PERSPECTIVES | *Regulation of Coronary Blood Flow in Normal and Ischemic States*

Myocardial ischemia: lack of coronary blood flow, myocardial oxygen supply-demand imbalance, or what?

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Heusch G. Myocardial ischemia: lack of coronary blood flow, myocardial oxygen supply-demand imbalance, or what? *Am J Physiol Heart Circ Physiol* 316: H1439–H1446, 2019. First published April 19, 2019; doi:10.1152/ajpheart.00139.2019.—This opinionated article reviews current concepts of myocardial ischemia. Specifically, the historical background is briefly presented. Then, the prevailing paradigm of myocardial oxygen-supply-demand imbalance is criticized since demand is a virtual parameter that cannot be measured and data on measurements of myocardial blood flow and contractile function rather support matching between flow and function. Finally, a concept of myocardial ischemia that focusses on the reduction of coronary blood flow to below 8–10 µl/g per beat with consequences for myocardial electrical, metabolic, contractile and morphological features is advocated.

coronary blood flow; hibernation; myocardial infarction; myocardial ischemia; reperfusion; stunning

INTRODUCTION

Ischemic heart disease has become the most frequent cause of death worldwide in 2017 (11). In the Western world, the mortality from acute myocardial infarction has decreased over the last 2-3 decades, largely secondary to better interventional therapy and better medication (statins, ACE inhibitors/AT_1 antagonists, and antiplatelet drugs), but it has not declined further over the most recent years and persists at a significant level (41, 52), i.e., at around 7% 1-year mortality in trials (12) and around 15% in large registries (54). From a clinical point of view, ischemic heart disease comprises acute myocardial infarction [ST segment elevation myocardial infarction (STEMI) and non-STEMI], stable angina, and ischemic cardiomyopathy. From a conceptual point of view, however, it is not so clear what myocardial ischemia is, other than that it concerns coronary blood flow and the myocardium. In most current textbooks of physiology, internal medicine, or cardiology, myocardial ischemia is defined as an imbalance between supply (of oxygen or of coronary blood flow) and demand (largely for contractile function). While this is an intuitive and persuasive definition, there are in fact a number of conceptual and factual problems with it.

David Hearse collected definitions of myocardial ischemia from a number of "eminent" clinicians and scientists 25 years ago (31), and these definitions varied from short and precise to more lengthy and sophisticated explanations, many of which elaborated on the relation of coronary blood flow to myocardial metabolism and the energetic demand of the myocardium to sustain its function. Hearse grouped my brief definition "myocardial ischemia is any reduction in blood flow that has functional and/or metabolic consequences for the affected myocardium" together with those of Eric Feigl and John Ross, and I felt and still feel very comfortable in that company. I also still stick to my definition from 25 years ago, and I dislike the more popular ideas about "supply-demand imbalance" (39).

HISTORICAL BACKGROUND

Historically, the term "ischemia" (ἰσχαιμία = withholding of blood) goes back to Rudolph Virchow, who in 1858 coined it to characterize reduced perfusion of an organ or tissue with its consequences (31). Of note, ischemia in its strictest sense defines lack of blood, not even blood flow. The *Merriam-Webster Dictionary* defines ischemia as "deficient supply of blood to the body part (such as the heart or brain) that is due to the obstruction of the inflow of arterial blood" (www.merriam-webster.com/dictionary/ischemia). As for the heart, John Erichsen in 1842 reported on experiments in rabbits and dogs where he observed the rapid cessation of cardiac contraction upon ligation of the coronary arteries (18). Julius Cohnheim in 1881 published experiments in dogs where he induced myocardial infarction by coronary artery ligation (51). Coronary obstruction as the cause of myocardial infarction in patients was established by James Herrick at the end of the nineteenth century (32). Whereas the causal relation of total cessation of coronary blood flow to myocardial infarction was easy to conclude, situations of repeated episodes of angina where the coronary circulation was compromised but not totally obstructed and where the consequences were obviously reversible were more difficult to conceptualize. Hermann Rein in the 1930s developed a technique to measure blood flow without opening the vessel (thermostromuhr), and using this technique in dogs, he found coronary blood flow closely related to cardiac output and not simply dependent on perfusion pressure (29). He proposed that coronary blood flow is adapted to cardiac function by coronary vasomotion. Franz Büchner in the 1950s to 1960s used a combination of reduced oxygen supply (hypoxia, anemia) with exercise in rabbits to induce patchy myocardial necrosis and fibrosis, as typically seen at autopsy in patients with ischemic heart disease. With respect to these experiments, Büchner first used the quantitative relation of coronary blood or oxygen supply to myocardial function as a definition of coronary sufficiency or insufficiency (34). In parallel, in the United States, Eugene Braunwald and

