Coronary autoregulation protects against harmful effects of commonly used cardioplegia delivery pressure

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Abstract  Objective. Hearts or parts of hearts are often ischemic prior to infusion of the cardioplegic solution and have a more or less dilated coronary bed. We made an investigation whether coronary dilation just prior to induction of cardiac arrest by aortic clamping and infusion of crystalloid cardioplegic solution would influence cardioprotection.

Methods. Isolated buffer-perfused rat hearts (100 cm H2O pressure (=73.5 mmHg), 37°C) were used. After a stabilization period the perfusion of 8 rats (group 1) was stopped and the hearts arrested with 5 ml CS (100 cm H2O, 12°C). Equal amounts of cardioplegic solution were then delivered every 20 minutes for the entire 3½ hour hypothermic ischemic period. Following ischemia the hearts were reperfused for 60 minutes. In group 2 (n=8) 1 ml 10⁻² mmol Papaverine was given into the aortic root just prior to the first cardioplegic solution infusion in order to induce coronary vasodilation. The procedure was identical in the two groups during ischemia and reperfusion.

Results. During the ischemic period coronary resistance increased in group 2. During reperfusion group 2 had lower coronary flow (P=0.001), left ventricle developed pressure (P=0.002) and a higher creatine kinase release (P=0.003) than group 1 hearts. Group 2 also had a lower adenosine-triphosphate (6.51±0.40 mmol·g⁻¹ and 14.03±0.59 mmol·g⁻¹, respectively, P=0.011), creatine phosphate (24.70±1.02 mmol·g⁻¹ and 36.50±1.31 mmol·g⁻¹, respectively, P=0.020) and a larger fall in dry/wet-weight ratio (1.7±0.4 and 0.8±0.5, respectively, P=0.043).

Conclusions. Vasodilation (i.e. ischemia) just prior to infusion of crystalloid cardioplegic solution may impair myocardial protection even when the cardioplegic solution is delivered at a relatively low and presumably safe pressure.

Key words  Cardioplegia • Cardioprotection • Delivery pressure • Postischemic performance

Introduction

In a previous study we found that, with intermittently given cardioplegic solution (CS) both a low cardioplegic solution delivery pressure (CSDP) (22 mmHg) and a high CSDP (175 mmHg) are unfavorable for the heart, while moderately high CSDP (73.5 mmHg and 106.5 mmHg) gives better protection [11]. Hearts preserved at the highest delivery pressure fared poorly and had considerable edema. In other studies it was found that extending the ischemic period increases the leakage through the capillary wall with myocardial edema as a result [14]. Lindal and colleagues have shown that a gradual rise in pressure and temperature at the beginning of the reperfusion period ameliorates reperfusion injury and is favorable for the resumption of normal cardiac function [15].
The cardiac arrest period starts with aortic clamping, CS infusion and a physiological autoregulation which is gradually compromised, mainly due to hypothermia but ischemia and hyperkalemia are also contributing factors. In the clinical setting, hearts or parts of hearts that are ischemic prior to infusion of the CS have a more or less dilated coronary bed. We hypothesized that compromising the preischemic autoregulation exposes the microcirculation of the heart to harmfully high CSDP when administered in a standard fashion. To test this we have undertaken an in vitro study in rat hearts where papaverine or ischemia dilated the coronary tree just prior to cardiac arrest.

Material and methods

Male rat hearts (body weight 250–280 g) of the Wistar strain were used. Retrograde perfusion and antegrade cardioplegic infusion were performed as described earlier [11] with a 15 min stabilization period, 3/4 h 12°C cardiac arrest and 60 min reperfusion period at 37°C and 100 cm H₂O perfusion pressure (=73.5 mmHg) (n=8). During the cardiac arrest period 5 ml St. Thomas' cardioplegic solution Nr. 2 (CS) [12] were perfused every 20 min at 12°C and 100 cm H₂O pressure. In group 2 (n=8) we infused 1 ml 10⁻² mmol papaverine at 37°C diluted in 5 ml Krebs-Henseleit solution 1 min prior to aortic clamping and thus before the first cardioplegic infusion via a side arm on the aortic cannula. In an initial pilot study we observed that this papaverine quantity increased the coronary flow by 75%. During the cardiac arrest and reperfusion period the procedure was identical in the two groups.

