METABOLIC AND HEMODYNAMIC EFFECTS OF INTRAVENOUS GLUTAMATE INFUSION EARLY AFTER CORONARY OPERATIONS

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Amino acids, particularly glutamate, have been proposed to play an important role in the recovery of cardiac oxidative metabolism after ischemia. In this investigation, the metabolic and hemodynamic effects of glutamate infusion after coronary operations were studied. From 220 to 240 ml 0.1 mol/L l-glutamic acid solution was infused in 10 patients during 1 hour starting 2 hours after operation. A control group of 10 patients received an infusion of 240 ml saline solution. During glutamate infusion, there were significant increases in the uptake of glutamate (from 0.7 ± 0.2 μmol/min in the basal state to a peak of 5.7 ± 1.2 μmol/min at 20 minutes) and lactate (from 4.9 ± 2.0 μmol/min in the basal state to 14.1 ± 4.4 μmol/min at 60 minutes; $p < 0.01$), whereas the uptake and release of other substrates remained essentially unaffected. Arterial glutamate levels (in whole blood) increased from 103 ± 10 μmol/L to 394 ± 20 μmol/L at 60 minutes. Thirty minutes after discontinuation of the glutamate infusion, arterial levels had decreased to 129 ± 17 μmol/L. The markedly improved utilization of lactate and the unchanged release of alanine together suggest that the oxidative metabolism of the heart was stimulated by glutamate. The metabolic changes were associated with improved myocardial performance. Left ventricular stroke work index increased from 26.8 ± 2.1 gm · beat^{-1} · m^{-2} body surface area to 31.3 ± 3.1 gm · beat^{-1} · m^{-2} body surface area during glutamate infusion. Metabolic support with amino acids may provide a means to improve recovery of metabolic and hemodynamic function of the heart early after cardiac operations. (J Thorac Cardiovasc Surg 1996;112:1468-77)

Defective oxidative metabolism of the heart after ischemia has been suggested as a major cause for reversible myocardial dysfunction early after cardiac operations.[1, 2] Previous studies performed early after coronary operations demonstrated a markedly deranged myocardial metabolism, with no significant uptake of the normally dominant substrates, free fatty acids (FFAs) and glucose.[2, 3] There is uptake of amino acids, however, mainly glutamate.[4] Glutamate has been shown to be important for the recovery of cardiac oxidative metabolism after ischemia.[5] Because myocardial uptake of glutamate may be limited by substrate availability (arterial levels) during the first hours of reperfusion,[4] it has been suggested that metabolic recovery could be enhanced by the administration of exogenous glutamate.[1]

The aim of this study was to determine whether intravenous glutamate infusion increases myocardial uptake of glutamate and enhances the metabolic and functional recovery of the heart early after coronary artery bypass grafting (CABG) operations.

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Patients and methods

Patients. Twenty male patients with stable angina pectoris and well-preserved left ventricular function who were admitted for elective CABG operations were included in the study. None of the patients had either diabetes

Table I. *Patient data*

	Glutamate group	*Control group*
No.	10	10
Age (yr)	62 ± 2	62 ± 1
Weight (kg)	76 ± 4	80 ± 3
BSA (m^2)	1.92 ± 0.05	1.99 ± 0.04
No. of distal anastomoses	2.6 ± 0.2	2.9 ± 0.3
Aortic crossclamp time (min)	34 ± 5	32 ± 4
CPB time (min)	82 ± 8	70 ± 7
AST day 1 (μkat/L)	1.72 ± 0.17	1.41 ± 0.18

Patient data are mean ± SEM. There were no statistically significant differences between the groups. *CPB,* Cardiopulmonary bypass; *AST,* aspartate aminotransferase.

mellitus or any other major metabolic disorder. Demographic data are presented in Table I.

Clinical management. After an overnight fast, the patients were given intramuscularly 10 mg morphine hydrochloride and 0.4 mg scopolamine. Anesthesia was induced with thiopentone at a dose of 1 to 2 mg/kg body weight and fentanyl at a dose of 10 μg/kg body weight. Pancuronium bromide was used for neuromuscular blockade. Anesthesia was maintained with fentanyl and isoflurane.

Cardiopulmonary bypass was conducted with a membrane oxygenator and a roller pump generating nonpulsatile flow. A crystalloid fluid containing no glucose or lactate (acetate Ringer's solution) and containing mannitol was used to prime the extracorporeal circuit. Moderate hemodilution (hematocrit approximately 25%) and moderate hypothermia (30° to 32° C) were employed. Antegrade delivery of St. Thomas' cold crystalloid cardioplegic solution was used for myocardial protection. Weaning from bypass was started when the patient was at a rectal temperature of 36° C. Heparin was neutralized with protamine chloride.