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his collaborators worked out the determinants of myocardial oxygen consumption (6); of note, they always used global heart preparations, and it was global oxygen consumption. Subsequently, Braunwald and his collaborators found infarct size from coronary artery occlusion in dogs increased, when the hemodynamic determinants of myocardial oxygen consumption were increased, notably by catecholamines, and conversely infarct size reduced when the hemodynamic determinants of myocardial oxygen consumption were decreased, e.g., by beta blockade (4, 60). From such data, Braunwald and collaborators derived and advocated the idea that the fate of myocardial tissue in the face of an obstructed coronary artery depends on the balance between myocardial oxygen supply and demand (5). Of note, this concept simply equates the oxygen consumption which is derived from global hemodynamics with the oxygen demand of the myocardial region which is dependent on the obstructed coronary artery. Many studies were published that reported reduced infarct size after favorable manipulation of the hemodynamic determinants of myocardial consumption and apparently confirmed the concept. However, on rigorous examination in a National Heart, Lung, Blood Institute cooperative study the idea of infarct size reduction by reducing myocardial oxygen consumption (verapamil) was not confirmed (73). More importantly, in an early clinical trial led by Braunwald, the beta blocker propranolol in patients with acute myocardial infarction reduced heart rate but did not reduce infarct size (74). Up until today, infarct size reduction by beta blockade in patients with acute myocardial infarction is equivocal (50, 53, 75), may depend on the specific beta blocker used rather than on reduced systemic hemodynamics, may occur during ischemia and/or during reperfusion when blood flow/supply is no longer limited, may involve complex cardioprotective signaling (40), and may not be related to effects on cardiomyocytes but on neutrophil stunning and attenuation of coronary microvascular obstruction (21). Nevertheless, following the authoritative view of Braunwald, the supply-demand paradigm was generalized from the situation of acute myocardial infarction to all ischemic heart disease and has become textbook knowledge. The paradigm of supply-demand is then often pictured as a scale.

I have never been comfortable with the oxygen supply-demand paradigm as the cornerstone criterion to define myocardial ischemia (31). Of course, oxygen supply can be measured as coronary blood flow × arterial oxygen content. However, myocardial oxygen demand is not a real, but a virtual parameter. What can be measured, is myocardial oxygen consumption (not demand), and all the estimations of myocardial consumption from hemodynamic determinants relate to global heart preparations and not to myocardial regions with truly reduced coronary blood flow. Thus, I find it far-fetched to assume that the demand of a myocardial region with reduced blood flow can be estimated from the hemodynamic determinants of myocardial oxygen consumption in a whole heart with normal or elevated coronary blood flow. As a side note, the picture of a scale is obsolete, because manipulation of one side of the scale moves the other side into the opposite direction: Why would reduced coronary blood flow/oxygen supply increase contractile function/oxygen demand?

THE CORONARY CIRCULATION PER SE

I have now criticized the oxygen supply-demand definition of myocardial ischemia. Can we define myocardial ischemia from coronary blood flow alone?