In addition, (group 3; n=8) reactive hyperemia was induced with cessation of the buffer-perfusion for 5 min followed by a 29% increase in flow 3 min after the buffer-perfusion had been re-established. The perfusion was then stopped and the cardiac arrest period completed as in the two other groups. Because 5 min of ischemia induces preconditioning of the healthy, well oxygenated heart, reperfusion studies were not performed in this group [3, 13, 16].

During the cardiac arrest period the time for each 5 ml CS infusion was measured and hence coronary resistance calculated from the equation: perfusion pressure (mmHg)=coronary resistance - CF (ml/min). Like others, we give the coronary resistance in resistance units (RU) [2]. Throughout the reperfusion period we measured coronary flow (CF), left ventricular developed pressure (LVDP) and heart rate (HR). Two milliliters effluvate was regularly sampled, rapidly put on ice and analyzed for creatine kinase (CK) within 2 h.

At the end of reperfusion the hearts were freeze-clamped and kept on liquid nitrogen until analyses for ATP and CP were performed by high-pressure liquid chromatography (HPLC)¹ according to the method of Sellevold and associates [21]. High-energy phosphate levels at the end of stabilization were obtained from eight hearts which were freeze-clamped at this stage of the protocol. At the end of the stabilization period eight hearts were first weighed (W), then dried and then weighed again (D). Based on these weights we calculated the dry/wet-weight ratio (WR); D/W*100. After ending the reperfusion period we calculated WR in the same way from a small sample of the hearts in groups 1 and 2.

For statistical analysis, values are expressed as the mean±standard error of the mean (SEM). Differences were considered to be significant when P<0.05. Summary data were compared by analyses of variance (ANOVA) and differences among the groups were analyzed by Student’s t-test.

¹ Waters Chromatography Div., Millipore, Mass., USA

Results

The stabilization period

There were no statistical differences between group 1 and group 2 with respect to CF (12.1±0.8 ml/min, 12.0±0.7 ml/min), LVDP (103.0±6.0 mmHg, 105.8±9.1 mmHg) and HR (270±10 beats/min, 281±12 beats/min) during the stabilization period. The resistance in the coronary tree was calculated to 6.1±0.6 and 6.1±0.5 RU, respectively. In eight hearts we calculated WR to 14.0±0.4. The acidity of the mixture of papaverine and KH-buffer was measured to pH between 6.9 and 7.2.

The cardiac arrest period

There was a significantly higher resistance in the coronary tree in group 2 (changing from 8.8±0.8 RU to 21.0±0.4 RU) than in group 1 (mean 4.1±0.4 RU) during the ischemic period (P<0.001). Even with the moderate preischemic vasodilation in group 3 a significantly increased coronary resistance was found (12.5±0.5 RU, P=0.001) (Fig. 1).

The reperfusion period

Coronary flow in group 2 was significantly lower during the first 10 min of reperfusion than in group 1 (P=0.049), indicating a higher coronary resistance (Fig. 2). Left ventricular developed pressures were significantly higher in group 1 during the reperfusion period than in group 2.
Fig. 2 Percent change in coronary flow during the reperfusion period. Group 1 = control group, group 2 = papaverine-induced coronary vasodilation just before cardiac arrest. (S stabilization period, I ischemic period, * mean value)

Fig. 3 Percent change in left ventricular developed pressure during the reperfusion period. Group 1 = control group, group 2 = papaverine-induced coronary vasodilation just before cardiac arrest. (S stabilization period, I ischemic period, * mean value)

(P=0.002) (Fig. 3). Heart rate did not change significantly in the two groups during the reperfusion period, but HRs were significantly higher in group 1 (266±16 beats/min) than in group 2 (158±31 beats/min, P=0.014). During the whole reperfusion period we measured a significantly higher CK release in group 2 (P=0.001), indicating more myocardial damage (Fig. 4) and after 60 min of reperfusion there were significantly lower ATP and CP concentrations in the hearts of group 2 than in group 1 hearts (P=0.011 and P=0.020, respectively) (Fig. 5). There was a significant fall in WR in group 2 from the stabilization period till the end of reperfusion (14.0±0.4 to 12.3±0.3 respectively), and no such drop in group 1 (13.2±0.6) (P=0.043), indicating increasing myocardial edema in group 1.

