Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2000; 3 (2), 135-139

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Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

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Beneficial Effect of Glucose on Short-Term, Perfusion-Pressure Induced Changes of Contractile Efficiency in Isolated Rabbit Hearts

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Objective: As adaptation to decreased coronary perfusion, both mechanical function and oxygen consumption are reduced in short-term hibernating myocardium. Changes in the energy supply-demand balance are reflected by changes in contractile efficiency (E_{con}; = relation between oxygen consumption and the pressure volume area; PVA). We investigated the influence of supplementation with free fatty acids (FFA) alone versus a combination of FFA with glucose on E_{con} in moderately or severely hypoperfused myocardium. Methods: 30 isolated rabbit hearts were perfused with buffer containing either 1.4 mM FFA (group FA) or 1.4 mM FFA plus 11 mM glucose (group FAG). During control, the coronary arterial pressure (CAP) was 90 mmHg. CAP was reduced either to 60 mmHg (n = 19, HYP60) or to 30 mmHg (n = 11, HYP30). Results: Myocardial systolic function (aortic flow, peak left ventricular pressure, slope of the end-systolic pressure volume relation, and PVA) did not show any dependency on the substrate composition during control, HYP60, HYP30, and reperfusion. In group FA, hypoperfusion did not significantly affect the slope of the MVO_2-PVA relation compared with control: 40.1 ± 15.2 vs. 37.6 ± 12.3 (HYP60) and 29.8 ± 9.2 vs. 30.3 ± 10.4 µl/beat/(mmHg·ml) 10^{-4} (HYP30). In group FAG, the slope decreased during HYP60 (26.3 ± 3.0 vs. 16.5 ± 1.9, $^{\star}p < 0.05$) and during HYP30 (21.8 ± 8.5 vs. 20.5 ± 4.5 µl/beat/(mmHg ml) × 10^{-4}; n.s.). Conclusion: Additional supply with glucose in comparison to FFA alone increases E_{con} during moderate hypoperfusion. Since E_{con} was not significantly changed during severe hypoperfusion, when no autoprotection is possible, this might reflect autoprotective changes in metabolic pathways facilitated by glucose. The change in E_{con} might be explained by a beneficial effect of glucose on supply-demand balance, e.g. lower energy cost of carbohydrate oxidation in comparison to FFA oxidation and diminished deleterious effects of FFA oxidation on the myocardium. *J Clin Basic Cardiol 2000; 3: 135–9.*

Key words: myocardial hibernation, substrate, efficiency, rabbit, isolated heart

Myocardial hibernation is defined as a stable, reversibly impaired myocardial contractile function in adaptation to restricted coronary flow [1–3]. The presence of viable tissue [4] and the recovery of the intracellular content of high-energy phosphates despite continued moderate ischaemia [5–7] show that the energy demand is in equilibrium with the energy supply. Such a down-regulation of mechanical function is interpreted as a self-protecting mechanism to prolong the metabolic integrity of the ischaemic myocardium [5, 7–10]. The underlying mechanism of myocardial hibernation is still unclear.

Changes in energy balance during hypoperfusion can be demonstrated by assessing the efficiency of chemo-mechanical coupling. This contractile efficiency can be derived from the reciprocal of the slope of the relation between the oxygen consumption and the pressure-volume area, a measure of the total mechanical work performed by the ventricle [11].

Deleterious effects of high free fatty acid concentrations on normo- or hypoperfused myocardium are well known [12, 13] and are attributed to a higher oxygen demand for free fatty acid metabolization [14, 15], or to decoupling effects of accumulating lysophosphoglycerides on oxidative phosphorylation [16, 17]. Inhibition of fatty acid oxidation and stimulation of glucose oxidation improves the function in ischaemic myocardium [14, 18–20].

On the hypothesis that glucose might have a beneficial effect not only on function but also on initiation and preservation of autoprotective mechanisms, we investigated contractile efficiency during normoperfusion and hypoperfusion as a reflection of supply-demand balance in isolated rabbit hearts supplied with free fatty acids alone or in combination with glucose.

