Withdrawal of vasoconstrictor influences in local metabolic coronary vasodilation

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The coronary circulation has a remarkable ability to match myocardial oxygen delivery with myocardial metabolism (3, 22). For many years this coupling between coronary blood flow and myocardial oxygen consumption has been proposed to be primarily dependent on production of local metabolites released from cardiomyocytes in proportion to the metabolic rate. Despite decades of intensive research, the mechanisms responsible for local metabolic vasodilation have yet to be clearly defined (3, 22). However, recent research has revealed that β-adrenoceptor “feed-forward” dilation (4, 9), H₂O₂, and flow-mediated dilation (11, 18), as well as release of ATP from erythrocytes (2, 6, 8), could play a (major) role in balancing coronary blood flow with myocardial oxygen consumption during conditions such as exercise (see Fig. 1).

In the present issue of the American Journal of Physiology-Heart and Circulatory Physiology, Merkus et al. (16) examine the mechanism of withdrawal of endothelin-mediated coronary vasoconstriction in exercising swine. They found that inhibition of nitric oxide or prostanoid production augmented the influence of endothelin on coronary vasomotor tone during exercise (see Fig. 1). This effect was evidenced by an increase in coronary venous PO₂ (decreased myocardial oxygen extraction) at high levels of myocardial oxygen consumption when nitric oxide synthase and/or cyclooxygenase were inhibited in the presence of nonselective endothelin receptor blockade. This investigation extends the investigator’s previous findings (13, 14) that endothelin exerts a tonic vasoconstrictor influence when metabolic demand is low (i.e., resting conditions) but that this effect wanes as metabolism is elevated with exercise. Withdrawal of endothelin-mediated vasoconstriction at high levels of metabolism has also been documented by other laboratories (7, 20). It does not appear that the diminished vasoconstriction is related to alterations in endothelial release of endothelin because arterial-coronary venous differences are unaltered with exercise. However, there is abluminal release of endothelin, so plasma levels may not adequately reflect the contribution of endothelin to coronary vasomotor tone. Although, in their present study, Merkus et al. (16) demonstrated that blockade of nitric oxide synthase significantly elevated endothelin release at the highest level of exercise, thus it is possible to observe/measure alterations in plasma endothelin levels.

The implications of this study are intriguing in that they suggest that withdrawal of endothelium-dependent coronary vasoconstriction during exercise is mediated by nitric oxide and prostanoids. Thus increases in endothelial shear stress associated with exercise hyperemia likely counteract the effect of endothelin at high levels of oxygen consumption. The authors hypothesize that the following mechanisms could be responsible for their findings: 1) endothelin augments nitric oxide and prostanoid production via activation of endothelial endothelin B receptors (19), 2) nitric oxide and prostanoids inhibit endothelin production and release via a cGMP-dependent pathway (10, 17), and 3) nitric oxide and prostanoids modify endothelin-mediated constriction by altering endothelin receptor sensitivity (23). Another question is whether alterations in cardiac α₁-adrenoceptor stimulation contribute to endothelin-mediated coronary vasoconstriction during exercise, because recent studies indicate that cardiac α₁-adrenoceptor activation promotes endothelin-induced vasoconstriction both in vitro (12, 21) and in vivo (1, 7). This mechanism would actually serve to augment endothelin production and constriction during exercise (see Fig. 1). Additional studies are needed to address these possible mechanisms, specifically coronary endothelin dose-response experiments in the presence and absence of nitric oxide synthase and/or cyclooxygenase blockade.

It is extremely difficult to separate out the direct vasodilatory roles of nitric oxide and prostanoids from their inhibitory effect on endothelin vasoconstriction; that is to say, that because both nitric oxide and, more importantly, prostanoids (15, 16) affect the balance between coronary blood flow and myocardial oxygen consumption at rest and during exercise in swine, it is unclear whether the withdrawal of the vasoconstriction is simply related to the dynamic interaction of endothelium-derived relaxing and constricting factors or whether these specific compounds directly alter/impair endothelin release and/or vasoconstriction. The authors suggest that the withdrawal of the constriction with exercise is not a generalized/nonspecific response because the effect of endothelin receptor blockade still waned during exercise after adenosine receptor blockade. Duncker et al. (5) previously found that adenosine exerts a tonic vasodilator influence at rest and during exercise in swine but that adenosine is not required for local metabolic coronary vasodilation. Whether inhibition of other vasodilatory influences would reverse the decrease in endothelin constriction with exercise is unknown.

Taken together, the findings of Merkus et al. (16) are important because they further question the classical dogma of local metabolic vasodilation, which is that cardiomyocytes release unknown vasodilators that couple coronary vascular resistance/oxygen delivery to the myocardial requirements for oxygen. In addition, their data suggest that there is a fine tuning of vasomotor tone at the vascular level that could more precisely regulate metabolic flow coupling. However, how much control this mechanism would afford is unclear, especially due to the potent, long-acting nature of endothelin-induced vasoconstriction. So, the critical question becomes, What is the relative importance of the withdrawal of endothelin-mediated coronary vasoconstriction to local metabolic control? The waning of vasoconstriction may be due to the overall balance of...
tonic vasodilator and vasoconstrictor pathways in combination with the elevated production of vasodilators that together act to diminish vascular tone, thereby decreasing the contribution of tonic vasoconstrictor pathways to arteriolar resistance. If this hypothesis is correct, then withdrawal of endothelin constriction with elevated oxygen consumption is likely not a mechanism of metabolic dilation and simply reflects increased production of dilators relative to a tonic vasoconstriction. It should be noted that the effect of endothelin receptor blockade on the balance between coronary blood flow and metabolism is quite small under resting conditions (~2 mmHg increase in coronary venous O2; no change in coronary blood flow; Refs. 7, 13, 16, 20). Therefore, even if there is active withdrawal of endothelin constriction with increases in myocardial metabolism, the effect is likely small and of questionable importance to metabolic dilation under normal physiological conditions. However, it is possible that the role of endothelin in coronary vascular regulation would be more prominent under pathological conditions when endothelial dysfunction is present (coronary artery disease, hypertension, diabetes, and heart failure), i.e., when there is diminished nitric oxide bioavailability and elevated endothelin vasoconstrictor influences. Clearly, additional studies are needed to address the physiological and pathophysiological significance of endothelin-mediated vasoconstriction in local metabolic control of the coronary circulation.

In conclusion, the present study of Merkus et al. (16) identified that nitric oxide and prostanoid production attenuates the influence of endothelin on coronary vasomotor tone in exercising swine. This study advances our understanding of the complex interaction between endothelium-derived dilator and constrictor compounds in the coronary circulation and raises intriguing questions pertaining to the classical views of local metabolic control mechanisms that certainly merit further research.

REFERENCES


