

Preventive Insulin Administration for Myocardial Protection in Cardiac Surgery

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The object of this study was to determine whether high doses of insulin administered preventively in combination with glucose and potassium exert a protective effect upon the myocardium. This approach should result in a preoperative accumulation of the myocardial glycogen stores with an increased anaerobic provision of energy-rich substrates (ATP) during coronary ischemia. Two comparable groups of seven dogs each, undergoing experimental extracorporeal circulation (ECC) with 90-min aortic cross-clamping were examined. Cardiac output (CO), systolic left ventricular blood pressure (p_{ventr}), left ventricular enddiastolic pressure (LVEDP), mean central venous pressure (CVP), and heart rate (HR) were recorded at left atrial (LA) pressures of 5, 10, 15, and 20 mmHg in order to construct ventricular function curves. These data were registered prior to the onset of ECC (preischemic value), after termination of ECC and after two 10-min periods of reperfusion. The first group served as control and the second group received high iv doses of insulin (total 25 U/kg) within 60 min prior to the onset of the ECC. In the control group, p_{ventr} and CO after termination of the ECC and after the first reperfusion were significantly ($P < 0.05$) less than the preischemic values; after the second reperfusion they reached the preischemic range. In contrast, p_{ventr} and CO in the insulin group already were within the preischemic range at the termination of the ECC. After the first and the second reperfusion, CO was even greater than the preischemic value. LVEDP changed inversely, while CVP and HR showed no significant differences. The calculated left ventricular peak power (LVP_{peak}) changed proportional to the change in CO, and the systemic vascular resistance (SVR) did not show any significant change. It is concluded that preventive insulin administration helps maintain myocardial cell function during ischemia. By this method an earlier restitution of a vigorous cardiac performance can be achieved, indicating increased ischemic tolerance and improved myocardial protection. (Key words: Heart: cardiac output; insulin; ischemia; protection. Hormones: insulin. Metabolism: insulin.

MYOCARDIAL PROTECTION usually is based on decreasing myocardial oxygen consumption, so coronary ischemia during aortic cross-clamping is less detrimental. To achieve this, myocardial metabolism is slowed down by general and local cooling and blocked by cardioplegic solutions.

Another possibility should be to increase the availability of energy (ATP) during aortic cross-clamping. This may be achieved by switching myocardial metabolism *prior* to

coronary ischemia from oxydative lipolysis, which is the usual metabolic pathway, towards anaerobic glycolysis and glycogenesis respectively, thus increasing the myocardial glycogen stores.¹⁻³ Both effects may be accomplished by the action of insulin with a sufficient supply of glucose. The simultaneous shifting of potassium into the cell additionally establishes a maximum cell membrane potential. Thus, the myocardium is put in an optimum initial condition prior to the aortic cross-clamping, and myocardial function should be more quickly and profoundly restored after coronary ischemia.

Materials and Methods

An experimental extracorporeal circulation (ECC) was established in two comparable groups of seven healthy mongrel dogs each, ranging in body weight from 26–35 kg (control group: mean 31.4 kg, insulin group: mean 30.5 kg) (see below). The heart–lung machine (SARNS apparatus with a Harvey Bubble Oxygenator) was primed with 2 l of Ringer's lactate, containing 8,000 U heparin, 40 mEq sodium bicarbonate, and 6 mEq KCl. Anesthesia was provided by pentobarbital (30 mg/kg) and halothane (inspired concentration 0.5%). After onset of anesthesia, a transcutaneous caval catheter was placed into the right external jugular vein. A cuffed orotracheal tube was placed with the aid of 1 mg/kg succinylcholine. The animals were ventilated with $O_2:N_2O = 1:1$ using an Engström respirator (tidal volume: 10 ml/kg) at a respiration rate of 20 breaths/min. A nasopharyngeal temperature probe was placed.