Materials and methods

Surgical preparation and experimental set up

Experiments were performed on 30 male New Zealand White rabbits (2.7 ± 0.4 kg body weight, age 4 to 5 months). All procedures for animal care and experimentation followed the German laws for animal protection that conform with the "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" (Council of Europe No 123, Strasbourg 1985). The animals were anaesthetized with ketamine (30 mg/kg body weight) and rompun (0.1 ml/kg body weight), tracheotomized, relaxed (1 mg pancuronium), and ventilated with room air enriched with oxygen. Respiration frequency was adjusted to 35/min and the tidal volume to 25–30 ml. After midsternal thoracotomy and anticoagulation with 1300 I.U. heparin, the aorta was cannulated and connected to a modified Langendorff apparatus. During preparation, a coronary arterial pressure (Statham, ID 123) of 80 mmHg was maintained, and the temperature of the perfusate was held constant at 38 °C throughout the experiment. After ligation of the Vv. cavae, a latex balloon (Hugo Sachs, #12) attached to the "systemic circuit" was inserted into the left ventricle via the mitral valve. The systemic circuit consisted of a reservoir filled with water at variable levels to alter preload, "mitral" and "aortic" valves connected to the latex balloon, a windkessel, and a vertical column with a flow probe (Transonic Systems; T200) to record "aortic" flow.

To assess preloading conditions, left ventricular diameter was measured using two ultrasonic crystals glued to either side of the latex balloon. The pulmonary artery was cannulated to collect the perfusate for recirculation and to measure coronary flow (Transonic Systems, T200), venous

Received May 21st, 2000; accepted June 27th, 2000.
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pO_2 (oxygen probe, Eschweiler & Co), and lactate concentration (L-Lactic Acid UV-Test, Boehringer Mannheim). To record left ventricular pressure and its first derivative dP/dt, a 3F microtip catheter (Millar; TC 5000) was introduced into the latex balloon. Since there were only slight differences in heart rate throughout the experiments and since calculation of the pressure-volume area is independent of heart rate, no pacing system was used.

Perfusion media

The perfusate, a modified Krebs-Henseleit buffer, contained either 1.4 mM free fatty acids (FFA) bound to albumin at a concentration of 40 g/l (group FA, n = 14) or 1.4 mM FFA plus 11 mM glucose (group FAG, n = 16). The mixture of FFA consisted of 28 % palmitic acid, 27 % oleic acid, 20 % stearic acid, 16 % linoleic acid, and 9 % palmitoleinic acid (assessed by gas chromatography). The coronary arterial pO_2 between 590 and 620 mmHg was achieved by using a baby oxygenator (dideco, D701).

Experimental protocol

After the end of preparation and instrumentation, a stabilisation period of 20 min was allowed during which the CAP was adjusted to 90 mmHg in all experiments. Then, control values were recorded. For hypoperfusion, the perfusion pressure was reduced in group FA (perfusion with FFA) to 60 mmHg in 9 and to 30 mmHg in 5 hearts and in group FAG (perfusion with FFA plus glucose) to 60 mmHg in 10 and to 30 mmHg in 6 hearts. To assess ventricular function at the different perfusion pressures, preload was changed every 3 min in 5–7 steps (within the range of 2–15 mmHg left ventricular end-diastolic pressure) and the functional parameters recorded in ejecting and in isovolumic mode. Except for the aortic flow, variables are presented only for steady state isovolumic contractions. Hypoperfusion lasted 20 min. The variation of preload and mode of contraction was repeated after 20 min of reperfusion at a perfusion pressure of 90 mmHg; this phase also lasted 20 min. At the end of the experiment, the tissue was weighed and then dried at 80 °C for 24 h to assess the dry/wet-weight ratio.

Data acquisition and statistics

Data were registered using an eight channel forced ink recorder (Gould, 481) and simultaneously stored on magnetic disc for later processing with a custom-made computer program (EASYDAT [21]). The same program was used to compute the end-systolic pressure-volume relation (ESPVR) and its y-axis intercept V_0 by extrapolation and to calculate the pressure-volume area (PVA).

Statistical calculations were performed using a commercially available statistical program (SYSTAT [22]). The data were tested using a one-way analysis of variance (ANOVA). A post-hoc test (Bonferroni) was used in cases when multiple comparisons were made. Comparisons were made between parameters of control, hypo- and reperfusion within each group with the same severity of hypoperfusion and substrate composition. The threshold of statistical significance was defined at $p < 0.05$. Results are presented as means ± SEM.

