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Abstract

The heart of subjects with hypertension and cardiac hypertrophy is more vulnerable to ischemia/reperfusion injury (IRI). Here we discuss the main mechanisms of IRI and possible targets for cardioprotection. In particular, we consider the viewpoint that hypertension and cardiac hypertrophy may act synergistically in increasing the predisposition to cardiovascular accidents and in worsening IRI. There is no doubt that hypertrophic hearts may be redirected to be less vulnerable to IRI. Some experimental evidences suggest that anti-hypertensive drugs may have beneficial effects, some of which are not directly related to hypertension lowering effect. However, more thorough experimental and clinical studies are necessary to understand the mechanisms and to maximize the beneficial effects of reperfusion after a heart attack in the presence of comorbidities, such as hypertension and cardiac hypertrophy.

Key words: Myocardial ischemia; Reperfusion injury; Ischemic heart disease; Cardioprotection; Hypertrophy; Hypertension; Research translation.

Hypertension is estimated to occur in about 30% young adults, increasing to about 60% for those over 60 and to 75% in older than 70 [1]. In about 90% of patients the cause of hypertension is unknown; actually they suffer the so-called *essential hypertension*. In about 20-30% of hypertensive patients left ventricular hypertrophy (LVH) is observed, which is associated with a poor prognosis. Thus hypertension is the most common cause of LVH and cardiovascular accidents [2,3]. The prevalence of LVH is even higher in aged patients [3,4]. In this mini-review, we briefly consider hypertension and the compensated LVH, *i.e.*, before the onset of overt cardiac failure, as a risk factor. We also discuss hypertension and LVH effects on responses to ischemia/reperfusion, and the effectiveness of cardioprotective strategies in these conditions.

In hypertrophic hearts the total O_2 consumption is high and any reduction of the coronary flow has more severe consequences. The narrowing of a coronary artery that produces no symptoms when the heart size is normal can produce acute myocardial infarction (AMI) when the heart is enlarged or hypertrophic. In the absence of coronary stenosis, the coronary flow reserve may decrease for several reasons, including a decrease of the vasodilatory reserve and an increase of the basal flow due to cardiac hypertrophy and small vessel disease, typical of hypertension [5,6].

Moreover, hypertension increases the incidence of atherosclerosis and myocardial infarction and these conditions are common even when the heart is not hypertrophic. In the long period, the ability of the heart to meet the increased peripheral resistance is overcome, and heart failure occurs. Hypertensive subjects are also predisposed to cerebral vessels thrombosis and hemorrhage. A further complication is kidney failure. However, the incidence of heart failure, stroke, and kidney failure can be greatly reduced by the active treatment of hypertension, even when hypertension is relatively moderate. At present, essential hypertension is treatable, but not curable. An effective lowering of blood pressure may be produced by different drugs which have diverse mechanisms of action: diuretics, inhibitors of converting enzyme of angiotensin, calcium channel antagonists, and blockers of angiotensin, α-adrenergic or β-adrenergic receptors. Experimentally, inhibition of

aldosterone has also been observed to prevent fibrosis and myocardial hypertrophy due to a prolonged adrenergic action on the heart [7].

Myocardial infarction is usually due to the occlusion of a coronary branch following atherosclerotic plaque rupture. Usually, in order to have necrosis, ischemia should last about 20-30 minutes, but patients may die because of tachyarrythmias and ventricular fibrillation before irreversible injury has time to appear. Interestingly, along with increased interstitial fibrosis, the hypertrophic myocardium may display prolongation of the cardiac action potential and abnormalities in individual currents, such as ICaL, INa, and Ito, which may predispose to arrhythmias, through different mechanisms [8-11]. Importantly, in epidemiological studies, sudden cardiac death is closely associated with hypertensive LVH [12].

Of note, if the occluded artery is reopened, the damage caused by ischemia is exacerbated in the first minutes of a subsequent reperfusion. It follows that the reopening of an occluded coronary artery is paradoxically a cause of worsening of the damage, leading to a greater extension of the infarcted tissue. To emphasize the role of reperfusion injury in myocardial damage, this phenomenon is called ischemia-reperfusion injury (IRI).

The IRI affects both the myocardium and the coronary vessels. Vascular damage comprises the acute endothelial dysfunction and its consequences. Indeed, not only is coronary vasculature affected by atherosclerotic disease, but it is also injured after myocardial ischemia/reperfusion. Damaged vessels display edema, due to increased vascular permeability, as well as endothelial dysfunction and impaired vasomotility. Often atherothrombotic debris are the cause of microembolization leading to stasis with intravascular cell aggregates, and finally, to capillary destruction with hemorrhage. In the clinical scenario, the so-called *no-reflow phenomenon* (a reduced or absent reperfusion that occurs after the end of ischemia in a previously patent vessel) often occurs after artery reopening, and this is a worrying prognostic event [13].

