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Review

Roles of collateral arterial flow and ischemic preconditioning in protection of acutely ischemic myocardium

Robert B. Jennings, MD,* Galen S. Wagner, MD

Duke University, Durham, NC

Abstract The extent and rate at which necrosis develops in experimental acute myocardial infarction in the dog heart is presented together with an analysis of the role played by protective mechanisms in myocyte death. Preconditioning with ischemia delays but does not prevent myocyte death. Arterial collateral flows exceeding 30% of control flow essentially prevent myocyte death, while lesser amounts of collateral flow delay myocyte death to a variable extent. Flows of <0.09 ml min^{-1} g^{-1} wet exert no protective effect. Cell death occurs as quickly as it does with zero flow.

Electrocardiography provides a means of detection of the preconditioned state in the dog heart in that the amount of ST elevation observed during the preconditioning episode is reduced during subsequent episodes of ischemia. Also, marked depression of arterial collateral flow can be detected by an increase in the duration of the QRS segment.

Keywords: Collateral flow; Preconditioning; Acute ischemia; Physiology; Electrocardiography

Introduction

It has been known for almost 50 years that myocytes do not die immediately after being exposed to very low or no-flow [1]. This was established by subjecting canine myocardium to episodes of ischemia of 5–60 minutes duration followed by reperfusion with arterial blood to eliminate the ischemia. This procedure resulted in no myocyte death if the period of ischemia was 15 minutes or less. The myocardium exposed to the ischemic episode was *reversibly injured* and remained indistinguishable grossly from control myocardium. However, monuments to the damage that occurred while the tissue was ischemic were present and included stunning, a 50% reduction in the amount of ATP, ADP, and AMP, and an excess of intracellular glucose, water, and K + [2–6]. Over the next 5–7 days of reperfusion, the monuments disappeared leaving myocardium metabolically and structurally indistinguishable from control. On the other hand, when the ischemic period was extended to 25 minutes, islands of cell death appeared in the ischemic myocardium and, after 60 minutes of ischemia, virtually the entire inner third of the ischemic bed was dead [1]. This dead tissue was *irreversibly injured* but again was indistinguishable grossly from adjacent non-ischemic control myocardium.

After 60 minutes of ischemia followed by reperfusion gross signs of damage appear in less than 60 seconds including loss of the red color of the myocardium because of the washout of cytochrome C and myoglobin from the dead myocytes plus obvious marked swelling and the changes of contraction-band necrosis [7,8]. The proof that this tissue was dead was confirmed by allowing the animals to survive for 4 days before excising the heart [1]. The presence of necrosis, i.e. the complete structural disorganization of the affected myocytes confirmed their death as did the fact that they were eventually replaced by scar tissue [9].

The molecular changes that are associated with or caused the death of the affected myocytes developed during the reversible phase. Over the next 40 years, these changes were identified and investigated in a series of studies that are summarized in references [10–12]. Myocyte death was associated with depletion of high energy phosphate to very low levels along with destruction of much of the adenine nucleotide pool, marked acidosis (pH of 5.8) due to the accumulation of lactate, and structural and functional evidence of sarcolemmal disruption. Disruption of the sarcolemma is considered to be the lethal event because it allows critical sarcoplasmic proteins and cofactors to leak from the cell into the extracellular space where they can no longer participate in metabolism [11,12]. Sarcolemmal disruption is accelerated in vivo by the contraction of adjacent viable myocardium. Identical metabolic and ultrastructural events occur in pieces of myocardium

* Corresponding author at: Duke University Medical Center, Box 3712, Durham, NC 27705.

E-mail address: jenni004@mc.duke.edu

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incubated at 37 C in a moist environment (total ischemia). However, membrane disruption develops more slowly in totally ischemic tissue than in vivo because contracting tissue is not present in this model to provide the mechanical stress required to disrupt the sarcolemma [13,14]. Virtually identical events occur in the isolated perfused rat heart subjected to anoxia followed by reperfusion or by simply traumatizing the ischemic acontractile, damaged anoxic heart by expanding a balloon in the cavity of the left ventricle [15].

