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EDITORIAL

Effects of hypoxia on coronary microcirculation during postnatal development

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Coronary microcirculation, functioning as an exchange system for solutes (e.g., oxygen, carbon dioxide, substrates, metabolites) between blood and tissues in the myocardium, is anatomically based on the microvasculature including arterioles, capillaries, and venules. Arterioles (30–300 μm in diameter), surrounded by one or two layers of smooth muscle cells, regulate their vascular tone by constriction or dilatation.[1] Capillaries (10 μm or smaller in diameter), not accompanied by smooth muscle cells but by occasional pericytes, serve as the main functional elements in the solute exchange by diffusion.[1] Small venules (10–50 μm in diameter) are accompanied by pericytes and larger venules (up to 200 μm in diameter) by one or two layers of thin smooth muscle cells.[1] Resistance vessels of coronary vasculature (i.e., small arteries and arterioles) play important roles in coronary flow regulation[2] and turgor effect (e.g., myocardial stiffness).[3,4] Myocardial blood flow is known to be determined by myocardial oxygen demand (heart rate, contractility, ventricular work), oxygen-carrying capacity of arterial blood (hemoglobin, arterial blood saturation of hemoglobin), perfusion pressure, extravascular compressive force, and coronary vascular resistance (smooth muscle tone).[5] Also, myocardial blood flow is influenced by structural alteration of coronary vasculature, for example, vascular growth during postnatal development and vascular hypertrophy during ventricular pressure overload.[6,7] A concept of minimal coronary vascular resistance, calculated by coronary perfusion pressure and flow during maximal coronary vasodilatation, reflects total cross-sectional area (CSA) of the resistance vessels, which helps in assessing structural alteration of coronary vasculature such as vascular growth or hypertrophy in an entire heart.[6] During postnatal development, coronary vasculature is exposed to greater arterial pressure age-dependently with concomitant progression of vascular cell maturity. In response to ventricular pressure overload during postnatal development, the CSA of the resistance vessels increases in proportion to increase of cardiac mass in the early phase (immature phase) but does not change in the later phase (mature phase),[6–9] suggesting that the potential of pressure load-induced vascular growth may be reduced with age and that structural adaptation to a hemodynamic load may shift to adult-type vascular alteration. Similarly, capillary proliferation as a result of hemodynamic overload during fetal or early postnatal development has been demonstrated in the myocardium of several kinds of mammals.[7,10] Capillary growth potential in response to pressure overload has been shown to exhibit an age-dependent reduction.[11]

Hypoxia has been shown to be a potent inducer of capillary growth through vascular endothelial growth factor (VEGF) expression. Tomanek et al. investigated VEGF expression and localization in rat hearts from the first embryonic day of myocardial vascular tube formation through the early postnatal period and found that VEGF expression remained high during the early postnatal period when capillary proliferation is high. They also demonstrated that during the embryonic period the VEGF expression was localized at the epicardial region, farthest from ventricular lumen (i.e., source of oxygen),

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and subsequently it become more evenly distributed transmurally, suggesting that a transmural hypoxic gradient might be related to the vascularization process during perinatal development.[12] Hypoxic preconditioning in adult rats exposed to low-oxygen environment (4-h hypoxia followed by 24-h reoxygenation) has been shown to be protective against coronary occlusion-induced myocardial damage, where the preconditioned heart was accompanied by increased capillary density through VEGF induction even before the ischemic insult.[13] A longer exposure to hypoxia, however, has been shown to result in an opposite effect on VEGF induction. The rat heart pretreated with longer-term hypoxia exhibited failure to increase VEGF mRNA during the subsequent hypoxia following reoxygenation,[14] suggesting inadequate compensatory angiogenesis in the myocardium exposed to chronic hypoxia or cyanosis. In human endothelial cells, chronic hypoxia has been demonstrated to result in loss of VEGF-mediated signaling and angiogenic responses, the mechanism of which is related to inhibition of VEGF-induced endothelial nitric oxide synthase (eNOS) phosphorylation, leading to failure of eNOS activation and resultant decrease of the endothelial NO production required for endothelial cell proliferation, migration, tube formation, and angiogenesis.[15]