The cardiovascular instrumentation was established according to figure 1. After a right sided thoracotomy, a left atrial catheter was placed by transauricular puncture and a left ventricular catheter by transmural puncture. Two venous return cannulas (USCI, 22–24) were placed into the upper and lower caval vein. The arterial cannulation (Bardic, 16–18) was performed via a cut-down of the femoral artery. A bypass line was established from the arterial line and from the reservoir of the heart–lung machine to the left atrium via a pulmonary vein (Polystan catheter; type bent), for filling or emptying the left atrium (see below). An electromagnetic flow probe (14–18 mm) was placed upon the root of the ascending aorta. The blood pressures were monitored by Statham transducers. Blood–gas analysis was performed by an AVL blood–gas check apparatus; blood glucose was measured photometrically (Reflomat); and serum potassium level was

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measured by a flame photometer (FLM 3 Radiometer). The blood samples for these measurements were taken from a separate femoral artery catheter prior to surgery; after hemodilution; after the infusion period of insulin, glucose, and potassium; after 5 min, 30 min, and 90 min of ECC; and at the first and second reperfusion (see below).

In order to obtain comparable situations for the preischemic as well as for the postischemic hemodynamic recordings, the ECC (for hemodilution) was stopped 5 min after onset, and the preischemic parameters were recorded. These recordings were systolic left ventricular pressure (p_{ventr}), cardiac output (Q_{aorta}), left ventricular enddiastolic pressure (LVEDP), mean central venous pressure (CVP), and heart rate (HR). The systemic vascular resistance (SVR) and the left ventricular peak power (LVP_{peak})^{4,5} were calculated. For recording these variables at different left atrial (LA) levels in order to construct ventricular function curves, the LA pressure was increased stepwise in 5 mmHg intervals, ranging from 5–20 mmHg, by filling the left atrium directly from the heart–lung machine via an arterial bypass line (see above).

After recording of the preischemic hemodynamic variables the insulin group received 100 U of insulin (Actrapid, Novo) every 10 min over a period of 60 min (total 25 U/kg), and a 33% glucose solution was infused at a rate of $0.2\text{--}0.4 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ to maintain a stable blood sugar level. In the control group, only 33% glucose solution was infused whenever necessary ($0.1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), thus keeping the blood sugar level in the same range as in the insulin group. After the infusion period, the ECC was started again, and after cooling (27°C) the aorta was cross-clamped for 90 min. A cardioplegic solution ($18\text{--}20 \text{ ml/kg}$ at 4°C) was infused into the ascending aorta with an infusion pressure of $60 \text{ cmH}_2\text{O}$. The composition of the solution was per liter: 15 mEq NaCl, 10 mEq KCl, 1 mEq MgCl, 250 mEq mannitol, and 20 mEq sodium bicarbonate. Every 15 min of ECC 0.25 mEq potassium/kg was administered routinely. Additional potassium was given whenever necessary according to the potassium serum level.

The ECC was terminated after rewarming (37°C), and the above-mentioned variables were recorded again (first weaning off ECC). These recordings were repeated after 10 min of reperfusion (second weaning off ECC) and once again after another 10 min reperfusion (third weaning off ECC) (fig. 2). The significance of the differences of the data within one group and between both groups was calculated by means of the U-test of Mann-Whitney.[§]

§ The statistical analysis was performed by the biostatistician of the Institute of Environmental Hygiene of the University of Vienna, M. Kundi, Ph.D.