Some mechanisms of myocardial damage, such as necrosis and apoptosis, initiate during the period of ischemia and worsen during the first minutes of reperfusion. Other mechanisms of myocardial injury and vascular damage occur only in the first minutes of reperfusion. The overall result of IRI is represented by necrosis and apoptosis, as well as a transient reduction of contractility of surviving myocardium (*myocardial stunning*). This is in part due to the presence of non-necrotic tissue no longer able to contract, or contracting with less force. Stunning can last from minutes to days, in relation to the severity of the preceding ischemia and in relation to the severity of reperfusion injury.

The myocardial damage from IRI is due in large part to the long-lasting opening of the so-called mitochondrial permeability transition pore (mPTP) and the consequent explosive swelling of the cells. The mPTPs allow the passage of molecules of weight less than 1500 Dalton and their opening leads to swelling of mitochondria and cell death [14]. At the beginning of reperfusion, the opening of mPTP is the consequence of the worsening of the Ca^{2+} overload and of the production of reactive oxygen species (ROS).

The cellular Ca^{2+} overload is also responsible for the contraction of the heart in the so-called *contracture*, that is the incomplete diastolic relaxation of the myocardium that results in an increase of the diastolic ventricular pressure.

Another phenomenon responsible of IRI is the so-called *pH paradox*, that is the consequence of pH recovery from acidosis that occurs during ischemia, when the cellular pH drops inhibiting hydrolytic enzymes, such as phospholipase and proteases, which otherwise can damage the sarcolemma. In this sense, acidosis plays a protective role. At the onset of reperfusion instead the pH returns back to normal, reaching the optimum level for the action of the aforementioned enzymes that can target cell membranes causing the membrane rupture.

The vascular reperfusion injury is also due to the lack of production of nitric oxide (NO) by the endothelium at the end of ischemia. As a result of NO deficiency we can observe vasoconstriction, platelet aggregation and activation of cell adhesion molecules or cellular adhesion molecules

(CAM), which favor the interaction between leukocytes and endothelial cells. The main CAM molecules involved in this mechanism are: selectins (P, L, E), integrins (CD11, CD18) and immunoglobulins such as intracellular adhesion molecule-1 (ICAM-1), the vascular cell adhesion molecule-1 (VCAM -1) and the platelet endothelial cell adhesion molecule-1 (PECAM-1).

The aggregation of platelet and leukocyte adhesion to endothelial cells can lead to a reduction in the sectional area of small vessels with an increase in the flow resistance; however, this area reduction is exacerbated by the vasoconstriction due to NO deficiency. The concomitant presence of these factors can be the cause of the *no reflow phenomenon*, above described. It is obvious that this phenomenon can be the basis of a further worsening of myocardial damage.

As said, IRI may be exaggerated by myocardial hypertrophy (Fig. 1). Actually, at the beginning of hypertrophy the heart may be more resistant to ischemic injury. However, this protection is lost a few weeks afterwards, and IRI is increased as hypertrophy develops [15,16]. Mølgaard et al.[17] have recently confirmed that hearts from spontaneous hypertensive stroke-prone rats with LVH are more susceptible to IRI and propose mitochondrial complexes III and IV as possible targets of the heart increased vulnerability. Already in the nineties, biochemical and metabolic modifications have been proposed as explanations for this increased susceptibility to IRI. Among such modifications, alterations in mitochondrial energetics, ATP production, glycolytic metabolism and lactate accumulation during ischemia are included [18-20].

Clearly, chronic models of hypertrophy better reflect the clinical situation of hypertension leading to cardiac hypertrophy. We have shown that sub-chronic use of high concentrations of nandrolone, improves post-ischemic cardiac function in postconditioned hearts. However, chronic treatment with nandrolone induces marked myocardial hypertrophy, increases cardiac susceptibility to IRI and abolishes the possibility to induce *postconditioning protection* [15,16], a protection obtained with brief periods of ischemia (a few seconds) at the beginning of reperfusion [21-23]. Actually, in animal experiments, local and remote ischemic pre-, per- and post-conditioning not only reduce

cardiomyocyte death, but also the typical events of coronary vascular injury, such as no-reflow phenomenon[24]. Moreover some drugs may activate signal transduction pathway typical of conditioning protocols. However, the translation of these protective interventions to clinical practice has been disappointing to date [25,26].

