Consequences of reperfusion
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Abstract
Coronary artery reperfusion after temporary coronary occlusion is the only measure that can prevent irreversible damage of cardiac tissue. The later that reperfusion is established, the less myocardial tissue can be salvaged: in the dog, complete salvage can be achieved after brief episodes of ischemia of less than 20 min, whereas nearly complete necrosis of the area at risk occurs with reperfusion after more than 6 h. Consequences of reperfusion may manifest as progressive microvascular damage (“no reflow”) in infarcted myocardium and reversible contractile dysfunction (“stunning”) in salvaged cardiomyocytes. Very brief ischemic episodes followed by reperfusion can put the heart into a “preconditioning” state, a condition that increases myocardial tolerance towards a long ischemic insult.

Keywords: Ischemic preconditioning, myocardial salvage, no reflow, reperfusion, stunning

Introduction
In most species, coronary artery occlusion results in myocardial ischemia because the collateral circulation is insufficient to maintain adequate supplies of oxygen and substrate [1]. In effect, coronary reperfusion is the only means of restoring aerobic metabolism and preventing irreversible damage of cardiac tissue. Therefore, the consequences of reperfusion – the most important of which will be discussed in this review – are always implicitly the consequences of the preceding period of temporary ischemia. Factors that potentially determine the final consequences of reperfusion, in a qualitative or quantitative manner, are: the duration and severity of ischemia, the volume of the ischemic area at risk, adjunctive therapeutic interventions before and during ischemia, and energetic demands during ischemia. Whether the specific mode of reperfusion and adjunctive therapy given during reperfusion can influence the ultimate volume of necrosis remain under investigation.

Salvage of myocardium at risk
In the dog, proximal coronary artery occlusion for up to 20 min, followed by re-opening of the artery, results in reversible alterations to the myocardium; however, after more than 20 min, significant amounts of necrosis develop (figure 1) [1–3]. In their landmark publication in 1977, Reimer et al [4] described a wavefront of myocardial necrosis progressing from the endocardial towards the epicardial surface of the canine heart as the duration of the coronary artery occlusion was increased. When the occluded circumflex coronary artery was re-opened after 40 min of ischemia, 38% of the myocardium at risk had become necrotic; after 3 h 57% developed necrosis, after 6 h 71% was necrotic, and after 24 h 85% became necrotic. In most experimental studies in the dog, reperfusion within a period of 6 h after the onset of ischemia was associated with significant subepicardial salvage, with variation depending upon the amount of collateral flow; after 6 h of coronary occlusion, nearly the entire area at risk was already necrotic [5,6]. However, if ischemia during coronary occlusion is more severe, for instance in
species with negligible collateral flow, or when energy demands during ischemia are greater (for example as a result of increased tissue temperature or increased contractility), earlier reperfusion may be required in order to achieve myocardial salvage [7,8]. Moreover, certain cardioprotective interventions before or during ischemia such as ischemic preconditioning or pharmacologic interventions, and hypothermia during ischemia, may extend the period up to which reperfusion still results in complete or partial myocardial salvage [9–11]. In addition, final infarct size may not be invariably determined at the time when reflow is initiated: a “stuttering” reperfusion, termed “postconditioning” and referring to brief re-occlusions of the coronary artery early during the reperfusion period, may result in a smaller infarct size than occurs after an immediate, single and complete re-opening of the occluded artery [12]. The findings of many experimental investigations have also suggested that various adjunctive pharmacologic interventions during the reperfusion period may further reduce the size of the infarct. However, not all laboratories have observed benefits from therapies, such as postconditioning, that are initiated only at reperfusion [13].

Whether initiating reperfusion at a time when myocardial salvage is no longer achievable is of significant benefit (“open artery hypothesis”) remains a matter of debate [14]. Data from experimental studies have suggested that healing of infarcted tissue may be favorably influenced even by late coronary artery reperfusion, which could attenuate infarct expansion, scar thinning, and aneurysmal dilatation beyond myocardial salvage [15].

In summary, reperfusion of ischemic myocardium will result in necrotic and salvaged myocardium within the risk area, ranging from complete salvage with very early reperfusion to almost complete necrosis with late reperfusion. Necrotic myocytes will eventually be replaced by scar tissue, but salvaged cardiomyocytes are characterized by various abnormalities that will normalize after a variable time course.

**Morphologic and metabolic changes induced by reperfusion**

With initiation of reflow, marked hyperemia (up to approximately 500% of basal flow) develops for approximately 15 min, restoring aerobic metabolism in reversibly altered myocardium [2–5]. Re-phosphorylation of adenine nucleotides to adenosine triphosphate, a pronounced increase in creatine phosphate, and normalization of lactate concentrations and pH are accompanied by transient swelling of mitochondria and cardiomyocytes [16,17]. During the first 10 min of reperfusion, oxygen-derived free radicals show a marked peak in concentration [18]. In addition, activation of a pattern of genes occurs during reperfusion, eventually leading to increased tissue concentrations of (for example) heat shock proteins and inducible nitric oxide synthase after 1 day of reperfusion [19].
Reversible contractile dysfunction: stunning

Prolonged, posts ischemic dysfunction of viable myocardial tissue salvaged by reperfusion, termed “stunning”, develops reproducibly after brief periods of ischemia followed by reperfusion. Despite adequate restoration of coronary flow, contractile dysfunction, in particular also diastolic dysfunction, may persist for periods ranging from hours to several days, depending on the duration and completeness of the initial ischemic insult. Besides this typical flow–contraction mismatch in stunning, another of its characteristics is that inotropic stimulation of stunned myocardium results in enhanced contractility without altering the partial pressure of tissue edema. These areas of no reflow were contained within the necrotic zone and finally comprised approximately 80% of the infarct size in this model [22]. Several pathophysiological mechanisms for this phenomenon (including endothelial swelling and bleb formation, progressive leukocyte plugging, and vascular compression by tissue edema) are under debate; however, this progressive vascular obstruction may be regarded as reperfusion injury at the microvascular level, with potentially significant prognostic implications [23].

Putting the heart in the “preconditioned” state by reperfusion

Brief coronary occlusions beneath the threshold for irreversible damage, followed by reperfusion, can induce cardioprotective effects via a complex, as yet incompletely understood, cascade of signals that renders the myocardium more tolerant towards a subsequent more prolonged ischemia insult [10]. This process is termed “ischemic preconditioning”. In the dog, infarct size is substantially reduced if an episode of 3–10 min of ischemia, followed by 5 min of reperfusion – the preconditioning procedure – precedes a longer episode of ischemia and reperfusion [24]. The cardioprotection conferred by such a preconditioning stimulus may no longer be detectable if the final ischemic insult is instituted after more than 3 h, but there seems to be a second window of delayed protection, evident if the long-duration coronary occlusion is performed 24–96 h after the preconditioning stimulus [25].

Summary

The earlier the coronary reperfusion is established, the greater the portion of myocardium that can be salvaged, thereby limiting the amount of myocardial necrosis. Nonetheless, reperfusion itself may also result in unfavorable consequences. The most important are progressive microvascular alterations (no reflow), and reversible contractile dysfunction of salvaged myocardium (stunning). Reduction of irreversible cardiomyocyte damage may be accomplished by administration of cardioprotective therapies before ischemia, such as preconditioning or drugs that mimic preconditioning or cardioprotective interventions during ischemia, such as hypothermia. Whether modifying the specific procedure for reperfusion (for example, postconditioning) or administering adjunctive therapy only at reperfusion reduces irreversible myocyte injury remains controversial.

REFERENCES