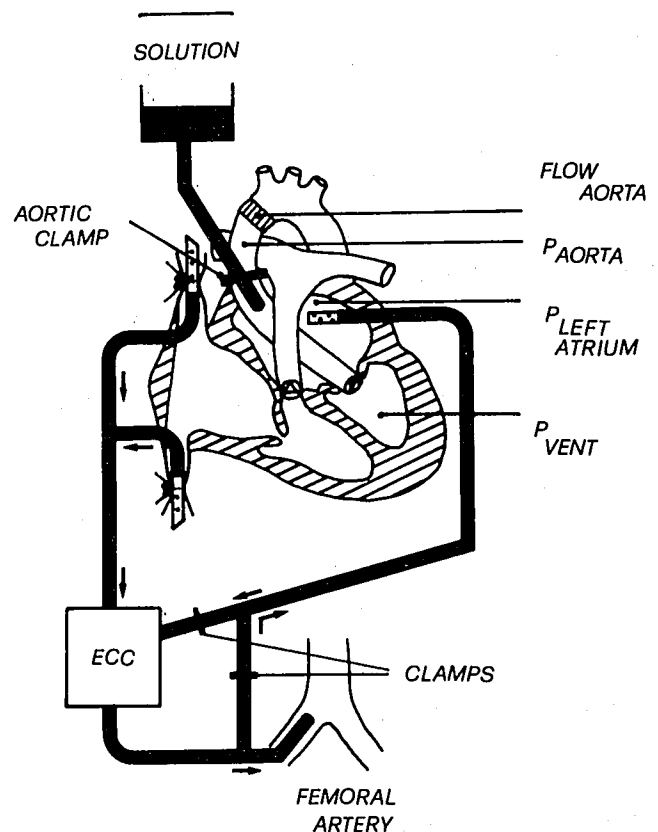


FIG. 1. Scheme of cardiovascular instrumentation.

Results

The mean data and the significant differences of systolic left ventricular pressure (p_{ventr}) and cardiac output (Q_{aorta}) are shown in figures 3 and 4. It is obvious that the postischemic data in the control group were distinctly and significantly ($P < 0.05$) less than the preischemic range after the first and second weaning off ECC. Only the values after the third weaning off ECC returned to the preischemic levels. The insulin group, however, showed values similar to the preischemic readings already after the first weaning off ECC. The corresponding values of the second and third weaning off ECC are in part even greater than the preischemic values. These facts also are underlined by a significant ($P < 0.05$) difference between both groups.

The mean data of the left ventricular peak power (LVP_{peak}) are shown in figure 5. In the control group there was a significant ($P < 0.05$) decrease to 38–42% of the preischemic level after the first weaning off ECC at every LA pressure level. This is in the range of the findings of Benzing *et al.*⁴ After the second weaning off ECC, a significant ($P < 0.05$) decrease can be seen at LA levels of 10 and 20 mmHg, compared with the preischemic values. This does not appear in the insulin group: on the

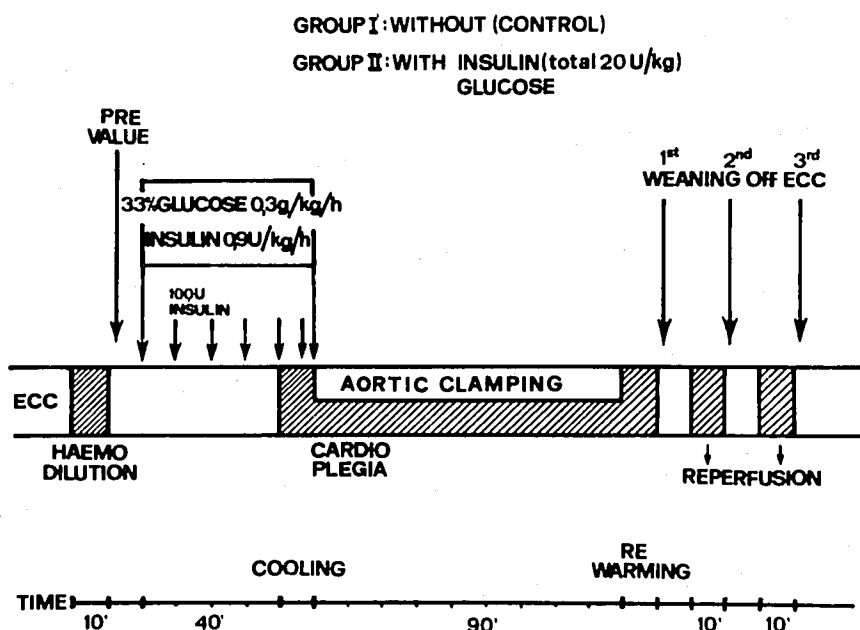


FIG. 2. Time schedule of the study.

contrary, there are five significantly ($P < 0.05$) greater postischemic values compared with the preischemic state.

The mean data of the left ventricular enddiastolic pressure (LVEDP) after the first and second weaning off ECC were distinctly and in part significantly ($P < 0.05$) lower in the insulin group, suggesting an improved cardiac performance compared with the control group (fig. 6). As the LA pressure was increased by directly filling the left atrium from the heart-lung machine, the left atrium was somewhat distended and made hypervolemic artificially. Probably the infusion rate was rather fast and

therefore a functionally established mitral stenosis may account for a poor correlation of LA and LVEDP.