Use of reperfusion therapy in man to salvage ischemic myocardium

In 1975, most investigators and many cardiologists believed that ischemic cell death was caused by a thrombus obstructing flow through a large coronary artery. Unfortunately, autopsies performed on patients with clinical myocardial infarction 48–96 hours after the onset often showed no thrombi in the vessel supplying the area of acute myocardial infarction. This observation made the importance of thrombi controversial. DeWood and his colleagues, using catheterization techniques, established that thrombi were virtually always present in patients with infarcts studied during the first 4 hours after the onset of symptoms [16]. The loss of the thrombus in the 48-hour-old fatal infarcts was presumably due to the action of endothelial fibrinolysins that digested the thrombus and opened the artery but did not restore flow because of the death of capillaries in the area of necrosis [17].

In the early 1980s, Rentrop et al performed a dramatic test of the role of thrombi by infusing clot-lysing agents into patients with early acute myocardial infarct [18]. This had a dramatic effect in that the hemodynamic status of the patients usually improved and the electrocardiographic changes of acute ischemia disappeared or were markedly ameliorated. Finally, reperfusion washed out large quantities of intracellular enzymes such as creatine kinase into the venous blood [19,20]. These results also provided objective, evidence that arterial thrombi in a major coronary artery were the cause of ischemia in acute myocardial infarction. This was a big step forward and was followed by a direct clinical "attack" on the atherosclerotic plaque over which the thrombus developed using balloon dilatation techniques [21,22]. Unfortunately, the dilated opened arteries sometimes reoccluded because of the repair of flaps of disrupted plaque. As a consequence, placing stents to hold the plaque laden artery open after it was dilated refined and improved the procedure. Placing stents is a very precise technique that increases the time required to open the occlusion. The intravenous thrombolysis technique often leads to prompt opening of the vessel and elimination of the ischemia if a substantial lumen results from the thrombolysis while the catheterization technique involves delays occasioned by the time required to get the patient to a catheterization laboratory plus the time required to open the occluded artery. The clinical choice between the intravenous pharmacologic and intracoronary mechanical therapies requires a consideration of the timing of myocyte death under controlled experimental conditions in the large animal heart.

Infarction in large animal hearts such as those of the dog or pig is virtually identical in all respects to that observed in man except that the coronary arteries are normal in the animals and are usually extensively diseased in man. The timing of the events occurring in man with evolving acute myocardial infarction and in dogs with acute surgically induced infarcts is generally similar with respect to the timing of the evolution of the electrocardiographic changes and the timing of enzyme release from the dying myocytes [23]. Unfortunately, at present, no methods are available to prove that the timing of the evolution of cell death in man is slower or faster than that observed in the hearts of anesthetized dogs. Until better data and methodology are developed in man, it is prudent to consider that the dog data provides good timing of the acute myocardial ischemia infarction process in man.

Evolution of acute myocardial ischemia and infarction in the dog heart

In the early 1970s, Braunwald, Sobel and Ross tested the interesting hypothesis that one could treat acute myocardial ischemia with drugs and thereby delay or prevent myocyte death [24–27]. This idea had not been presented before because most scientists did not think that it was possible for a drug to enter into ischemic myocardium when such myocardium received very little or no arterial flow. Nevertheless, the hypothesis still had merit in that it was theoretically possible to pretreat the entire heart prior to occlusion with a drug that possessed potential antiischemic effects if an occlusion occurred. Their original studies on this subject were flawed in the sense that our understanding of the evolution of infarction in acute ischemia in the experimental animal heart was poor, particularly with respect to infarct size, which, in fact, is the ultimate measure of the success of therapy. The impact of arterial collateral flow also was not well understood at this time. As a consequence of the difficulty in designing experiments when the variables affecting cell death were not well understood or even recognized, at least 90 agents have been reported to reduce infarct size when administered during ischemia in the dog or pig heart. When tested in well-controlled blinded studies, virtually all of these agents have no effect on infarct size [28].

However, the hypothesis that final infarct size could be limited created great interest and the variability of the results eventually led to detailed studies of the effect of acute myocardial ischemia on the tissue in the mid- and subepicardial myocardium because this is the tissue generally available for salvage by either intrinsic collateral flow or therapeutic reperfusion [23].

One of the chief problems impeding experimentalists was the difficulty in quantitating the severity of the ischemia. It clearly varied because some dogs did not develop infarcts after occluding a major coronary artery and others developed massive areas of ischemia and died within a few minutes after occlusion of the same artery at the same site. This difference was due to variation in the amount of collateral arterial flow received by the myocardium and the absence of