Regional myocardial blood flow and contractile function in ischemic myocardium are well matched, and there is no evidence for an oxygen supply/demand imbalance. Thus, myocardial ischemia is lack of coronary blood flow with electric, functional, metabolic, and structural consequences for the myocardium. All therapeutic interventions must aim to improve blood flow to ischemic myocardium as much and as quickly as possible.

Virchow in 1858 originally coined the term “ischemia” (ἰσχαιμία—withholding of blood) to characterize the reduction of blood flow to an organ or tissue and its consequences.1 and Cohnheim in 1881 first performed coronary artery ligation in dogs to demonstrate that myocardial infarction results from coronary obstruction.2 Rein and Büchner in the 30s of the last century performed experiments to show that coronary blood flow was closely related to myocardial function and that myocardial necrosis could be induced by a combination of reduced oxygen supply (hypoxia or anemia) with exercise; they suggested that the relation of coronary blood flow to myocardial function is the criterion for sufficiency or insufficiency of coronary blood flow and that coronary insufficiency resulted in myocardial necrosis and fibrosis.3 In the 1950s and 1960s of the last century, Braunwald et al4 worked out the hemodynamic determinants of myocardial oxygen consumption.5 In the 1970s of the last century, they showed in a series of dog experiments that interventions which increased the hemodynamic determinants of myocardial oxygen consumption, notably catecholamines, increased infarct size after coronary artery occlusion in dogs and that, conversely, interventions which decreased the hemodynamic determinants of myocardial oxygen consumption, notably β-blockade, reduced infarct size.6,7 On the basis of these studies, they advocated the concept that the survival of myocardial tissue with an obstructed coronary artery depends on the balance between myocardial oxygen supply and demand.8 The imbalance between myocardial oxygen supply and demand has since become the dominant paradigm of myocardial ischemia, it is found in all textbooks of cardiology and often illustrated as a scale (Figure).

I have never been comfortable with the oxygen supply/demand paradigm.1 In this ratio of oxygen supply/demand, the oxygen supply is a real parameter which can be measured in the ischemic myocardium, for example, as blood flow or blood flow arterial oxygen content. In contrast, the demand for oxygen in ischemic myocardium is a virtual parameter, which cannot be measured. What can be measured in ischemic myocardium is myocardial oxygen consumption; as myocardial oxygen consumption is largely determined by contractile function, the contractile function of ischemic myocardium can serve as a surrogate of its oxygen consumption. In fact, when both regional blood flow and regional contractile function in ischemic myocardium are measured simultaneously, no imbalance between the two parameters is apparent. They are rather closely, more or less linearly related (Figure),9 that is, ischemic myocardium is characterized by perfusion–contraction matching.10 This close, more or less linear relationship between regional myocardial blood flow and regional contractile function is also maintained during exercise when both blood flow and contractile function are normalized to expressed per heart beat.9,10 Even with a mild coronary stenosis and normal myocardial blood flow at rest, exercise reduces subendocardial blood flow per heart beat and in consequence regional contractile function.11 In the normoperfused myocardium, metabolic coronary vasomotion adjusts blood flow to myocardial oxygen consumption.12 In the ischemic myocardium where coronary regulatory reserve is exhausted, the available oxygen supply and ultimately the free energy change from ATP hydrolysis dictates, which energy-consuming processes are upheld, that is, contraction, ion pumps, etc.13 The matching of regional myocardial blood flow and contractile function in ischemic myocardium can be maintained over several hours,14,15 that is, there is a short-term hibernation that may contribute to preserved myocardial viability in patients with acute myocardial infarction for ≤24 hours after symptom onset.16

If an oxygen supply/demand mismatch cannot be demonstrated, how is then the beneficial effect of interventions, which reduce myocardial function and myocardial oxygen consumption, notably β-blockade, explained? First of all, β-blockade reduces heart rate, prolongs diastolic duration, and thereby improves coronary blood flow, particularly blood flow per heart beat.17 Then, β-blockade reduces contractile function of normoperfused myocardium and, in consequence, through metabolic vasomotion also its blood flow (Figure). In species with an existing collateral circulation, such as dogs and many humans with coronary artery disease, the reduced blood flow in normoperfused myocardium induces a favorable blood flow.

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redistribution from normoperfused to ischemic myocardium, ultimately resulting also in increased contractile function and presumably oxygen consumption in ischemic myocardium. In fact, β-blockade increases the reduced regional myocardial blood flow per heart beat in the ischemic region and even permits an increase in its contractile function. In the absence of heart rate reduction (atrial pacing), β-blockade is not beneficial at all, but reduces regional myocardial blood flow and contractile function in the ischemic region. Apparently, β-blockade does not reduce the oxygen demand of ischemic myocardium but even permits an increase in its oxygen consumption secondary to an increase in blood flow. Thus, β-blockade does not reduce the virtual oxygen demand of the ischemic myocardium, but the real oxygen consumption of the nonischemic adjacent myocardium, resulting in a beneficial redistribution of blood flow from the nonischemic toward the ischemic myocardium. Also, all other drugs that attenuate myocardial ischemia (calcium antagonists, bradycardiac agents, and nitrates) operate along an unchanged more or less linear relationship of regional myocardial blood flow and contractile function. The bottom line is: blood flow to the ischemic myocardium must be increased, either by recruitment of persistent coronary dilator reserve or by a more favorable blood flow redistribution, and then contractile function and oxygen consumption will follow.

The size of a myocardial infarction, that is, the irreversible structural consequence of myocardial ischemia, for any given ischemic area at risk and any given duration of coronary occlusion is again determined by blood flow and not by oxygen supply/demand. The most powerful interventions to reduce infarct size, that is, the conditioning phenomena, act through activation of molecular cardioprotective signaling programs but not through favorable alterations of either blood flow or myocardial oxygen consumption. However, any reduction of infarct size requires eventual reperfusion, that is, restoration of coronary blood flow.

So I propose to abandon the oxygen supply/demand paradigm and go back to Virchow’s original view of ischemia simply as reduced blood flow. All therapeutic strategies must be directed to improve blood flow to the ischemic myocardium as much and as quickly as possible, no matter what its oxygen demand is.

Disclosures

None.

References


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