The mean data for systemic vascular resistance (SVR) and heart rate (HR) are shown in figures 7 and 8. The values for the SVR showed a tendency to decrease with increasing LA pressures. This trend seemed to be more pronounced in the insulin group, although there was no statistically significant difference between the two groups. The data for the HR and the CVP showed no significant differences in either group.

The mean data for temperature, uncorrected blood

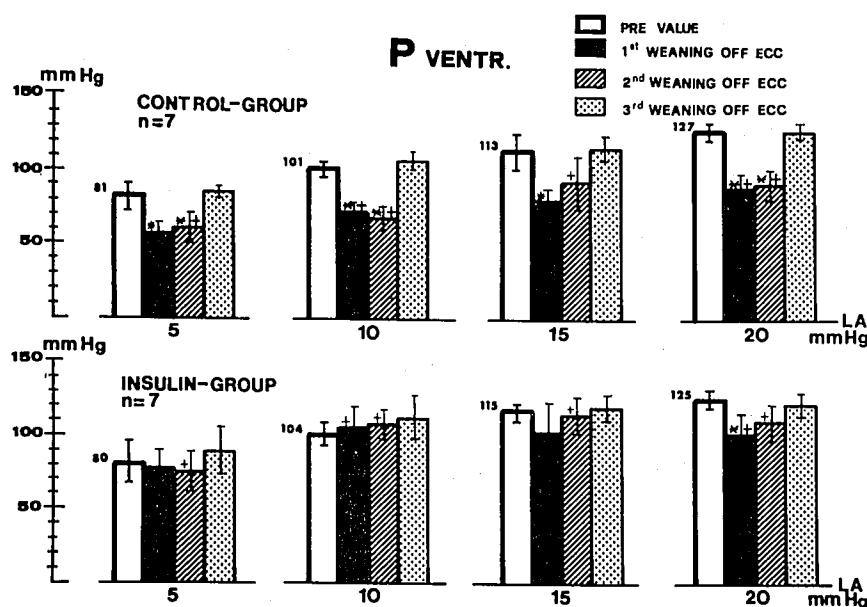


FIG. 3. Mean data of systolic left ventricular pressure (p_{ventr}) of both groups. The measurements were performed before onset of extracorporeal circulation (ECC) (prevalue = white columns), after termination of ECC (first weaning = black columns), after reperfusion of 10 min (second weaning = hatched columns), and after another reperfusion of 10 min (third weaning = dotted columns). Every measurement was repeatedly recorded at 5, 10, 15, and 20 mmHg of left atrial (LA) pressure. The bars represent \pm SD. The data indicated by * are significantly ($P < 0.05$) different from the preischemic value of the same group; the data indicated by + are significantly ($P < 0.05$) different from the corresponding value of the other group.

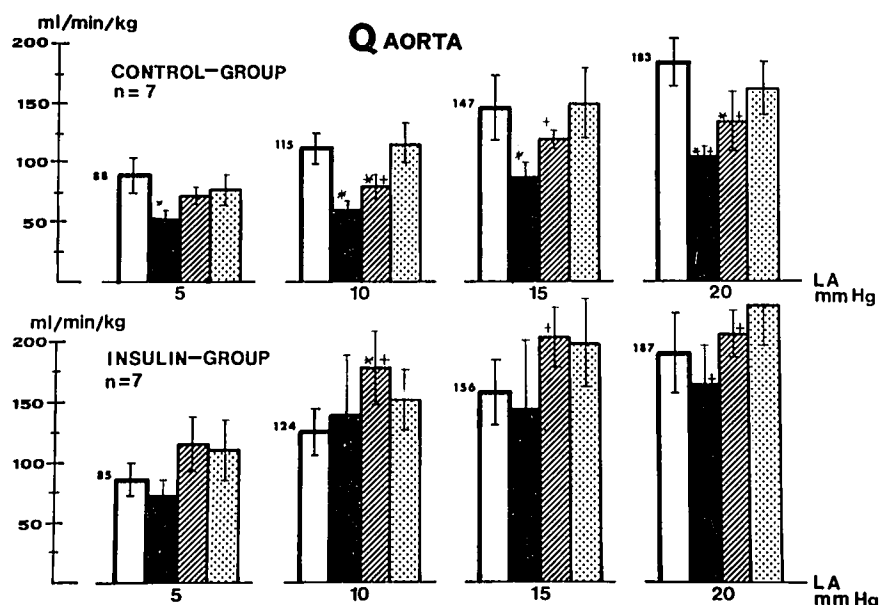


FIG. 4. Mean data of cardiac output (Q_{aorta}) of both groups. For symbols and significance see figure 3.