Results

Because we did not detect significant differences between the isovolumic and the ejecting contractions, we present values for the isovolumic contractions, where applicable.

Myocardial contractile function

The hypoperfused myocardium showed a substantial decrease in systolic mechanical function in both groups within the first five minutes of reduced perfusion pressure. Throughout the following 15 min of hypoperfusion, function remained stable on the decreased level, therefore allowing measurement of the different functional parameters on varying pre- and afterload conditions needed to assess the pressure-volume area.

In the hearts perfused with the buffer containing FFA (group FA), the impairment in systolic function was slightly more pronounced than in the hearts perfused with buffer containing FFA plus glucose (group FAG) and depended on the severity of hypoperfusion: aortic flow (AoF) was about 60 % lower during hypoperfusion with a coronary arterial pressure (CAP) of 60 mmHg and about 70 % lower at a CAP of 30 mmHg compared with control values of each group. During reperfusion, AoF recovered to only 45 % of control (statistically significant after severe hypoperfusion). Left ventricular peak pressure fell to 80 % (CAP = 60 mmHg) and to 75 % (CAP = 30 mmHg) of control and did not recover. In the subgroup undergoing hypoperfusion with a CAP of 30 mmHg, heart rate was slightly lower than in the other subgroup, but in no case were significant changes within the time course of the experiment noted (Tab. 1).

In group FAG, the decrease in AoF and in LVPmax was statistically significant, but independent of the severity of hypoperfusion. Since heart rate changed only slightly (as in group FA) the decrease of AoF to 25 % was mainly due to the reduction in stroke volume (Tab. 2). During reperfusion, AoF dropped even further to only 15 % of control after moderate hypoperfusion and recov-

Table 1. Group FA: buffer containing 1.4 mM FFA. Effect of perfusion pressure on aortic flow (AoF), maximum left ventricular pressure (LVP_{max}), pressure-volume area (PVA), slope of the end-systolic pressure-volume relation (ESPVR), dP/dt_{max}, early relaxation (dP/dt_{min}), and heart rate (HR) in group FA and in group FAG during isovolumic contractions. Values are means ± SEM (* $p < 0.05$ vs. control).

	Control	Moderate hypoperfusion	Severe hypoperfusion	Reperfusion
AoF	36.9 ± 3.9	14.0 ± 2.9*		16.9 ± 3.5
[ml/min]	64.8 ± 7.8		18.8 ± 6.1*	28.2 ± 6.3*
LVP_{max}	88 ± 2	71 ± 3*		70 ± 4*
[mmHg]	107 ± 4		80 ± 5*	84 ± 7*
PVA	638 ± 87	483 ± 65		430 ± 73
[mmHg × ml]	1292 ± 146		995 ± 150	1028 ± 41
ESPVR	100 ± 29	89 ± 23		100 ± 22
[ml/mmHg]	91 ± 15		75 ± 12	44 ± 13
dP/dt_{max}	1289 ± 61	945 ± 44		
[mmHg/s]	1502 ± 92		1064 ± 66	
dP/dt_{min}	1119 ± 39	804 ± 50*		
[mmHg/s]	1297 ± 90		979 ± 102	
HR	187 ± 8	183 ± 8		183 ± 13
[1/min]	160 ± 13		157 ± 14	166 ± 5

ered after severe hypoperfusion only to approximately 50 % of control.

The pressure-volume area (PVA) was decreased during moderate and severe hypoperfusion in both groups (Tab. 1 and 2). The slope of the end-systolic pressure-volume relation decreased during moderate and severe hypoperfusion in both groups and thus, similarly indicated decreased systolic function. Owing to the relatively large scatter, these differences did not reach statistical significance. Likewise, the decrease in PVA in the slope was not statistically significant, and in none of the groups, was a significant recovery during reperfusion observed.

The decreases in contractility (assessed in terms of dP/dtmax) caused by hypoperfusion were significantly influenced by the substrate composition. In group FA (Tab. 1 and 2), a decrease in CAP to 60 and to 30 mmHg caused a significant reduction in dP/dtmax. In group FAG (Tab. 1 and 2), the reduction in dP/dtmax was more pronounced at a CAP of 30 mmHg than at 60 mmHg, but neither difference was statistically significant. Again, no recovery of these parameters could be noted. Early diastolic relaxation, reflected in dP/dtmin (Tab. 1 and 2), was significantly impaired during moderate hypoperfusion in both groups, but during severe hypoperfusion only in group FAG, not in group FA. dP/dtmin was decreased during reperfusion in comparison to control (statistically significant in group FA, but not in group FAG). The slope of the end-systolic pressure-volume relation (ESPVR) decreased only slightly during hypoperfusion with the exception of group FA. Here, ESPVR further decreased during reperfusion following severe hypoperfusion without being significantly lower than control.

