Improved myocardial preservation with short hyperthermia prior to cold cardioplegic ischemia in immature rabbit hearts

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Abstract

Objective: Recent observations have been shown that the induction and accumulation of heat shock proteins (HSPs) by short exposure to nonlethal whole-body hyperthermia with normothermic recovery are closely associated with transient resistance to subsequent ischemia-reperfusion challenges. Here, this study was performed to investigate whether a shortly heat shock pretreatment affects the left ventricular (LV) function after cold cardioplegic ischemia in reperfused neonatal rabbit hearts. Methods: Hearts from neonatal New Zealand White rabbits were isolated perfused (working heart preparation) and exposed to 2 h of cold cardioplegic ischemia followed by reperfusion for 60 min. To induce the heat shock response neonatal rabbits ($n = 5$, HT-group) were subjected to whole-body hyperthermia at 42.0–42.5\textdegree C for 15 min, followed by a normothermic recovery period of 60 min, before harvesting and the onset of global hypothermic cardioplegic arrest. Another set of hearts ($n = 5$, control group) without a heat treatment underwent a similar perfusion and ischemia protocol served as control. The postischemic recovery was assessed by measuring several parameters of LV function. LV biopsies from all control and heat treated animals were taken before ischemia and at the end of reperfusion to examine myocardial HSP levels by Western blot analysis. Results: At 60 min of reperfusion the HT-group showed significant better recovery of ventricular function such as LV developed pressure (DP) (74.6 ± 10 vs. 52.1 ± 8.5\%, $P < 0.05$), LV positive dP/dt (910 ± 170 vs. 530 ± 58 mmHg/s, $P < 0.01$) and LV end-diastolic pressure (LVEDP) (8 ± 2 vs. 18.4 ± 5 mmHg, $P < 0.05$) than control. Myocardial oxygen consumption (MVO\textsubscript{2}) was significantly higher in the HT-group compared with control (0.054 ± 0.006 vs. 0.041 ± 0.002 ml/g per min, $P < 0.05$). Significant postreperfusion lower level in lactate production was observed in the HT-group (0.83 ± 0.11 vs. 1.67 ± 0.8 mmol/l, $P < 0.05$). Also, the recovery of hemodynamic parameters such as aortic flow, coronary flow and cardiac output was significantly superior ($P < 0.05$) in the HT-group. Furthermore, high expression of HSP\textsubscript{72+73} were detected in the myocardial tissue samples of heat-treated rabbits by immunoblotting, appearing even at 60 min of normothermic recovery after heat stress. Conclusions: These data in the immature rabbit heart indicate that previous shortly heat treatment with high level expression of heat shock proteins (HSP\textsubscript{72+73}) before hypothermic cardioplegic ischemia provides transient tolerance against myocardial injury and could be an improvement for the postischemic functional recovery of neonatal hearts. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Neonatal rabbit hearts; Hyperthermia pretreatment; Cold cardioplegic ischemia; Reperfusion; Heat shock proteins; Left ventricular performance

1. Introduction

Hypothermia, cardioplegia or a combination of both is sometimes a necessary adjunct for myocardial protection during cardiac surgery in adults, infants and neonates. However, despite obvious benefits, some disadvantages of clinical surgical cardioprotection have been noted, particularly in the neonatal heart [1–7]. Because of structural, functional and metabolic differences, the immature heart may be even more prone to a ischemia-reperfusion injury results in impaired postoperative myocardial function [1,2,8,9]. The mechanisms responsible for ventricular dysfunction in immature myocardium may be less defined, as are their relationship to intrinsic myocardial alterations after surgical ischemia which include changes in myocardial metabolism, ion hemostasis, morphology and contractile function [1–7,10,11]. Previous experimental studies in adult animals to examine heat shock proteins (HSPs) have been shown to be induced before ischemia and associated with improved protection in myocardium and lung [12–16]. Exposure to elevated temperatures provokes a sequence of events (heat

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shock response) in all living cells. Through this response, cellular protein synthesis is rapidly redirected from broad-spectrum proteins for normal growth to a small group of heat-shock or stress proteins (HSP) [12,13,15,16]. In mammalian cells, HSP70 (molecular mass 68, 70, 72, and 73 kDa) is the major product of the heat shock response. In the past decade, the heat shock response has been postulated to play an important role in cellular repair, membrane stabilization and cell protection against ischemia-reperfusion injury [12,13,15,16].