After operation and during the study period, the patients were ventilated normally. Analgesia and sedation were achieved by a 10 to 15 ml/hour continuous infusion of alfentanil (0.46 mg/ml) and midazolam (0.4 mg/ml). Vecuronium bromide was given intermittently to prevent shivering. Postoperative rewarming was facilitated by radiant heat provided by a thermal ceiling. Acetates Ringer's solution was used for volume substitution to maintain atrial filling pressures at a constant level. None of the patients received blood or blood products either during the study period or later in the postoperative course.

According to clinical routines, nitroglycerine, with nitroprusside if necessary, was used to prevent postoperative hypertension to a pressure greater than 150 mm Hg. In the glutamate group, six patients received vasodilating agents before glutamate infusion and at the end of glutamate infusion. In the control group, three patients received vasodilating agents before the infusion and two patients required vasodilators at the end of the saline solution infusion. The dosages employed were low (nitroprusside dose range 0.16 to 0.83 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and there were no significant changes during the study period in the requirements for nitroglycerine or nitroprusside in either group.

Table II. *Composition of the 0.1 mol/L L-glutamic acid solution employed in the study*

Component	*Amount*
Glutamic acid (gm)	14.7
Sodium chloride (gm)	3.0
pH (adjusted with sodium hydroxide)	6.0
Osmolality (mOsm/kg)	280

Water was added to produce 1 L solution.

Study protocol. The study period commenced approximately 1 to 2 hours after completion of the operation. Ten patients received an infusion of 220 to 240 ml 0.1 mol/L L-glutamic acid during 1 hour (glutamate group). The composition of this solution, which was prepared in the hospital pharmacy, is shown in Table II. To achieve variation in arterial glutamate levels, the infusion rate was changed between the first and second 30-minute periods. The infusion rates for individual patients are listed in Table III. The 10 patients in the control group were given an infusion of 240 ml isotonic saline solution during 1 hour.

Blood samples were taken from the coronary sinus and radial artery immediately before the start of the L-glutamic acid or saline solution infusion (0 minutes, basal state), every 10 minutes during the infusion period, and also at 90 minutes for analysis of glucose, lactate, glutamate, alanine, and oxygen. In the basal state, at 30 minutes, at 60 minutes, and at 90 minutes, samples were taken in duplicate. Blood samples analysis were taken for FFAs in the basal state, at 60 minutes, and at 90 minutes. Hemodynamic measurements were performed at 0, 30, 60, 90, and 150 minutes.

Catheterization procedure and hemodynamic measurements. The right atrium, left atrium, pulmonary artery, radial artery, and coronary sinus were catheterized for hemodynamic monitoring and blood sampling. The final midcoronary position of the coronary sinus catheter (Wilton Webster Labs Inc., Altadena, Calif.) was checked by fluoroscopy and measurement of oxygen saturation. Coronary sinus blood flow (CF 300A flowmeter; Webster Labs Inc.) and cardiac output were determined by thermodilution technique; the mean values were calculated from three measurements.[6]

Biochemical analyses. Samples were obtained from the radial artery and the coronary sinus and analyzed in whole blood for glucose, lactate, glutamate, and alanine. Samples were analyzed in plasma for FFAs. Whole blood was immediately deproteinized with ice-cold perchloric acid, as described by Jorfeldt and Juhlin-Dannfelt.[7] After centrifugation, the plasma and the protein-free extracts were deep-frozen to −70° C. Analysis was done by batches, with care being taken to ensure that corresponding arterial and venous samples were analyzed simultaneously. Glutamate concentration was determined fluorometrically by an adapted glutamate dehydrogenase method.[8]

The D-glucose concentration was analyzed through a modification for fluorometry of the hexokinase method described by Schmidt,[9] Barthelmai, and Czok.[10] Lactate and alanine concentrations were also determined fluoro-