Oxygen consumption (MVO_2)

Since data for both isovolumic and ejecting conditions did not differ, only the values for isovolumic contractions are given in the following text. In group FA, MVO_2 decreased at a CAP of 60 mmHg non-significantly by 25 % from 26.2 ± 2.4 to 19.6 ± 1.6 and recovered to 22.6 ± 2.0 μlO_2/100 g/beat in reperfusion. If CAP was more severely decreased to 30 mmHg, the decrease in MVO_2 was more pronounced, but still not statistically significant ($p = 0.06$): MVO_2 decreased by 36 % from 32.9 ± 2.5 to 21.2 ± 2.9 and recovered to 24.5 ± 3.8 μlO_2/100 g/beat.

Moderate hypoperfusion in group FAG resulted in a non-significant decrease in MVO_2: from 29.9 ± 1.8 to 24.0 ± 1.9 and decreased further to 22.0 ± 1.7 μlO_2/100 g/beat in reperfusion. The reduction of MVO_2 in response to severe hypoperfusion (CAP = 30 mmHg) was statistically significant: MVO_2 fell from 28.8 ± 1 to 22.3 ± 1.5 and recovered to 25.5 ± 2.6 μlO_2/100 g/beat in reperfusion.

MVO_2-PVA relation and contractile efficiency

The myocardial oxygen consumption for the unloaded contraction (=MVO_2-axis intercept of the MVO_2-PVA relation; MVO_{2unl}) was slightly decreased in both groups during hypoperfusion compared with control (Tab. 3). This decrease was statistically significant during severe hypoperfusion and ejecting conditions. The changes in the slope of the MVO_2-PVA relation, the reciprocal of contractile efficiency, were affected both by the severity of hypoperfusion and by the substrate composition (Tab. 3). In group FA, the slope did not change during moderate (CAP = 60 mmHg) nor during severe (CAP = 30 mmHg) hypoperfusion. In contrast, group FAG showed a significant decrease in the slope of the MVO_2-PVA relation during moderate hypoperfusion, but not during severe hypoperfusion, ie, the contractile efficiency increased only during moderate hypoperfusion and during supply with free fatty acids plus glucose.

The MVO_2-PVA relation exhibited no significant differences for control and reperfusion. Although there was a tendency towards lower values in group FA after severe hypoperfusion, the MVO_2-axis intercept MVO_{2unl} did not change compared with control (Tab. 3). The slope of the

Table 2. Group FAG (buffer containing 1.4 mM FFA plus 11 mM glucose). Effect of perfusion pressure on aortic flow (AoF), maximum left ventricular pressure (LVP_{max}), pressure-volume area (PVA), slope of the end-systolic pressure-volume relation (ESPVR), dP/dt_{max}, early relaxation (dP/dt_{min}), and heart rate (HR) during isovolumic contractions. Values are means ± SEM (*$p < 0.05$ vs. control).

	Control	Moderate hypoperfusion	Severe hypoperfusion	Reperfusion
AoF	41.7 ± 3.6	116 ± 2.3*		6.3 ± 1.0*
[ml/min]	43.8 ± 6.8		11.2 ± 2.4*	22.0 ± 5.9*
LVP_{max}	87 ± 3	64 ± 3*		65 ± 5*
[mmHg]	89 ± 4		66 ± 5*	69 ± 4*
PVA	498 ± 55	397 ± 43		432 ± 61
[mmHg × ml]	582 ± 53		449 ± 40	455 ± 45
ESPVR	123 ± 11	92 ± 15		96 ± 11
[ml/mmHg]	103 ± 15		80 ± 11	104 ± 17
dP/dt_{max}	1157 ± 38	869 ± 48		
[mmHg/s]	1253 ± 72		900 ± 54	
dP/dt_{min}	1042 ± 26	767 ± 34*		
[mmHg/s]	1168 ± 48		811 ± 48*	
HR	184 ± 6	169 ± 7		171 ± 10
[1/min]	195 ± 17		182 ± 17	172 ± 19