The purpose of this study was to compare the postischemic recovery of left ventricular (LV) performance of heat pretreatment and non-heat pretreatment after extended hypothermic cardioplegic ischemia and reperfusion. An isolated neonatal rabbit ‘working’ heart was used for functional evaluation. We also assessed the induction of the heat-shock response by immunoblot analysis of small LV tissue samples.

2. Material and methods

2.1. Animals and anesthesia

Hearts (mean weight: 0.63 ± 0.05 g) from male, neonatal New Zealand White rabbits (n = 10, age 8–10 days; mean body weight: 0.18 ± 0.02 kg) were used. All animals were anesthetized with pentobarbital sodium (65 mg/kg intraperitoneally) and heparinized (150 IU/kg intravenously). The hearts were rapidly excised through a median sternotomy and placed in cold buffer-solution. An cannula was placed into the aorta and used to perfuse the hearts by the non-recirculating Langendorff technique detailed below.

Animals used in this study received humane care in compliance with the ‘Principles of Laboratory Animal Care’ formulated by the National Society for Medical Research and the ‘Guide for the Care and Use of Laboratory Animals’ published by the National Institute of Health (NIH Publication No. 86-23, revised 1985). Approval was obtained from the Institutional Animal Research Committee and the experiments conformed with the recommendations of the European Council for Laboratory Animal Science and the Animal Care Law of the Federal Republic of Germany.

2.2. Heat shock treatment

Heat treatment was similar to that previously described [12,14,16]. Briefly, after being anesthetized a group of the neonatal rabbits (n = 5) were heated gently with a temperature-controlled water bath and an electric heating pad (heating rate of 0.5–0.7°C/min). When the rectal temperature reached 42°C, they were maintained between 42 and 42.5°C for 15 min after which the heating pad and water bath was removed. The rectal temperature was kept at 37°C and the heat-treated animals were replaced in their cages to recover for 1 h.

2.3. Perfusion system

The used isolated working heart with split circulation setup (Hugo Sachs Elektronik, March-Hugstetten, Germany) provide a physiological LV pressure-volume work for neonatal rabbits and the function mode has been described in detail previously [3,7]. Briefly, this is a left heart preparation in which the perfusate was delivered from an oxygenator into the left atrium at an 8 mmHg preload and then passes to the left ventricle, from which it is ejected from beating hearts through a flow resistor into the aortic outflow line. The hydrostatic afterload was set at a column height equivalent to 40 mmHg pressure [3,7].

2.4. Perfusion media and cardioplegic solution

All hearts were perfused with modified Krebs–Henseleit buffer solution (pH 7.41, oxygenated with 95% O2 and 5% CO2). The perfusate was filtered (5 μm pore size) in-line and had the following composition: NaCl, 118 mmol/l; NaHCO3, 25 mmol/l; KCl, 4.8 mmol/l; CaCl2, 1.8 mmol/l; MgSO4, 1.2 mmol/l; KH2PO4, 1.2 mmol/l; and glucose, 11 mmol/l [3,7]. A commercially available crystalloid cardioplegic solution (modified ‘Eppendorf’ cardioplegia, Fresenius AG, Oberursel, Germany), (composition: D,L-magnesium aspartate, 2.0 mmol/l; procain hydrochloride, 4.0 mmol/l; NaCl, 25 mmol/l; KCl, 5 mmol/l; CaCl2, 0.5 mmol/l; glucose, 10 mmol/l; mannitol, 200 mmol/l; poly(0-2-hydroxyethyl)starch (HES 450/0.7) 60 g/l), was infused retrograde into the coronary system prior the onset of hypothermic global ischemia.