Coronary blood flow is determined by perfusion pressure and by coronary vasomotion, secondary to multiple vasomotor mechanisms, including autoregulatory/myogenic, metabolic, endothelial, and neurohumoral, as viewed in detail elsewhere (1, 10, 17, 22). Extravascular compression by the contracting myocardium renders coronary blood flow essentially a diastolic phenomenon, and extravascular compression is of particular importance in the inner myocardial layers at reduced perfusion pressure (9). Atherosclerosis impairs each of these regulatory mechanisms and eventually also physically obstructs the coronary circulation. Through autoregulation, coronary blood flow and contractile function are maintained at a plateau over a range of perfusion pressures and becomes pressure dependent below a pressure of around 40–50 mmHg after exhaustion of autoregulatory mechanisms (8). The level of the plateau and also the position of the left knee below which flow becomes pressure dependent are determined by myocardial metabolism (Fig. 1) (9, 67). The left knee below which flow becomes pressure dependent is markedly increased when endothelium-dependent vasomotion is eliminated by inhibition of nitric oxide synthesis (85). One could conceivably define myocardial ischemia as any situation where coronary blood flow is below the left knee of the autoregulatory curve and is pressure dependent. While such definition might be conceptually sound, on the basis of true rather than virtual data, and could be used on a regional level for a given coronary perfusion territory of an epicardial coronary artery, it would be very difficult to use such definition from a pragmatic point of view. One would have to determine at least the lower part of the autoregulatory curve and would also have to consider that the left knee of this curve will move (upward right with higher myocardial metabolism and with endothelial dysfunction, downward left with lower myocardial metabolism). With coronary atherosclerosis,
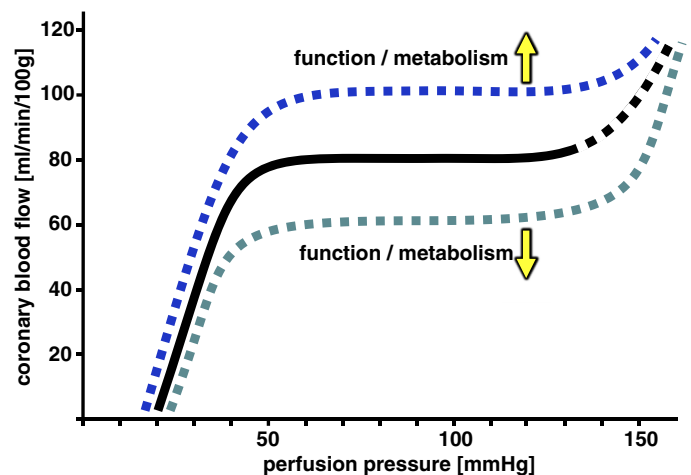

Fig. 1. Relationship of coronary blood flow to perfusion pressure. There is an autoregulatory plateau that is shifted upward with increased cardiac function and metabolism and conversely shifted downward with decreased cardiac function and metabolism. Below a perfusion pressure of about 40-50 mmHg flow is pressure-dependent modified. Modified from Mosher et al. (67) with permission.

the autoregulatory pressure-flow characteristics are further altered.

So, against this background, I am advocating my definition of myocardial ischemia as "any reduction in blood flow that has functional and/or metabolic consequences for the affected myocardium" from both a conceptual and a pragmatic point of view. What exactly are these consequences of reduced coronary blood flow?

ELECTRICAL ACTIVITY

Clearly, the action potential characteristics and the ECG change after reduction of coronary blood flow. However, ECG changes are difficult to interpret mechanistically. The detected changes do not only depend on the relative position of the "ischemic" myocardium to the respective ECG lead. It is also unclear which ECG parameter most sensitively detects "ischemia" and is proportionate to the reduction of coronary blood flow (55). Arrhythmias are a characteristic and often ominous consequence of myocardial ischemia (59).

METABOLISM

The myocardium uses the free-energy change from ATP hydrolysis to sustain its energy-consuming processes, i.e., ion pumps, contractile function, and maintenance of its structure by synthesis, degradation, and recycling processes. Thus, a reduced free-energy change from ATP hydrolysis reflects a lack of adequate energy supply to maintain myocardial functions. During steady-state conditions, such reduced free-energy change of ATP hydrolysis can be calculated from measurements of ATP, creatine phosphate, and inorganic phosphate in biopsies (61) or from nuclear magnetic resonance spectroscopy (25), but such measurements are sophisticated, tedious, and available only in a few centers, and they are certainly not on line with an acute reduction in coronary blood flow. A shift from aerobic to anaerobic glycolysis is more easy to assess from the arterio-coronary venous lactate concentration difference and net lactate production in severe myocardial ischemia. However, with more subtle and only regional ischemia, possibly only in subendocardial layers, net lactate production in some myocardial regions can be obscured by lactate uptake in other regions. A sophisticated lactate labeling technique is then required to ascertain regional myocardial ischemia from lactate production and to distinguish it from reduced lactate uptake in other areas (28).