gas analysis,⁷ blood sugar level, and serum potassium level are summarized in table 1. The pH was decreased, and the base excess (BE) was more negative in the insulin group after the infusion period and during early ECC. For compensation of this metabolic acidosis, a mean total of 122 mEq bicarbonate was necessary in the insulin group in comparison to 19 mEq in the control group. To keep the serum potassium level in both groups between 3.6–4.5 mEq/l, the insulin group required a high potassium substitution, averaging 143 mEq. The control group was substituted with an average amount of only 34 mEq potassium.

Discussion

The beneficial effect of insulin on cardiac performance has been documented in animal experiments.^{8–10} Clinical and experimental data have shown an increased myocardial contractility due to the administration of high doses of insulin also in shock situations.^{11–14} In severe cardiogenic shock, *i.e.*, in cardiac surgery patients, who initially could not be weaned off ECC due to impaired ventricular function, it was finally possible to successfully terminate ECC after administration of insulin.^{15–17}

Moreover, the administration of insulin with the onset

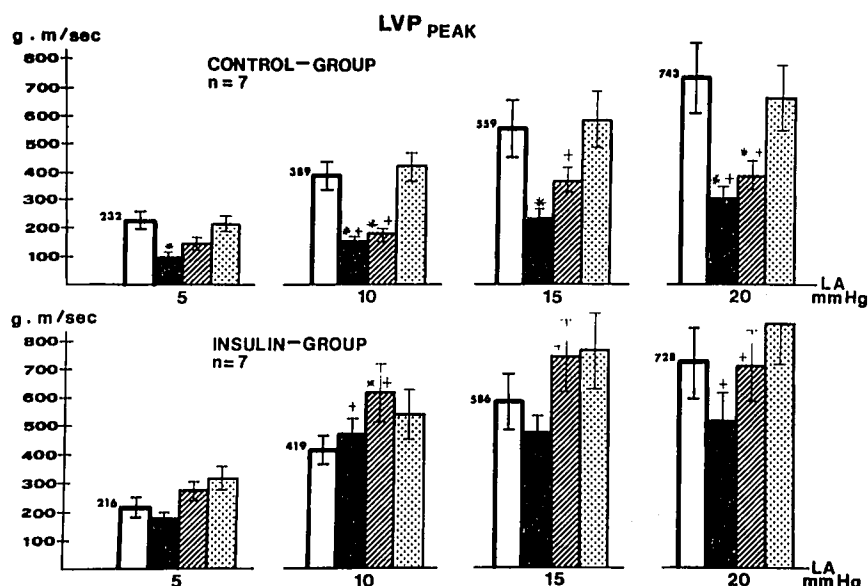


FIG. 5. Mean data of left ventricular peak power (LVP_{peak}) of both groups. For symbols and significance see figure 3.