2.5. Experimental preparation and measurements

During the initial retrograd perfusion mode a second cannula (inflow during ‘working’ mode) was inserted into the left atrium and secured with a purse string suture in the left atrial wall. Spontaneously beating hearts were used throughout the studies and LV pressure waveforms were obtained by a ultraminiature pressure sensor-catheter (2 Fr Micro-Tip® catheter, SPR-407, Millar Instruments, Inc., Houston, TX) inserted into the left ventricle through a special port in the left atrial inflow line. LV pressure was differentiated to obtain maximum rate of rise during isovolumic contraction (LV dP/dtmax). Reperfusion systolic function was assessed by the recovery of developed pressure (DP), expressed as percentage, as the difference between end-systolic pressure (ESP) and end-diastolic pressure (EDP).

A 22 gauge catheter was inserted in the pulmonary artery to allow the perfusate to drain from the coronary sinus. The coronary effluent was timed collected in a graduated chamber to determine the coronary flow rate and filtered before it recirculated. Aortic flow was measured by an calibrated inline flowmeter and represented the ability of the heart to pump perfusate against the artificial resistor. The sum of aortic and coronary outflows was calculated as the cardiac...
The proteins were subsequently transferred into nitrocellulose membranes and probed with a primary monoclonal antibody that recognizes both the constitutive HSP73\(^+\) and inducible HSP72\(^+\) (Anti HSP70, BRM-22, H 5147, Sigma-Aldrich, Deisenhofen, Germany) and an monoclonal antibody directed against HSP72\(^+\) (RPN 1197, Amersham). Immune complexes were visualized using horseradish-peroxidase and 4-chloro-1-naphthol (Sigma-Aldrich, Deisenhofen, Germany).

2.8. Statistical analysis

Data are expressed as mean ± standard error (SE) of the mean. The recovery of DP was expressed as a percentage of its preischemic value. Comparisons within the hearts group were performed using paired Student’s t-test and between the two groups using the unpaired Student’s t-test with a Mann–Whitney rank sum test as a non-parametric second step. A \(\chi^2\)-test was used to compare categorical data (reperfusion arrhythmias) as appropriate. Differences were considered statistically significant at \(P < 0.05\).

3. Results

There were no significant differences in left ventricular parameters between the heat treated and control group immediately prior to the onset of cold cardioplegic arrest (Tables 1 and 2).

3.1. Western blot analysis: preliminary experiments

Separate experiments were performed to determine the minimal normothermic recovery time for heat-shock response in the immature rabbit myocardium. Small groups of neonatal rabbits were subjected to heat shock by immersion in a water bath rectal temperature set at 42–42.5\(^\circ\)C for 15 min, allowed to recover for various time periods at 37\(^\circ\)C

### Table 1

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<tr>
<th>Postischemic recovery for various indices of cardiac function at 60 min of reperfusion(^a)</th>
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<td>Control group</td>
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\(\^a\) Data are expressed as mean ± SE of the mean; control group \((n = 5)\), without heat shock pretreatment and HT-group \((n = 5)\), with heat pretreatment. LVEDP, left ventricular end-diastolic pressure; MVO\(_2\), myocardial oxygen consumption; NS, no significance.
(15, 30, 60 and 120 min) and then analyzed by Western blotting. The expression of heat-shock induced HSP70 levels in the heart tissues of heat-treated animals were detectable even at 15±30 min of normothermic recovery following heat stress when compared to their counterparts obtained from non-treated control animals. Stronger expressed HSP70 levels were seen at 60 and 120 min (data not shown).

### 3.2. Ischemia-reperfusion experiments

No HSP72\(^+\) and 73\(^+\) band could be visualized in samples obtained from non-heated rabbits before the onset of cardioplegic global ischemia (Fig. 1). As shown in Fig. 1 small amounts of HSP73\(^+\) could be detected in samples obtained from non-heated shocked (control group) animals after ischemia but no appreciable HSP72\(^+\) levels. On the contrary, after heat-treatment high HSP70 levels were monitored in LV myocardial samples obviously resulting from the expression of the induced HSP72\(^+\) and HSP73\(^+\) (Fig. 1). After reperfusion still elevated HSP72\(^+\) and HSP73\(^+\) levels were observed in all heat-treated hearts (Fig. 1).

