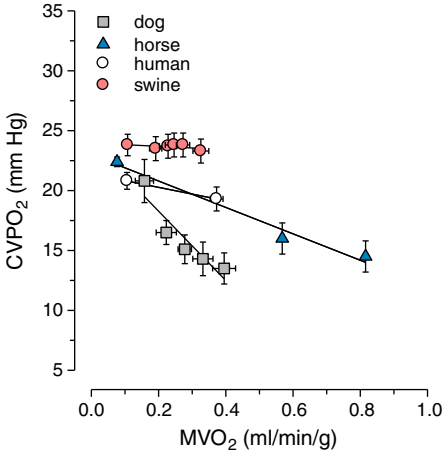

Fig. 2. Relation between myocardial oxygen consumption (MVO_2) and coronary venous oxygen tension ($CVPO_2$) at rest and during treadmill exercise in dogs [33], horses [10,14], humans [68], and swine [79]. Note that exercise does not alter coronary venous oxygen tension in swine, whereas it is already reduced at low levels of exercise in dogs. Horses and humans demonstrate an intermediate oxygen tension response. Data are mean ± SE. *$P<0.05$ vs corresponding Rest. See text for further explanation. Modified from [27] with permission of the American Physiological Society.