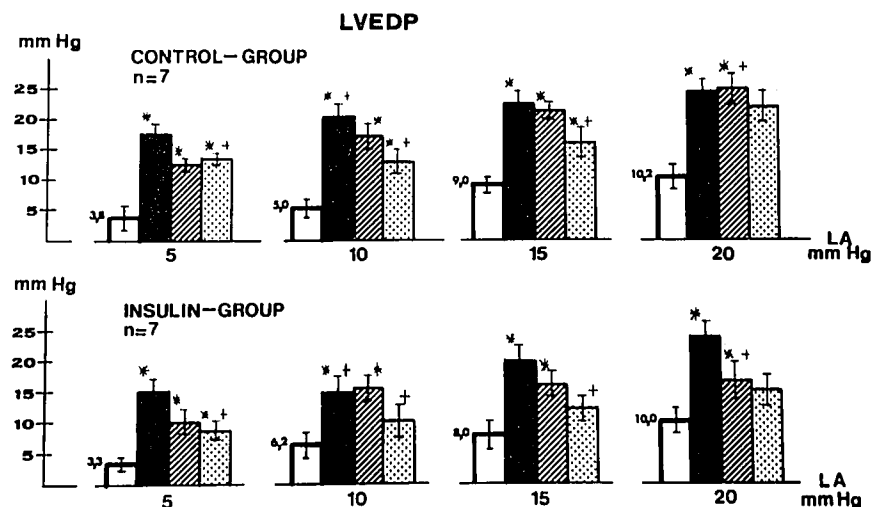


FIG. 6. Mean data of left ventricular end-diastolic pressure (LVEDP) of both groups. For symbols and significance see figure 3.

of a planned experimental shock situation is reported to prevent a negative effect of coronary ischemia upon the heart. Hiatt *et al.*¹⁸ were able to prolong survival time in dogs with experimental coronary artery ligation by therapeutic administration of massive doses of insulin (2,400–7,500 U). The animals in the insulin group survived 80 h, maintaining sinus rhythm, whereas the animals in the control group died within 16 min in ventricular fibrillation.

A phenomenon that can be regarded as “phylogenetically developed prevention” appears in seals and is reported by Kjekshus¹⁹: in the hypoxic phase during diving (15 min) acute inhibition of myocardial lipolysis and shifting of myocardial metabolism towards anaerobic glycolysis takes place and the myocardial glycogen stores are utilized while lactate production is increased.

The problem of an increased lactate production occurring with an augmented glycolytic flux is discussed also by Opie *et al.*²⁰ There is some evidence that this effect also occurred in this study, since the base excess is more negative in the insulin group after the insulin-glucose infusion period and during early ECC. It should be mentioned, however, that the base excess randomly was more negative in the insulin-treated group of dogs before the administration of insulin. Nevertheless, a much greater amount of bicarbonate was necessary in the insulin-treated group to compensate for a metabolic acidosis and to finally obtain a similar acid base balance in both groups after ECC.

There is some evidence that during ischemia, increased anaerobic glycolysis does not provide increased ATP because of the lack of washout of H^+ and lactate.²¹ The

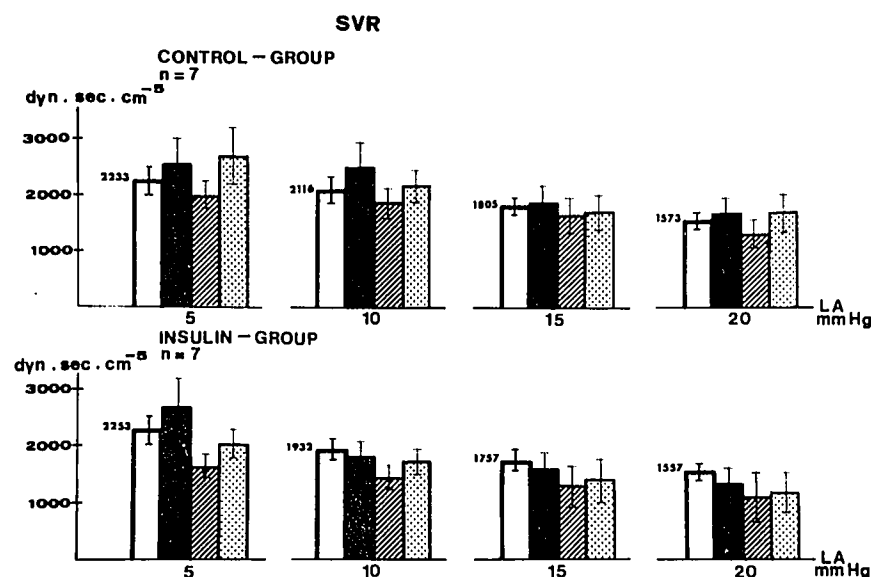


FIG. 7. Mean data of systemic vascular resistance (SVR) of both groups. For symbols and significance see figure 3.