#### 3.2.1. Reperfusion arrhythmias

The control group demonstrated a significantly higher incidence of VF compared with the HSP-group (control: \(n = 2\) vs. HSP: \(n = 0\), \(P < 0.05\)).

#### 3.2.2. Posts ischemic diastolic compliance

Significantly postreperfusion increase in LV end-diastolic pressure as index of LV diastolic function was observed in the control group (\(P < 0.05\)) (Table 1, Fig. 2). However, no significant changes in diastolic function were observed in HT-group hearts during reperfusion (Fig. 2).

#### 3.2.3. Posts ischemic systolic cardiac function

Heat-pretreatment resulted also in significantly improved recovery of LV developed pressure compared with the control group (\(P < 0.05\)) (Table 1, Fig. 3). Hypothermia and cardioplegia alone did less provide posts ischemic recovery of DP (Table 1, Fig. 3). At 60 min of reperfusion, the maximum positive dP/dt did significantly differ between the two groups (\(P < 0.01\)) (Table 1). Therefore, two indices of LV systolic function (the DP and maximum positive dP/dt) were significantly improved at 60 min of reperfusion compared with control hearts.

#### 3.2.4. Myocardial oxygen consumption

The posts ischemic myocardial oxygen consumption (MVO\(_2\)) in heat-shock pretreated hearts was significantly higher than those only with cold cardioplegic arrest (\(P < 0.05\)) (Fig. 4, Table 1).

#### 3.2.5. Myocardial lactate levels

Myocardial lactate production was significantly increased after reperfusion in the control group when compared to HT-group (\(P < 0.05\)) (Table 1).

![Fig. 1. Left ventricular tissue specific expression of heat shock protein levels (HSP72\(^+\)/73\(^+\)) detected by Western blotting in control and heat pretreated animals. Lane 1 represents negative control in non-heated treated hearts (control group), lane 2 show HSP72\(^+\) (72 kDa) and HSP73\(^+\) (73 kDa) expression in HT-group after whole-body hyperthermia with normothermic recovery as described and lanes 3 and 4 demonstrate HSP-amounts after reperfusion in both groups.](image-url)
3.2.6. Hemodynamic parameters

There were no significant changes in heart rate between the two groups at 60 min of reperfusion (Table 2). However, the recovery of aortic flow, coronary flow and cardiac output were significantly improved ($P < 0.05$) at 60 min of reperfusion in the HT-group compared with control hearts (Table 2).

4. Discussion

There are two important findings from our study. First, we found in neonatal rabbits exposed to a heat shock pretreatment an myocardial induction of heat shock protein HSP70 with increases in both the 72 and 73 kDa proteins by Western blot analysis even at 60 min of normothermic recovery. Second, the postischemic recovery in neonatal rabbit hearts can be improved by hyperthermia pretreatment before exposure to cold cardioplegic ischemia. This minimized the impairment in postreperfusion systolic function and diastolic properties of the LV compared with immature rabbit hearts that were not pretreated.

Among the members of the major heat shock gene family which encode proteins of molecular mass of approximately 70 kDa, the heat inducible HSP70 is the most prominent and well studied [12±20]. Most interestingly, it appears that the induction of HSPs confers a protective effect against exposure to a severe stress in cardiac as well as other cell types [12–20]. Especially, exposure of myocardium to a mild hyperthermic or ischemic stress which is sufficient to induce HSP expression protects the myocyte against a subsequent exposure to a more severe ischemic stress [12–14,16,17,19].

All the HSPs act as ‘chaperones’ in the cell by binding to and stabilizing unfolded or nascent proteins. HSP70 especially assist in synthesis, translocation, correct folding and subunit assembly of proteins while consuming ATP [12,13,14,16].

Extended surgical induced myocardial ischemia and reperfusion can initiate a variety of pathophysiological mechanisms, especially altered diastolic and systolic

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**Fig. 2.** Effects of no heat-shock (control group, solid bars, $n = 5$) and heat stress pretreatment (HT-group, pointed bars, $n = 5$) on postischemic left ventricular end-diastolic pressure (LVEDP). Results are expressed as mean values ± SE of the mean. (*$P < 0.05$ vs. preischemic LVEDP-values).