Fig. 4 Creatine kinase leakage (IU/l) during the reperfusion period. Group 1 = control group, group 2 = papaverine-induced coronary vasodilation just before cardiac arrest. (S stabilization period, I ischemic period)

Fig. 5 Myocardial content of adenosine triphosphate (ATP) and creatine phosphate (CP) during the stabilization period (S) and after 60 min of reperfusion following 3½ h ischemia. Group 1 = control group, group 2 = papaverine-induced coronary vasodilation just before cardiac arrest

Discussion

The present study shows impaired cardioprotection when the first dose of CS is infused into an unappropriately dilated coronary vascular tree. In standard situations (as in
group 1) cardiac arrest is induced with a hypothermic, hyperkalemic CS which gives relaxation of the precapillary sphincters and coronary vasodilation mostly due to ischemia and hyperkalemia [1, 4, 18, 19]. In group 2 we first produced a considerable coronary vasodilation with papaverine and then induced cardiac arrest with the same CS in equal amounts and given with the same pressure and temperature as in group 1. In our model we obtained approximately 75% increased flow with the papaverine infusion. The first dose of CS in group 2 was consequently infused into the already vasodilated coronary arteries with about 75% higher flow than during the stabilization period. The half-life of papaverine is only minutes and it is therefore likely that the second cardioplegic dose 20 min later was infused into a vascular bed without that additionally vasodilatory influence. The flow was now reduced to 67% of the initial CF and to half the flow in the control group (group 1) (Fig. 1) indicating that the harm was induced immediately.

To test whether our results were not just a toxic effect of papaverine, we induced vasodilation in another group of hearts (group 3) via ischemia. In this group, too, we observed increased coronary resistance, but to a lesser degree than in group 2. Group 3 was initially exposed to 5 min of ischemia which results in preconditioning of the heart [3, 13, 16]. The degree of recovery would hence not be representative of our problem, and we therefore desisted from doing reperfusion studies in this group.

Inducing coronary vasodilation prior to the first cardioplegic infusion did indeed cause an increased coronary resistance, most likely because of interstitial edema, as indicated by the high water content in group 2 hearts. Normally only some of the capillaries are open at a given time - then others take over and so on; the dynamics of the precapillary regulation probably lets CS into only some parts of the capillary bed at any one time [8]. Maybe CS is even shunted past the capillary bed when the temperature is down. This fine tuning of the autoregulatory system seems to be lost when papaverine or ischemia reduces smooth muscle vascular tone and thus exposes the capillary endothelium massively to the toxic CS at inappropriate capillary pressures. The harm seems to be done in just a few minutes. Papaverine is known to produce marked vasodilation through a direct relaxation of arteriolar smooth muscles [6]. Furthermore, its effect is short-acting and gives a near complete vasodilation [23]. Papaverine per se in the concentration we gave is not toxic to endothelium [10].

Apart from species differences, this is an in vitro study where the coronary tree is perfused with a buffer solution. It is well known that buffer perfusion entails vasodilation because of decreased capacity of oxygen delivery [7, 20, 22]. Studying effects related to autoregulation on an already dilated coronary tree may not be ideal but the model is, on the other hand, the standard for studies on cardioplegia and ischemia-reperfusion [5, 9]. In vivo there are extracoronary collaterals which give oxygenated blood to the heart and wash out cardioplegia and toxic metabolites to an individually varying degree during cardiac arrest [17]. This collateral flow may well explain why the phenomenon we describe here has never attracted clinical attention. During cardiac surgery, however, there may well be regional or global ischemia just prior to the cardiac arrest period caused by coronary stenoses, recent occlusions or suboptimal oxygenation. Our results show the importance of optimal oxygenation of such areas before delivering CS, to secure normal autoregulation of the coronary vascular bed. It is likely that this conclusion also pertains to local areas given CS through established vein grafts and it may be an argument for the retrograde oxygenated blood cardioplegia in cases with known ongoing ischemia.

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References