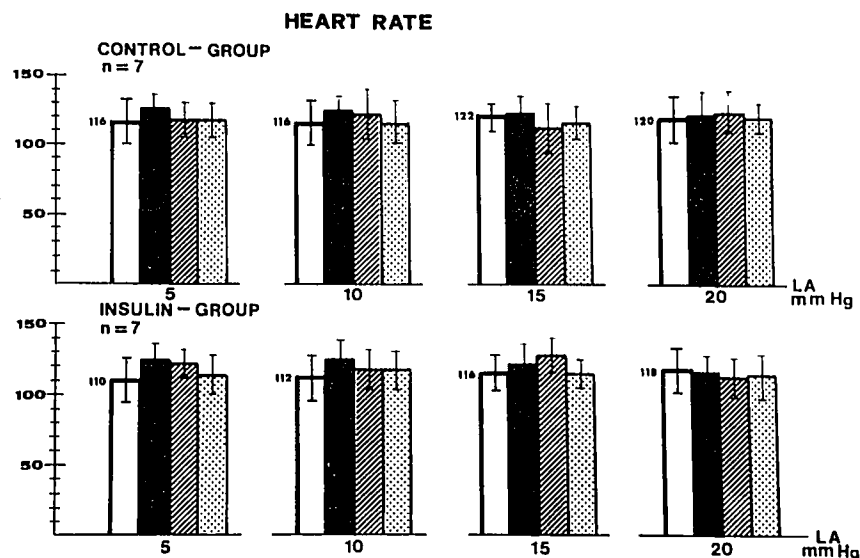


FIG. 8. Mean data of heart rate (HR) of both groups. For symbols and significance see figure 3.

cardioplegic solution in this study, however, was infused during the whole aortic cross clamping time. This method should help to overcome an increased myocardial lactate production by achieving a sufficient washout during the entire period of ischemia.

The present study shows that low cardiac output after 90 min of coronary ischemia can be avoided by the *pre-ventive* administration of high doses of insulin in combination with glucose and potassium. It is even possible to achieve increased cardiac output compared with preischemic levels. Even with LV systolic pressures and aortic blood flow close to the preischemic state, however, the

filling pressures remain somewhat elevated and might indicate a still impaired myocardial function. As this effect is more distinct shortly after termination of ECC, it is obviously due to an overall ischemic injury and a following recovery of the heart. The significantly lower postischemic filling pressures in the insulin group, however, as compared with the control group, indicate a tendency to a better myocardial function.

Although there appears to be a trend to lower values of SVR in the insulin group, no significant difference was to be found between the two groups. As the heart rate does not show any difference at all, the improved cardiac

TABLE 1. Data of Temperature, Blood Gases, Blood Glucose, Serum Potassium (K⁺) (Mean \pm SD)

	Preischemic	Hemodil.	Prior ECC	5' ECC	30' ECC	90' ECC	First Reperfusion	Second Reperfusion
Temp. °C	37	36	36	32	27	29	37	37
Control group (n = 7)								
pO ₂ mmHg	120 \pm 21	192 \pm 78	110 \pm 28	372 \pm 56	385 \pm 47	393 \pm 49	221 \pm 78	216 \pm 52
pCO ₂ mmHg	31 \pm 3.0	30 \pm 6.2	32 \pm 4.1	31 \pm 4.7	32 \pm 4.0	31 \pm 5.5	30 \pm 4.0	29 \pm 2.3
pH	7.43 \pm 0.06	7.44 \pm 0.10	7.42 \pm 0.11	7.43 \pm 0.10	7.43 \pm 0.09	7.44 \pm 0.10	7.36 \pm 0.12	7.33 \pm 0.04
BE mEq/l	-2.0	-2.2	-2.3	-2.5	-1.6	-1.8	-6.6	-9.0
Bic corr. mEq					13	6		
Blood-glucose mg/dl	152 \pm 27	131 \pm 29	156 \pm 20	169 \pm 25	162 \pm 20	158 \pm 33	155 \pm 32	147 \pm 30
K ⁺ mEq/l	4.1 \pm 0.39	3.9 \pm 0.37	3.7 \pm 0.30	3.8 \pm 0.71	4.0 \pm 0.58	4.5 \pm 0.45	4.3 \pm 0.61	4.2 \pm 0.37
Insulin group (n = 7)								
pO ₂ mmHg	128 \pm 33	203 \pm 88	106 \pm 19	323 \pm 78	360 \pm 34	297 \pm 113	225 \pm 101	198 \pm 44
pCO ₂ mmHg	32 \pm 6.2	28 \pm 6.6	35 \pm 3.3	33 \pm 6.4	32 \pm 6.6	32 \pm 9.7	32 \pm 4.6	30 \pm 2.1
pH	7.36 \pm 0.09	7.47 \pm 0.13	7.33 \pm 0.13	7.28 \pm 0.05	7.40 \pm 0.11	7.36 \pm 0.15	7.38 \pm 0.08	7.36 \pm 0.02
BE mEq/l	-6.4	-1.8	-6.5	-10.4	-4.4	-7.3	-5.1	-7.5
Bic corr. mEq	10	3	13	46	18	32		
Blood-glucose mg/dl	168 \pm 34	153 \pm 38	128 \pm 23	151 \pm 35	137 \pm 24	158 \pm 51	142 \pm 44	195 \pm 49
K ⁺ mEq/l	3.9 \pm 0.45	3.8 \pm 0.33	3.6 \pm 0.35	3.7 \pm 1.15	3.6 \pm 0.69	4.2 \pm 0.55	3.8 \pm 0.83	3.6 \pm 0.42