**Fig. 3.** Percentage recovery of left ventricular (LV) developed pressure (%DP) in the absence (control, solid bars, $n = 5$) and presence (HT-group, pointed bars, $n = 5$) of heat pretreatment. Values are mean ± SE of the mean (*$P < 0.05$ vs. control).
compliance, impaired coronary blood flow (endothelial stunning), arrhythmias and myocardial cell swelling that will lead to severe myocardial injury [2,3,10,11]. Contractile dysfunction due to abnormalities of intracellular calcium and alterations in myocyte function have also been implicated to play a crucial role in reperfused neonatal hearts [1,2,5,8,9]. Immediately during reperfusion further deterioration can occur as a result of progressively biochemical, cellular and molecular events, especially dysregulation of various enzymes and proteins, ion imbalance, mitochondrial dysfunction, mitochondrial calcium overload, activation of lytic enzymes (particularly in activated neutrophils and the inflammatory response), membrane disruption or the consecutive inhibition of oxidative phosphorylation leading to more severe cellular and subcellular changes [2,10,11]. Three highly interrelated factors are implicated in the pathophysiology of reperfusion injury and thus represent potential targets for therapeutic interventions which include intracellular calcium overloading, free radical generation and loss of sarcolemmal phospholipids with corresponding accumulation of lysophosphoglycerides and free fatty acids [2,10,11]. Sarcoplasmatic reticulum (SR) dysfunction in conjunction with an inadequate adenosine triphosphate (ATP) supply leads to a debilitating cycle of uncontrolled, cytosolic calcium entry in the myocyte [9,21]. Therefore, a large increase in intracellular calcium combined with low ATP availability contributes to longer calcium binding with the cardiomyoocyte contractile proteins resulting in shorter myofilaments and higher LV end-diastolic pressures [21,22]. Furthermore, elevated cytosolic calcium in postischemic myocardium may aggravate cellular injury by mitochondrial and ATPase activity dysfunction, by activation of proteases and phospholipases and by myocardial hypercontraction [2,9,11,21].

More recently, many investigations demonstrated that expression of heat shock proteins (HSPs) after exposure of animals to brief periods of hyperthermia followed by periods of normothermic recovery initiate a most potent protective effect in the myocardium [12–14,16,17]. These adaptive responses appear to trigger a sequence of cellular events that lead to pronounced protection, which has been shown to manifest as improved tolerance to ischemia resulting in better recovery of myocardial function, reduced infarct size and decrease the development of ventricular arrhythmias [12–14,16,17]. Presently, the precise mechanisms underlying the cardioprotective properties of HSPs have not been delineated. However, some studies pointed out that many alterations may be involved in heat shock response, such as improved transport of repair proteins across cellular and subcellular membranes (affecting mitochondrial and sarcoplasmatic reticulum membrane), preventing intracellular calcium overload, altering calcium regulatory proteins, preservation of the endothelium, inhibiting leucocyte production of free radicals, increased superoxide dismutase (SOD) and catalase activity [13,14,16–18,23,24]; all of these changes potentially affect tissue viability and are important factors of ischemia-reperfusion injury [2,3,8,11]. In our experimental group heat shock was administered to the entire body at 42–42.5°C for 15 min – an established condition of heat shock in vivo – and secondary a ischemia-reperfusion protocol was performed after recovery for 1 h, compatible with the period for high level synthesis of inducible HSPs in neonatal rabbit myocardium. These findings also suggest that the early high level HSP-expression in neonatal tissue are mediated through age-related differences in myocardial structure and function. In contrast, heart tissue from adult animals show preferentially HSP-expression only at least 2–12 h post-treatment [12–17]. These pathways require further elucidation. The slightly enhanced HSP-levels from the control animals was explained as resulting from ischemia-reperfusion stress. A significant improved postischemic myocardial function and lower lactate levels was observed and no heart exhibited ventricular fibrillation on reperfusion in the hyperthermia group. Myocardial oxygen consumption was significantly higher in the HT-group compared with those in control
group and indicate more efficient oxygen use after cold cardioplegic ischemia in hearts pretreated by heat stress. The improvement in blood flow (coronary and aortic flow) in the HT-group may be further suppose that a association between expressed HSP70 and improved vascular endothelial protection exists. From the present results, it is tempting to speculate that the significantly less impaired postischemic LVEDP in heat-shock pretreated hearts indicate a preventive effect by previous heat treatment on cellular calcium homeostasis and may be responsible for the improved return of contractile function [9,18,23]. Further studies are needed to clarify these issues. Numerous studies with whole-body heat stress have suggested the direct role of expressed HSP70 in the better myocardial protection from ischemia-reperfusion injury in adult animals [12–14,16,17]. Similarly, Currie and associates for example found an improved functional recovery in heat-shocked hearts after low-flow and no-flow ischemia with subsequent reperfusion [12–14]. Furthermore, it was noted significantly reduced infarct size in adult rabbits after hyperthermic pretreatment and high amount of myocardial HSP72 produced by heat stress [14], whilst Hutter have also demonstrated a similar correlation between the expressed amount of HSP70 and the ability to limit infarct size following ischemia and reperfusion in rat hearts [16]. Heat pretreatment in rats with HSP expression also has been shown to improve contractile recovery after ischemia and reperfusion [17]. Moreover, the creatine kinase leakage to reflect membrane dysfunction and tissue injury, was considerably reduced and the levels of endogenous catalase, a known scavenger of hydroxyl radical, were significantly increased in the heat treated hearts compared with controls [17]. However, there may be evidence to suggest that HSP might have a ability to prevent or mitigate reactive free radical-mediated injury and this could potentially augment the protective phenomenon seen with heat treatment and expression of HSPs [17,24].