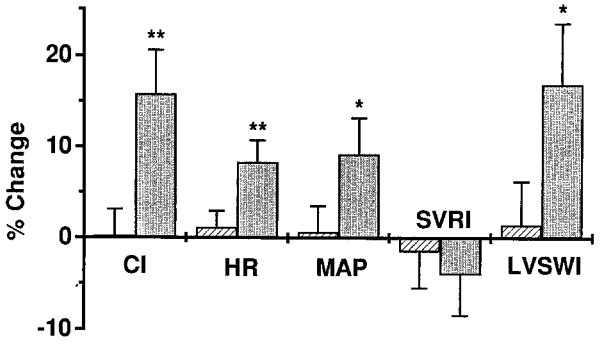

Fig. 1. Change in hemodynamic state from basal state to 60 minutes, expressed as percentages (mean ± SEM) in control *(hatched bars)* and glutamate *(gray bars)* groups. *CI,* Cardiac index; *HR,* heart rate; *MAP,* mean arterial pressure; *SVRI,* systemic vascular resistance index; *LVSWI,* left ventricular stroke work index. *Asterisks* indicate statistically significant differences from basal state, with *single asterisk* representing $p < 0.05$ and *double asterisk* representing $p < 0.01$.

metrically.[11] FFAs were analyzed according to the method of Ho.[12]

Oxygen saturation and hemoglobin concentrations were measured with an OSM3 oximeter (Radiometer AS, Copenhagen, Denmark).

Calculations and definitions. Oxygen consumption of the heart was estimated as the product of the arterial–coronary sinus blood oxygen content difference and the coronary sinus blood flow. Oxygen content of the blood (in millimoles per liter) was calculated according to the following formula: Oxygen content = $[B\text{-}Hb \cdot So_2 \cdot (6.2 \times 10^{-4})] + (Po_2 \cdot 0.01)$, where *B-Hb* represents blood level of hemoglobin (in grams per liter); So_2 is oxygen saturation expressed as a percentage; and Po_2 is oxygen tension (in kilopascals).

Myocardial fluxes of glutamate, glucose, lactate, and alanine were calculated as the product of arterial–coronary sinus blood concentration differences with coronary sinus blood flow.

Myocardial flux of FFAs was calculated as the product of arterial–coronary sinus plasma concentration difference with coronary sinus plasma flow. A release of substrates was defined as a flux value significantly less than zero ($p < 0.05$). An uptake of substrates was defined as a flux value significantly greater than zero ($p < 0.05$). The term *basal state* refers to measurements performed immediately before the start of glutamate or saline solution infusion. Hemodynamic parameters were calculated from standard formulas.

Statistical methods. Statistical analyses were performed with a computerized statistical package (RS/1; Bolt Beranek and Newman Inc., Cambridge, Mass.). The normal distribution of the samples was analyzed by the Wilk-Shapiro test, and the *t* test was used as appropriate for paired and unpaired comparisons. For samples lacking normal distribution, the statistical package automatically converted to nonparametric tests: the Wilcoxon test for matched pairs and the Mann-Whitney U-test for unpaired observations. Statistical significance was defined as a *p* value less than 0.05. Data are presented as means (± standard error of the mean [SEM]).

Table III. *Varying infusion rates of glutamate in individual patients during first and second 30-minute periods*

Patient No.	*0-30 min*	*30-60 min*
1	40.4	47.8
2	39.2	58.8
3	36.0	60
4	36.2	67.8
5	30.9	66.3
6	26.5	72.5
7	18.1	68.9
8	9.8	57.4
9	31.1	68.3
10	12.4	87.0

Rates are mg · kg^{-1} body weight · hr^{-1}.

Ethical aspects. The study was performed according to the principles of the Helsinki Declaration of Human Rights and was approved by the ethics committee for medical research at the University Hospital of Linköping. Informed consent was obtained from each patient.

Results

Clinical course. The postoperative course was uneventful in both groups, and no side effects of either infusion were seen. None of the patients required inotropic support and none had electrocardiographic or enzymatic signs of perioperative myocardial infarction (Table I).

Hemodynamic parameters. Detailed hemodynamic results are given in Table IV. The changes in hemodynamic state from the basal state to 60 minutes are demonstrated in Fig. 1.

Glutamate group. Left ventricular stroke work index increased from 26.8 ± 2.1 gm · $beats^{-1} \cdot m^{-2}$ body surface area (BSA; basal state) to 31.3 ± 3.1 gm · $beats^{-1} \cdot m^{-2}$ BSA after 60 minutes of glutamate infusion. Cardiac index increased during the same period from 2.0 ± 0.1 L · $min^{-1} \cdot m^{-2}$ BSA (basal state) to 2.3 ± 0.1 L · $min^{-1} \cdot m^{-2}$ BSA. There were also increases in mean arterial pressure and heart rate during glutamate infusion. There was no further improvement in the next 90 minutes. The left atrial filling pressure did not change significantly during glutamate infusion, but there was an increase in central venous pressure from 6.0 ± 0.7 mm Hg (basal state) to 6.5 ± 0.8 mm Hg (60 minutes).