output in the insulin group is obviously neither due to a marked peripheral vasodilation nor to an increased heart rate. As the left ventricular peak power also indicates a more vigorous myocardial performance in the insulin group, a positive inotropic effect can be confirmed.

Two points of view may render an explanation: The first point of view is that the cell membrane potential of skeletal muscle is improved by the administration of insulin.²² The insulin-induced increased shift of potassium into the cell²³ and the improved sodium pump activity²⁴ lead to a restoration of an optimum cell membrane potential; this also may be assumed for the present study, since a fourfold increased amount of potassium was required by the insulin group to keep a constant serum potassium level. Though the findings in skeletal muscle simply cannot be transferred to cardiac muscle, data from trauma patients have been reported,²⁵ showing insulin-induced reduced cell membrane permeability caused by improved sodium and potassium pump activity, thus increasing cardiac performance and protecting the myocardium during ischemia. A stabilization of myocardial cell membrane potential by administration of insulin may be assumed indirectly because of a decreased incidence of arrhythmias and a reduced necessity of defibrillation in patients undergoing ECC,²⁶ and because of persisting sinus rhythm after experimental coronary artery ligation.¹⁸ The second point of view is that preventive administration of insulin results in an augmented accumulation of the myocardial glycogen stores. Since an abundant shifting to carbohydrate metabolism takes place,^{26,27} an increased anaerobic provision of energy for the myocardium during ischemia is induced. Usually 60% of the heart's O₂ consumption is for fatty acid utilization. Due to the shift towards increased glycogen storage and glycolysis,² the myocardial provision of ATP by enhanced anaerobic glycolysis should be increased during ischemia. This also was proven by the evaluation of a higher post-ischemic myocardial ATP content in insulin-pretreated patients undergoing mitral valve replacement.²⁷ According to this concept, the myocardial cell viability in severe ischemia appears to be better than with normal²⁸ glycogen depots. At least in the anoxic perfused heart the addition of insulin produces a significantly higher myocardial amount of ATP and creatine phosphate compared with the absence of insulin.² The ability of the myocardium to shift under conditions of reduced oxygen tension from lipolytic to glycolytic energy sources is an important survival mechanism.² An improvement of the myocardial survival conditions should occur when this metabolic shifting, which is carried out by the heart in ischemia automatically, is anticipated by appropriate therapy. This was previously attempted by the administration of plain glucose³ or a fatty diet.^{1,29,30}

The addition of insulin and glucose to the cardioplegic

solution, however, is ineffective and may even be harmful due to unpredictable osmotic effects.³¹

It is concluded that the preventive administration of high doses of insulin in combination with glucose and potassium prior to the aortic cross clamping during ECC leads to an earlier postischemic restitution of vigorous cardiac performance, suggesting better ischemic tolerance during aortic cross-clamping. This obviously is based on the above-mentioned effects, especially a preischemic increased accumulation of myocardial glycogen and a provision of energy-rich substrates during ischemia. Apart from cooling and cardioplegia, this procedure represents an additional method of improved myocardial protection in cardiac surgery.

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