In a study of myocardial hibernation, Ferrari et al. suggested that an intracellular adaptional process with expression of HSP72 occurs at myocardial level during congestive heart failure or hibernation [19]. In his study, rat hearts were subjected to either short term acute hibernation or induced heart failure. He found an increased amount of HSP72 expression in the right and left ventricle [19]. Moreover, a gene transfer approach to enhance myocardial tolerance to ischemia-reperfusion injury was also described [20]. In their experiments, full-length of human HSP70 cDNA was cloned at the EcoRI/BamHI site of pcDNA3 and transfected into rat hearts by hemagglutinating virus of Japan (HVJ)-liposomes through intracoronary infusion. The results showed extensive cytoplasmatic overexpression of HSP70 in cardiomyocytes that received HSP70 cDNA compared to hearts that received no HSP70 gene [20]. The percentage recovery of LVDP, dP/dt max, and coronary flow, 30 min after reperfusion was also significantly higher in hearts transfected with HSP70 cDNA than all other groups [20].

In summary, preceding treatment by heat shock attenuates myocardial deterioration after 2 h of global ischemia combined with cold cardioplegia and reperfusion in an immature rabbit heart model. The postischemic recovery in both systolic and diastolic LV function was improved and myocardial lactate release was reduced by pretreatment with shortly whole-body heat stress and a normothermic recovery for 60 min. Furthermore, it is suggested that heat-induced high level expression of HSPs may have activated certain adaptive mechanisms of protection that probably preconditioned the myocardium against anticipated contractile and vascular injury associated with hypothermic global ischemia and reperfusion. Although the exact mechanism of improved ischemia tolerance and increased expression of HSP70 is currently under investigation, we suggest that the beneficial protective appearance during early reperfusion is probably due in part to the inducible synthesis and accumulation of HSPs. Further studies will be required to determine the physiological importance of these and other intrinsic molecular adaptations in neonatal myocardium.

References


Appendix A. Conference discussion

Mr P. Belcher (Glasgow, UK): What is the mechanism by which heat shock protein protects the heart?

Dr Vogt: I don’t know and I tried to find further details in the literature. I think it’s well known that heat shock proteins have several functions. We know that there is a cellular function together with apoptosis. It’s not only a protection mechanism. Furthermore it is suggested that HSP expression is probably dependent on the function of mitochondria. All the different authors agree in the importance of HSP function for hemostasis. But until now, in my investigations, I have not found any further details that we really can use here supporting this mechanism.