Trimetazidine, Oxidative Stress, and Cell Injury During Myocardial Reperfusion

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REPERFUSION-INDUCED CELL DEATH

In recent years, the notion that cell death secondary to transient myocardial ischemia occurs during reperfusion (reperfusion injury) and that it can be prevented at that time has become widely accepted. The days in which the existence of lethal reperfusion injury was questioned or considered a laboratory curiosity with no clinical relevance are beginning to be left far behind. Nevertheless, many aspects of the mechanism of reperfusion injury remain unknown. It appears to be increasingly evident that reperfusion-induced cell death occurs primarily during the initial minutes of the process, producing a characteristic histological pattern of contraction band necrosis,[1] and that the changes in calcium homeostasis, largely secondary to sodium overload,[2] provoke the contractile and enzymatic activation (calpain) that ultimately leads to the rupture of the cardiomyocyte plasma membrane.[3] More recently, it has been reported that mitochondrial permeabilization, caused by the abrupt opening of large-conductance channels, referred to as transition pores, may also play a relevant role in generating reperfusion-induced acute necrosis.[4] All these phenomena are the consequence of the changes that take place during the preceding ischemic period, above all, the decrease in ATP concentration and the accumulation of H^+ (intracellular acidosis), Na^+ (as a result of activation of the Na/H and Na/HCO_3 exchangers) and Ca^+ (which enters the cell via the Na/Ca exchanger when it operates in the reverse mode).[5] During the restoration of blood flow, the more or less rapid normalization of the cytosolic Ca^{2+} concentration depends on the degree of Na^+ and Ca^{2+} overload reached during the preceding ischemic period, as well as on the capacity of the mitochondria to produce sufficient quantities of ATP, which help to normalize cellular energy demands rapidly. Moreover, it must be taken into account that the correction of intracellular acidosis that occurs during the initial minutes of reperfusion can, in turn, have a highly negative effect by facilitating an excessive contractile activation (which, in the presence of elevated Ca^{2+} levels, leads to hypercontracture), calpain activation and the opening of the mitochondrial permeability transition pore.[6]

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REPERFUSION INJURY IN THE CLINICAL CONTEXT: DONOR HEART PRESERVATION

Cell death due to myocardial reperfusion is a characteristic event of thrombotic occlusion of the coronary artery with early recanalization, a process that is generally therapeutic. In this situation, the fact that it can be prevented by means of strategies applied at the time of reperfusion is of special interest since it permits pharmacological intervention to limit necrosis using treatments administered concomitantly with thrombolysis or primary angioplasty. However, it can also occur in other contexts, among which cardiac surgery and heart transplantation are of particular importance. The two situations differ markedly from the coronary occlusion occurring in acute coronary syndrome with regard to pathophysiological and clinical aspects. In both cases, ischemia is produced under controlled conditions. This circumstance, which does not exist in the acute coronary syndrome with ST segment elevation, makes it possible to perform preoperative elective interventions. Some of these interventions, such as ischemic preconditioning or Na/H exchanger block,[7,8] are highly effective and safe. Moreover, in both cases a more or less severe hypothermia is induced, a condition that significantly slows the progression of ischemic injury, in addition to modifying appreciably its molecular mechanisms

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due to the effect of the low temperature on the ion transporters and enzyme systems. As a result, myocardial cell death is usually very limited or undetectable during surgery with cardiopulmonary bypass or heart transplantation. Thus, in the latter situation, the donor heart can be treated prior to ischemia and exposed to hypothermia in a particularly effective manner.[9]

TRIMETAZIDINE AS A CARDIOPROTECTIVE AGENT

In the present issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA, Castedo et al[10] describe the beneficial effect of trimetazidine in the oxidative damage associated with heart transplantation in a porcine model of orthotopic heart transplantation involving a prolonged preservation period. The treatment consisted in adding trimetazidine to the cardioplegic solution of the donor heart and to the cardioplegia infused into the recipient prior to the unclamping of the aorta. As a result of the treatment, the authors observed a decrease in the indices of lipid peroxidation. They also demonstrated an increase in the endogenous antioxidant levels in blood samples obtained from coronary sinus prior to heparinization, immediately prior to the unclamping of the aorta and once the aorta had been unclamped. One of the strong points of the study is the special care taken by the authors to reproduce the clinical conditions, both in the surgical preparation and drug dosage, which could easily be applied in human transplantation.

A number of studies have focused on the protective effect of trimetazidine against ischemia-reperfusion-induced myocardial injury in different models, providing fairly conclusive evidence that it is possible to increase exercise-induced ischemia. This effect, in general, is recognized to be a consequence of the inhibition of lipid beta-oxidation and the shifting of ATP production to glucose oxidation, a more energetically efficient pathway.[11,12] A protective effect of trimetazidine against cell death secondary to ischemia-reperfusion has also been reported but, in this case, the results are less clear and the mechanisms involved appear to be more diverse. However, in contrast to expectations, it has not been possible to demonstrate a protective effect in clinical studies,[13] although this failure may be influenced by the limited efficiency of the design, particularly because of the very prolonged selection period (24 hours) following the onset of symptoms.[14] The mechanism of action of trimetazidine under these conditions is more obscure.

Among the antiischemic actions attributed to trimetazidine, an antioxidant effect has been proposed, explicable in part by a direct action on complex I of the mitochondrial respiratory chain,[15] which could delay the decrease in mitochondrial membrane potential during ischemia. In this respect, trimetazidine has been described as a "mitochondrial coupling agent" capable of counteracting the effect of uncoupling agents, such as dinitrophenol. In recent observations, the importance of the preservation of the mitochondrial protonmotive force during ischemia has been stressed, since this effect leads to a delay in the decrease in ATP and in the loss of intracellular homeostasis.[8] Our group has reported a protective effect of trimetazidine against the loss of plasma membrane integrity during reperfusion in isolated cardiomyocytes, independently of any effect on the hypercontracture.[16] The loss of membrane integrity is directly related to the degree of fragility developed during the preceding ischemia, and can be quantified as a decrease in the mechanical resistance of the cell to osmotic stress.[17] However, there may be several, little known mechanisms involved in this process. One of them, which we have demonstrated in a more recent study, implicates the opening of the mitochondrial transitional pore which, in turn, is favored by the oxidative stress, the correction of the intracellular acidosis, and the low ATP concentrations. The massive release of proteases into the cytosol by the mitochondrion and the energy failure produced as a consequence of the loss of mitochondrial integrity can cause the rupture of the cell membrane, independently of the hypercontracture.[4]

The study of Castedo et al[10] leaves many questions unanswered. First, the investigators detected no protective effect of trimetazidine treatment against cell death or postischemic contractile dysfunction, reporting only biochemical changes compatible with reduced oxidative damage. The inference that these changes are a valid marker of true protection against ischemia or reperfusion injury is not free of risks. Second, the method of collecting coronary sinus samples prior to and after aortic unclamping does not allow the distinction between the presence in the coronary sinus, at the moment of unclamping, of products previously accumulated in the extracellular space and the actual release of intracellular molecules into that space. Finally, the observations made in this mixed model involving hypothermic/cold preservation of the donor heart and treatment of the recipient can not be extrapolated to other situations with different pathophysiological conditions, such as myocardial protection during cardiopulmonary bypass or normothermic regional ischemia. Moreover, it should be taken into account that it will be possible to establish the utility of adjuvant treatment with trimetazidine in heart transplantation only when it has been demonstrated that its effects on relevant pathophysiological variables (cell death and, to a lesser extent, functional recovery) are greater than other currently available, and effective, means of organ preservation.

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