Table 3. Effect of perfusion pressure on the y-axis intercept (MVO_{2unl}) of the MVO_2-PVA relation and on the slope of the MVO_2-PVA relation in group FA and in group FAG during isovolumic contractions. Values are means ± SEM; *$p < 0.05$ vs. control

	Control	Moderate hypoperfusion	Severe hypoperfusion	Reperfusion
Group FA: Buffer containing 1.4 mM FFA				
MVO_{2unl}	18.2 ± 2.8	14.4 ± 2.6		14.6 ± 3.1
[μlO_2/ 100g/beat]	20.4 ± 1.6		13.8 ± 6.0	12.0 ± 4.4
Slope	59 ± 12	31 ± 8		
[μlO_2/beat/ +(mmHg*ml)*10^{-4}]	34 ± 8		32 ± 10	
Group FAG: Buffer containing 1.4 mM FFA plus 11 mM glucose				
MVO_{2unl}	19.8 ± 1.4	17.5 ± 1.2		13.1 ± 3.1
[μlO_2/ 100g/beat]	20.1 ± 1.5		16.0 ± 1.7	18.0 ± 0.8
Slope	36 ± 3	19 ± 2*		
[μlO_2/beat/ (mmHg*ml)*10^{-4}]	28 ± 12		25 ± 7	

MVO_2-PVA relation also showed no differences compared with control in both groups and did not depend on the severity of the preceding hypoperfusion (Tab. 3).

Lactate production

In group FA, no significant production of lactate was noted. In group FAG, in 6 out of 9 hearts, lactic acid was found in the coronary venous effluate. During control, production of lactic acid was 0.05 ± 0.02 mmol/100 g/min. The production was increased both during moderate hypoperfusion (0.17 ± 0.04 µmol/100 g/min) and during severe hypoperfusion (0.11 ± 0.03 μmol/100 g/min).

Discussion

The major finding of this study is that both substrate composition and severity of hypoperfusion significantly influence contractile efficiency. If the myocardium was supplied with glucose in addition to free fatty acids, contractile efficiency during moderate, but not during severe hypoperfusion, increased. Without glucose, no significant changes in contractile efficiency were observed.

In one group (hearts supplied only with free fatty acids and submitted to severe hypoperfusion) mechanical function during control was better compared with the other groups. This might be explained by interindividual biological variability. The decrease in contractile function in this group was more pronounced than in the other groups, showing that these conditions were the least favourable for sustaining systolic and diastolic function. However, contractile efficiency during control did not differ significantly between the groups, so it seems safe to compare the data concerning the MVO_2-PVA relation.

Our data demonstrate that, as also shown by others [3], energetically favourable changes in supply-demand equilibrium can only take place within narrow limits and are easily disturbed [3]. Similarly, clear-cut minimum levels of regional perfusion were described (0.18 ml/min/g subendocardially) in porcine hearts to allow short-term hibernation [23]. To understand the underlying mechanism of myocardial hibernation, the relation between myocardial oxygen consumption (MVO_2) and the pressure-volume area (PVA) could be useful. It permits partitioning of the MVO_2 in one proportion that is associated with ventricular work and another that is non-work related [11]. Changes in basal metabolism and/or in excitation-contraction coupling would affect the MVO_2-axis intercept of the linear MVO_2-PVA relation, ie, the MVO_2 for the unloaded contraction. In contrast to our results (changing substrate composition from exclusively FFA to FFA plus glucose), the graph was shifted downward in a parallel fashion when changing the metabolic substrate from hexanoate to glucose in another study [24], but we used medium and long chain free fatty acids, so these data are not directly comparable. In accordance with our results, the linear MVO_2-PVA relation in blood-perfused canine hearts was shifted downward in parallel by moderately reducing perfusion pressure [25].