CONTRACTILE FUNCTION

Within the autoregulatory range and above the left knee of the pressure-flow relationship, metabolic coronary vasodilation increases coronary blood flow in response to increased contractile function, i.e., flow follows function. The reverse causality, i.e., an increase in contractile function in response to increased coronary blood flow within the autoregulatory range (Gregg phenomenon), does not exist in the blood-perfused in situ mammal heart (78). Below the left knee of the pressure-flow relationship where flow is linearly related to perfusion pressure, function follows flow. In fact, there is a more or less linear relationship between regional contractile function, as assessed by sonomicrometry of systolic wall thickening or segment shortening, and regional myocardial blood flow, as assessed by microspheres, with progressive narrowing of an
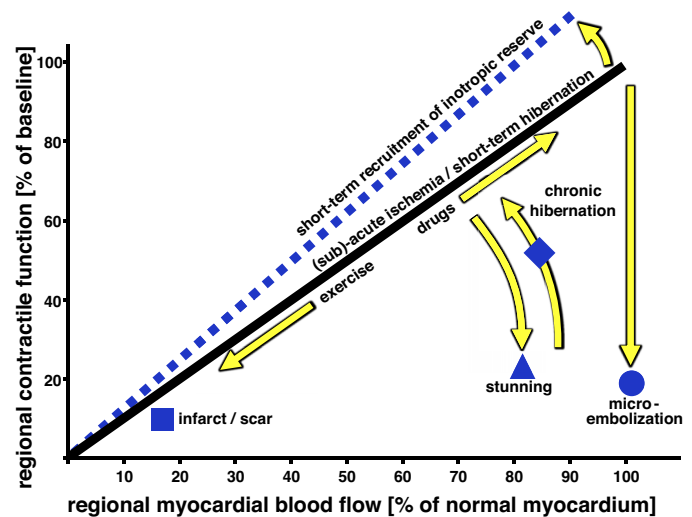

Fig. 2: Relationship of regional contractile function to regional myocardial blood flow. There is an almost linear relationship between function and flow such that during exercise-induced ischemia both flow and function are proportionately reduced and conversely proportionately increased by drug treatment. This flow-function relationship can persist for hours during short-term hibernation and can only be briefly shifted upwards by inotropic stimulation. With stunning (postischemic contractile dysfunction) and microembolization, contractile function is decreased in the absence of a detectable flow reduction. With chronic hibernation which results from repetitive stunning, matching of flow and function is restored. From Heusch (36) with permission.

epicardial coronary artery (Fig. 2) (19, 20, 36, 80, 90). Importantly, the regional myocardial blood flow measurement with microspheres also reflects the result of any flow redistribution within the perfusion territory of an obstructed epicardial coronary artery, notably transmural redistribution to subepicardial layers at the expense of subendocardial layers and flow distribution along collaterals between ischemic and nonischemic myocardial regions, i.e., steal and reverse-steal phenomena (2). The geometric shape of the flow-function relationship varied somewhat in different studies. Canty found the relation between subendocardial blood flow and subendocardial segment shortening linear (8), whereas Vatner found it more exponential but again mostly linear at more severe blood flow reduction (90). Transmural contractile function is largely determined by subendocardial blood flow, and there may be subepicardial dysfunction at (near-)normal subepicardial blood flow, possibly through a tethering effect (87, 88). The relation of subendocardial and transmural blood flow to transmural wall thickening was consistently linear (8, 19, 20). Of note, a quantitative relation between regional myocardial blood flow and function can only be determined under steady-state conditions, since the microsphere measurements require steady-state conditions. After acute coronary occlusion or after the onset of exercise-induced ischemia, such steady state is reached after 2-3 minutes. There is therefore a transient early phase where regional contractile function has not completely ceased after coronary occlusion or where it is even increased after the onset of exercise in a perfusion territory with a severely obstructed coronary artery. No data exist for the quantitative relation between oxygen supply and oxygen consumption in such early transient phase of ischemia. I would assume, however, that the myocardium uses the physically dissolved and hemoglobin-bound oxygen in the capillaries, the intracellular myoglobin-