Interactions between drugs and risk factors complicate the scenario. Angiotensin converting enzyme inhibitors (ACE-I) are widely used as antihypertensive drugs and were shown to prolong patients survival after myocardial ischemia [27-29]. In addition to reducing the formation of angiotensin II, ACE-I reduce the degradation of kinins thus prolonging their activity [30]. This prolonged activity on B2 receptors makes ACE-I particularly interesting in the context of IRI, since, by interfering with the B2 receptors [31] the heart responsiveness to cardioprotective interventions could be altered [32,33]. Yet, ACE-I have been shown to reduce cardiac hypertrophy and to be cardioprotective *per se* [27-30]. Actually, we have shown that in rats infarct size was larger in the presence of cardiac hypertrophy due to hypertension when compared to hearts of normotensive animals subjected to ischemia/reperfusion. Moreover, we have shown that a postconditioning protocol, which is able to induce cardioprotection against infarct size in normotensive rats, is not protective in hearts of hypertensive animals. Intriguingly, the postconditioning protocol does not add protective effects to the protection already provided by chronic Captopril treatment [34]. Recently an experimental study demonstrated that preventive treatment with either cardosten, enalapril, or losartan can attenuate LVH development in infarction-induced heart failure in rats [35] .

Overall, it seems that in hypertensive LVH before the onset of functional decompensation, conditioning cardioprotective mechanisms remain intact or are even up-regulated. Only the progression of LVH towards a decompensated state may compromise the possibility of protection. Only a few drugs (*e.g.*, exenatide, esmolol, metoprolol and brain natriuretic peptide) have demonstrated some satisfactory effectiveness in reducing infarct size in patients that underwent reperfusion after acute myocardial infarction. Nevertheless, also for these drugs more pre-clinical

and clinical studies are necessary, as little information on their mechanism of action in the presence of comorbidities or on their impact on the post-ischemic coronary circulation is available.

Some experimental data suggest that the concomitant presence of conditions such as age, hypercholesterolemia, diabetes, and hypertension, rather than LVH *per se*, is responsible of infarct size exacerbation and limitation of cardioprotective strategies' effectiveness [36,37]. Interestingly, in patients with multiple risk factors (high blood pressure, smoking, dyslipidemia, and diabetes) and a mean age of approximately 60 years, ischemic conditioning may reduce IRI and improve the patient's prognosis [38,39]. Yet, it is not clear whether this discrepancy between studies is due to drug interactions, to the compresence of hypertension and LVH or to other reasons [40].

Overall, it seems clear that the concomitant presence of high blood pressure and LVH is a dangerous condition. Treating hypertension, especially with ACE antagonists, regardless of blood pressure lowering and/or of LVH regression, may be useful to reduce the risk and the damage of ischemia and reperfusion, at least in animal experiments [36] .Whether this treatment is sufficient in humans to lower the risk and the ischemia/reperfusion damage has not been ascertained yet. Recently, chronic pretreatment with angiotensin receptor blockers has been associated with the reduction of the *no-reflow phenomenon* in 276 hypertensive patients with reperfused AMI. It seems that this treatment could preserve microvascular integrity after AMI. Also these beneficial effects seem not directly related to hypertension lowering function [41]. It is likely that these beneficial effects are due to the so-called pleiotropic effects. Indeed, it has been reported that telmisartan may protect against microvascular dysfunction during myocardial IRI in rabbits, by activating peroxisome proliferator-activated receptor gamma [42].

In conclusion, it is not surprising that a variation (ranging from highly protective to neutral and even negative results) in the magnitude of myocardial salvage can be observed among clinical studies testing cardioprotective strategies. In fact, similar to IRI, cardioprotective interventions may also be influenced by a number of conditions. Here, particularly relevant are the following

variables: 1) the duration of ischemia, 2) the extension of the area at risk; 3) the velocity and extension of artery reopening; 4) the presence of comorbidities, such as cardiac hypertrophy, hypertension and diabetes; 5) the therapies already used by the patients; to name only a few of the variables in play that are not easy to keep under the control of the physicians in the 'clinical arena'.

Relevant to the topic of this short commentary is the fact that hypertension and LVH may act synergistically in increasing the predisposition to cardiovascular accident and worsening of IRI. Of course, technical complications in the reperfusion strategies cannot be ignored, and more thorough experimental and clinical studies are necessary to understand the mechanisms of protection and to maximize the beneficial effects of reperfusion after an infarction in the presence of comorbidities such as hypertension and cardiac hypertrophy.

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Figure legend

Fig. 1. The concomitant presence of hypertension and cardiac hypertrophy predisposes to cardiovascular accidents and worsening of damage from ischemia/reperfusion injury (IRI). Some anti-hypertensive drugs, regardless of lowering in blood pressure, can reduce the consequences of IRI. The question mark indicates that the mechanisms of this protective effect are unknown.