Contractile efficiency can be assessed by employing the PVA concept. It is defined as the energy conversion of the MVO_2 used exclusively for mechanical contraction into PVA [26]. Contractile efficiency is defined as the reciprocal of the slope of the MVO_2-PVA relation. Therefore, changes on the level of the contractile machinery would be reflected by changes in contractile efficiency. Significant differences in the slope of the MVO_2-PVA relation, and hence in contractile efficiency, were shown to depend on the mode of contraction [24]. Afterload conditions allowing substantial fibre shortening were energetically favourable. We also observed a tendency towards a higher contractile efficiency in ejecting contractions. These results support the hypothesis that processes within the contractile apparatus play a major role in myocardial hibernation.

In isolated rat hearts, the slope of the MVO_2-PVA relation did not change with different coronary flows [24]. In contrast, the slope was decreased during severe hypoperfusion (CAP = 30 mmHg) in canine hearts [25]. Such an increase in contractile efficiency is in accordance with our experiments showing an increase during moderate reduction in oxygen supply with a buffer containing both FFA and glucose.

A concentration of 11 µM of glucose was chosen because glucose uptake is saturated at this concentration and tissue glycogen levels do not decline during normoperfusion [27]. The hearts were also supplied with free fatty acids in high concentration (1.4 mM) to exclude effects of the kinetics of the transmembrane transport [28].

Evidence that inhibiting lipid metabolism and stimulating glucose oxidation are beneficial for ischemic myocardium [14, 19, 20, 27] has led to the hope of future therapeutic employment. But which mechanism mediates the deleterious effects of free fatty acids during ischaemia still has to be investigated. It can not be explained by the stoichiometric differences in oxygen demand for FFA and glucose oxidation alone, but it has also been suggested that the intracellular accumulation of membrane-derived lipids plays an important role [29–31]. In addition, the uncoupling effect of lipid derivatives with detergent-like effects on membranes has to be discussed as well as a possible negative inotropic effect of FFA on ischemic myocardium [32]. Our data show a significant decrease in contractile state as reflected in dP/dt_{max} during hypoperfusion without glucose, so FFA-induced changes in inotropic state have to be considered.

The recovery of myocardial function during reperfusion was incomplete, as expected during reperfusion after hibernation [1]. Recovery of function in reperfused myocardium can be prolonged and can persist for days or weeks [2, 8]. The functional recovery of isolated, buffer-perfused rat hearts during reperfusion is delayed compared with blood-perfused hearts [33]. In that study, the nature of the perfusate did not appear to influence the severity of ischemic injury, but did influence the systolic and diastolic recovery during the first 15 min of reperfusion. We looked at the first 20 min of reperfusion, so a pronounced recovery of functional parameters would have been surprising.

The impaired myocardial function during reperfusion in this study using a Krebs-Henseleit buffer might in part be owing to oedema formation. Consequently, we used albumin, which should decrease the amount of oedema formation and improve function during reperfusion. In comparison with earlier studies with the same experimental model and protocol, however, no marked effect of albumin could be observed [34]. Since the oxygen consumption during increased workload in saline-perfused isolated rabbit hearts can be raised without any changes in concentration of high-energy phosphates [34], saline perfusion can provide sufficient supply of metabolic substrates [35]. The contractile dysfunction during reperfusion therefore can not be explained by a supply-demand imbalance. Nevertheless, contractile efficiency immediately decreased back to control suggesting a reversion of presumed metabolic changes during short-term hibernation.

In summary, our data show that an increase in contractile efficiency in short-term hibernating myocardium can only

be observed in moderate, but not in severe hypoperfusion. In addition, the myocardium has to be supplied with glucose in addition to free fatty acids. Ejecting working conditions seem to facilitate changes in contractile efficiency in comparison to isovolumic conditions.

Short-term myocardial hibernation seems – at least in part – to depend on the presence of the energetically favourable substrate glucose to establish a new, subtle energy supply-demand balance. Although the data of this isolated rabbit heart model can not be directly extended to the in vivo situation, we hypothesise that improvement of contractile efficiency during hypoperfusion might be part of the underlying mechanism of myocardial hibernation.

Acknowledgement

The study was supported by a grant from the German Research Foundation (DFG; SFB 242, Düsseldorf). We appreciate the measurements of fatty acid composition of albumin by Prof. Reinauer from the Institute of Diabetes Research. We are grateful to Drs. U. Schwanke and U. Sunderdiek for their helpful suggestions and their support for this study, Ms. Palomero-Gallagher for reading and correcting the English language, and Mrs. Wieland for excellent secretarial help.

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