bound oxygen and the intracellular energy-rich phosphate stores to sustain or even increase contractile function for a short period of time, and function declines as soon as these energy sources are depleted. A forced increase in contractile function in response to dobutamine accelerates the depletion on energy sources and precipitates contractile dysfunction (79, 80, 82). Thus, again there would be no energetic imbalance but possibly a short-lasting imbalance between oxygen supply by coronary blood flow and contractile function. The transient phase of 2–3 minutes after the onset of exercise probably corresponds to the time until the onset of symptoms in patients with stable angina. The more-or-less linear flow-function relationship that evolves after 2–3 minutes and is seen under steady-state conditions also holds when systemic and regional hemodynamics are largely altered by exercise, as long as both contractile function and blood flow are normalized for a single cardiac cycle, i.e., blood flow is expressed not per minute but divided by heart rate and expressed per beat (20). A reasonable number for a normal regional myocardial blood flow per cardiac cycle is 8–10 µl/g per beat. It is important to note that this is regional myocardial blood flow/perfusion but not epicardial coronary blood flow, and it therefore considers for transmural and/or collateral redistribution of blood flow (39). Even more subtle myocardial ischemia during exercise with only a mild epicardial coronary stenosis is then characterized by decreased blood flow per beat and decreased contractile function (57). Anti-ischemic drug interventions, e.g., by beta blockers (65), calcium antagonists (42, 63), combined beta blockers, calcium antagonists, and nitrates (27, 64), as well as bradycardic agents (23, 46), all operate along a consistent flow

(per beat)-function relationship. Very different from the supply-demand paradigm, the attenuation of regional myocardial ischemia by beta blockade is then not explained by reduced demand but in fact not only by increased regional myocardial blood flow per beat but also increased regional myocardial blood flow per minute secondary to heart rate reduction (24, 65), and secondary to a redistribution of blood flow from the nonischemic myocardium that has reduced metabolic vasodilation in the face of beta blockade through collaterals into the ischemic myocardium (Fig. 3) (7). John Ross has termed such consistent linear flow-function relationship in ischemic myocardium "perfusion-contraction matching" (76). Such perfusion-contraction matching for which there is ample and robust experimental evidence firmly contradicts the idea of an imbalance between supply (perfusion) and oxygen consumption, which is largely determined by contractile function. The adaptive nature of the matching of contraction to the available perfusion is evidenced by the fact that contractile function can be artificially enhanced by inotropic stimulation but only briefly (79, 80). Perfusion-contraction matching can be sustained for many hours and is the main characteristic of short-term hibernation (Fig. 2) (45, 62, 81). Short-term hibernation is the mechanism behind the survival of some myocardium that can be rescued even after 24 hours from symptom onset of acute STEMI (68, 77).