The relationship between regional myocardial blood flow and metabolism has been extensively investigated during the past couple of decades because solute exchange in the microcirculation is of great importance in the fields of cardiac physiology and pathophysiology. Perfusion heterogeneity has been discussed on a macroscopic level (ventricular or atrial chamber, "chamber heterogeneity"), a transmural level (subepicardium–subendocardium, "layer heterogeneity"), and a within-layer level ("microheterogeneity").[16] Even in the physiological (resting) state, microcirculation including the levels of small arteries, arterioles, capillaries, and venules has been demonstrated to exhibit spatial heterogeneous distributions of blood flow, reflecting a close relationship between local perfusion and local metabolism (low metabolic rate in low-flow area versus high metabolic rate in high-flow area).[16] Microheterogeneity has been shown to decrease in response to increased workload (e.g., β-adrenoceptor stimulation), indicating flow-pattern adaptation to increased local metabolism.[17] These findings suggest that although the physiological significance of microheterogeneity has not been fully elucidated, blood flow microheterogeneity in the resting state may reflect heterogeneously-existing myocardial cells with lower aerobically metabolic activity (e.g., serving as reserve cells for increased workload). Similarly, myocardial low-flow perfusion or hypoxia has been shown to decrease spatial blood flow heterogeneity, suggesting a mechanism for more efficient oxygen delivery to the myocardial regions in response to decreased oxygen supply.[18,19] Both increased workload and decreased oxygen supply are considered to induce vascular adaptation processes for more homogenous regional blood flow to reduce mismatch between oxygen supply and consumption (i.e., intracellular dysoxia). Metabolically, Ince et al. have demonstrated, using an NADH fluorescence image technique, that the NADH/NAD^+ redox state (an indicator of the balance between oxygen supply and consumption) exhibited a large increase in its spatial heterogeneity during the conditions of reoxygenation after hypoxia or increased heart rate and that the heterogeneity pattern of NADH fluorescence was similar in both conditions,[20] suggesting that at the capillary level, there are certain areas (called "microcirculatory weak units") predisposed to become dysoxic first when exposed to decreased oxygen supply or increased oxygen demand.[21] Therefore, heterogeneous distribution of dysoxic myocytes (less aerobically metabolic myocytes) may play a role in the reduction of spatial blood flow microheterogeneity in the coronary microcirculation under hypoxia or increased workload.

Because spatial microheterogeneity (region-to-region flow variation) has been shown to be substantially greater than temporal microheterogeneity (time-to-time flow variation or "twinkling" in an identical region),[22,23] responsiveness of spatial microheterogeneity, rather than temporal microheterogeneity, to various stimuli (hypoxia, ischemia, or hemodynamic overload) is considered to be a main determinant of pathological alterations of microcirculation. Extrapolating from this to a clinical setting, investigation on alteration of the spatial microheterogeneity in a heart exposed to long-term hypoxia may be of great importance in understanding the mechanism responsible for the altered myocardial characteristics and the responsiveness of the myocardium to ischemia and reperfusion in patients with cyanotic congenital heart disease.

The article by Tomii et al. demonstrated that spatial microheterogeneity (within-layer flow heterogeneity) of blood flow tended to increase (but not significantly) in the myocardium of 4- and 8-week-old rats exposed to a low-oxygen environment during the postnatal period, the mechanism of which may be related to decrease of vascular growth ability as a result of (i) maturation of vascular cells or (ii) chronic exposure to hypoxia. The question that arises here is whether the increase of spatial microheterogeneity resulting from chronic hypoxia during postnatal development is adaptation or exacerbation. Also, Tomii et al demonstrated reoxygenation-induced reduction of spatial microheterogeneity in the

myocardium from chronically hypoxic rats. Would this indicate an acute adaptation to bail out the heterogeneously existing dysoxic myocytes resulting from chronic hypoxia? Additionally, it is still unclear whether alteration of spatial heterogeneity plays an important role in the development of myocardial damage after ischemia and reperfusion in newborns and infants undergoing surgical repair for cyanotic congenital heart disease.

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