MORPHOLOGY

The duration of cardiomyocyte survival in the face of reduced blood flow depends on the magnitude of flow reduction.
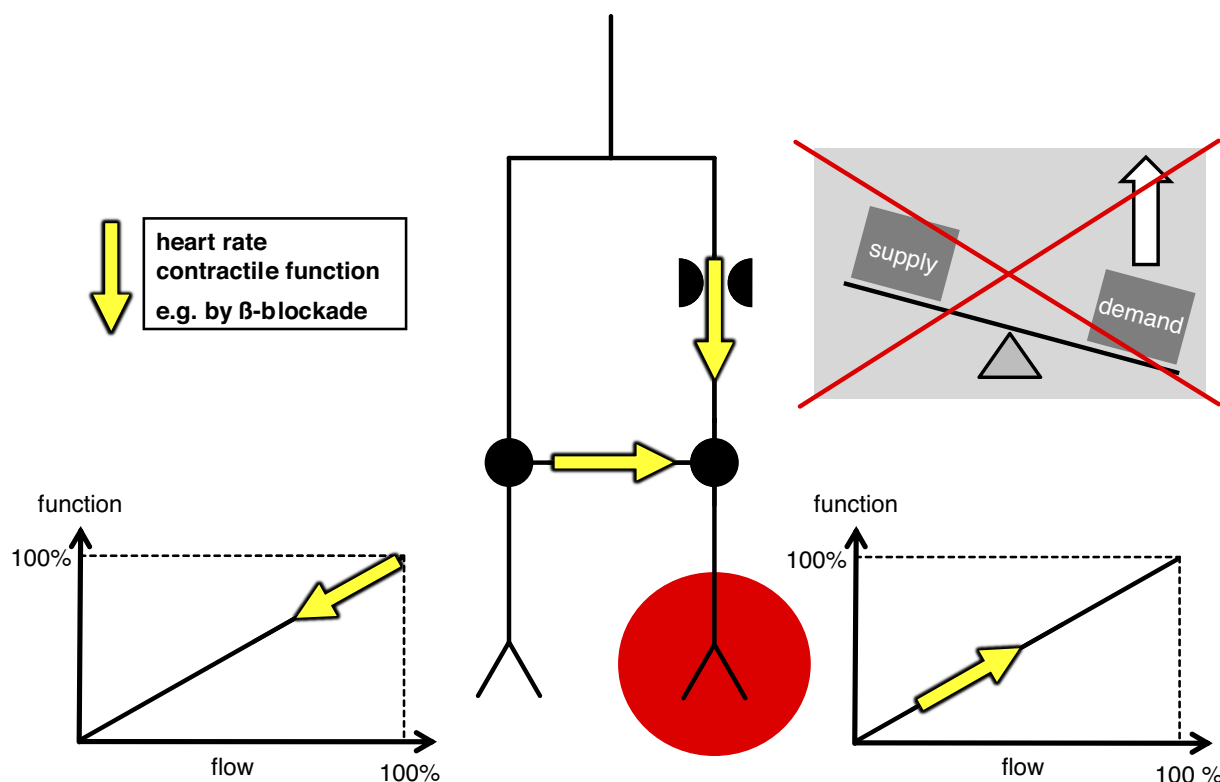

Fig. 3: In both, nonischemic and ischemic myocardial regions flow and function are proportionately changed, e.g., by beta blockade. In the nonischemic region, beta blockade reduces heart rate and contractile function, and flow follows function by metabolic vasomotion. The ischemic myocardium receives more blood flow through the stenosis and through collaterals at reduced heart rate. Here, function follows flow. From Heusch (39) with permission.

With more severe blood flow reduction, cell death occurs, mostly through necrosis, but apoptosis and autophagy also participate in cell death (52, 58, 91). Cell death is not simply secondary to an energetic deficit with failure of ion pumps and cellular maintenance processes, but in fact cell survival and cell death are regulated by complex signaling cascades, involving the mitochondria, cytosolic kinases, and proteinases (37, 52). In fact, regardless of the level of flow reduction, myocardial infarct size can be reduced by ischemia-conditioning interventions, as long as there is eventual reperfusion (35).

TIME COURSE OF MYOCARDIAL CONSEQUENCES

Obviously, the time course of the above consequences of any blood flow reduction varies. Cell death is a final event and can only be detected several hours after the flow reduction (3). In my experience in dogs and pigs, electrical signs of myocardial ischemia, even when derived from the same sonomicrometry that is used for the measurement of regional contractile function, occur slower than the reduction of contractile function that becomes apparent only a few cardiac cycles after a sudden reduction in coronary blood flow. Measurements of myocardial metabolism require steady-state conditions, and data are not readily available. Thus, regional contractile function is best suited to serve as an on-line monitor of the consequences of coronary blood flow reduction (26).

CHRONIC HIBERNATION AND HEART FAILURE

More moderate, prolonged, or repeated brief episodes of coronary blood flow reduction will not affect myocardial viability but may nevertheless cause profound molecular and morphological rearrangements, e.g., in hibernating myocardium and ischemic cardiomyopathy (44, 45). The question of whether or not chronically hibernating myocardium is considered as "ischemic" is somewhat semantic in nature. Clearly, chronically hibernating myocardium has reduced blood flow and reduced blood flow per beat. The reduced blood flow is part of the substantial molecular, metabolic, and structural remodeling (58, 71, 72) that has developed in response to repetitive brief ischemia and reperfusion (16). The hibernating myocardium may have reached a new set point from which a short-lasting submaximal increase in blood flow and contractile function is possible in response to an inotropic challenge (16). Whether the absence of net lactate production during such brief inotropic challenge provides firm evidence against ischemia is questionable (see METABOLISM). From my personal perspective, chronically hibernating myocardium is ischemic: there is reduced blood flow in the perfusion territory of an obstructed coronary artery with molecular, metabolic, contractile, and structural consequences, and the appropriate treatment is reperfusion/revascularization.

In heart failure of nonischemic origin, myocardial contractile function, oxygen consumption, and blood flow remain also matched at rest and during exercise (89).

MYOCARDIAL ISCHEMIA AT SMALL SCALE

While on the regional level of an obstructed epicardial coronary artery and its perfusion territory, the consistent flow (per beat)-function relationship provides a solid measure of regional myocardial ischemia: the case is not closed. At a smaller regional scale, the situation is more difficult to assess, largely because measurement techniques for flow, function and metabolism are not available at a much smaller and matched scale such that their quantitative relationships cannot be determined. With coronary microembolization, as may occur after spontaneous or iatrogenic erosion/rupture of an epicardial coronary atherosclerotic plaque (43, 47), there will be a microinfarct in the obstructed microvascular territory with a more widespread contractile dysfunction secondary to an inflammatory reaction (14, 15) at an unchanged or even slightly elevated coronary blood flow, reflecting reactive hyperemia in the myocardium surrounding the microinfarct (Fig. 2) (33, 84). More recently, microvascular angina (70) and myocardial infarction (69) in the absence of visible epicardial coronary obstruction have come into the focus of attention. These microvascular ischemic scenarios often develop in the absence of detectable changes in systemic hemodynamics and are therefore probably best characterized as consequences of reduced blood flow at a microvascular level. On an even smaller scale, there is substantial heterogeneity of myocardial blood flow with matched glucose and oxidative metabolism under normal baseline conditions (13, 83), but the respective contractile function in such microregions is not known. Whether microregions with low flow and low oxidative metabolism reflect a state of hibernation under normal baseline conditions at a microlevel is also not known.

Whereas I have dealt so far with the consequences of reduced blood flow in the affected myocardium, the coronary circulation itself is also a target of ischemia. Reduced coronary blood flow results in endothelial dysfunction, enhanced vascular permeability, impaired vasomotion, and even capillary destruction acutely (38) and in vascular wall remodeling in response to prolonged epicardial coronary obstruction more chronically (66, 86). The acute consequences of ischemia in the coronary circulation are augmented and become manifest during reperfusion following ischemia and may induce a no-reflow situation despite a reopened epicardial coronary artery (30, 56). Even when coronary blood flow is normalized during reperfusion, contractile function remains reduced for a prolonged time until it has fully recovered, i.e., there is stunning (48, 49), which is characterized by a mismatch of perfusion and contraction (Fig. 2) (36).

In conclusion, a unifying and fully satisfying definition of myocardial ischemia that would characterize all different scenarios of ischemic heart disease does not yet exist. For the classical scenario of post-stenotic exercise-induced myocardial ischemia, the prevailing paradigm of a supply-demand imbalance is not substantiated by the experimental data since there is obvious perfusion-contraction matching. Therefore, at this point, the definition of myocardial ischemia as a lack of coronary blood flow (to below $8-10$ $\mu l/g$ per beat) with consequences for the myocardium and also the coronary circulation remains the most reasonable one. Consequences, however, are not limited to the contractile function, metabolism, and morphology, but may entail beyond the current energetic situation, signaling events and molecular rearrangements that pave the way for myocardial and coronary vascular repair and/or remodeling.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

G.H. prepared figures and drafted, edited, revised, and approved final version of manuscript.

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