Cardiac index was significantly higher in the glutamate group than in the control group at 60 minutes. Mean arterial pressure was significantly

Table IV. *Hemodynamic results and myocardial oxygen consumption*

	0 min	*30 min*	*60 min*	*90 min*	*150 min*
CI					
Glutamate	2.0 ± 0.1	2.2 ± 0.1*	2.3 ± 0.1†‡	2.3 ± 0.2*	2.4 ± 0.2*
Control	2.0 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	2.1 ± 0.1	2.1 ± 0.1
HR					
Glutamate	77 ± 3	80 ± 4†	83 ± 4†	84 ± 3†	89 ± 4†
Control	75 ± 5	75 ± 5	76 ± 5	76 ± 5	81 ± 5
SVI					
Glutamate	26.7 ± 1.8	27.6 ± 1.8	28.2 ± 1.8	27.0 ± 1.7	27.1 ± 1.8
Control	27.9 ± 2.0	28.3 ± 2.3	27.8 ± 2.3	28.4 ± 2.5	26.7 ± 2.3
MAP					
Glutamate	81 ± 3	88 ± 4*‡	88 ± 4*	84 ± 3*	90 ± 5*
Control	81 ± 3	79 ± 2	81 ± 2	81 ± 3	81 ± 2
SVRI					
Glutamate	3026 ± 193	3051 ± 150	2844 ± 119	2784 ± 110*	2795 ± 106*
Control	2997 ± 180	2855 ± 152	2941 ± 192	2877 ± 184	2942 ± 175
PVRI					
Glutamate	352 ± 22	333 ± 23	332 ± 25	360 ± 34	365 ± 32
Control	326 ± 25	342 ± 45	367 ± 41	359 ± 39	388 ± 38
LVSWI					
Glutamate	26.8 ± 2.1	30.4 ± 3.2*	31.3 ± 3.1*	26.8 ± 2.9	31.0 ± 4.2
Control	29.4 ± 1.7	30.0 ± 3.0	30.1 ± 2.7	30.5 ± 2.8	29.2 ± 3.5
LAP					
Glutamate	6.9 ± 0.8	7.2 ± 1.0	7.2 ± 1.0	7.3 ± 0.9*	7.2 ± 0.8
Control	8.4 ± 0.5	8.8 ± 0.5	8.8 ± 0.5	8.3 ± 0.6	8.0 ± 0.5
CVP					
Glutamate	6.0 ± 0.7‡	6.3 ± 0.7‡	6.5 ± 0.8†‡	7.2 ± 0.6†‡	7.2 ± 0.8
Control	7.6 ± 0.5	8.0 ± 0.6	8.0 ± 0.3	8.0 ± 0.4	7.2 ± 0.5
Svo_2					
Glutamate	72 ± 2	73 ± 2	72 ± 2	71 ± 2	69 ± 2*
Control	72 ± 1	72 ± 2	73 ± 1	72 ± 2	70 ± 2
CSF					
Glutamate	136 ± 19	142 ± 16	151 ± 24	115 ± 21	136 ± 32
Control	143 ± 21	154 ± 26	148 ± 21	135 ± 16	§
$CSSo_2$					
Glutamate	45 ± 1‡	43 ± 1‡	42 ± 1*	42 ± 1‡	42 ± 2
Control	48 ± 2	48 ± 2	45 ± 2†	46 ± 2†	§
MVo_2					
Glutamate	529 ± 66	557 ± 58	603 ± 100	447 ± 72	555 ± 134
Control	551 ± 100	601 ± 114	597 ± 92	552 ± 78	§

Data are mean ± SEM for basal state (0 min) and at 30, 60, 90, and 150 minutes. *CI,* Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$ BSA); *HR,* heart rate (beats/min); *SVI,* stroke volume index ($ml \cdot beats^{-1} \cdot m^{-2}$ BSA); *MAP,* mean arterial pressure (mm Hg); *SVRI,* systemic vascular resistance index ($dynesec \cdot cm^{-5} \cdot m^{-2}$ BSA); *PVRI,* pulmonary vascular resistance index ($dynesec \cdot cm^{-5} \cdot m^{-2}$ BSA); *LVSWI,* left ventricular stroke work index ($gm \cdot beats^{-1} \cdot m^{-2}$ BSA); *LAP,* left atrial pressure (mm Hg); *CVP,* central venous pressure (mm Hg); Svo_2, mixed venous oxygen saturation (%); *CSF,* coronary sinus blood flow (ml/min); $CSSo_2$, coronary sinus blood oxygen saturation (%); MVo_2, myocardial oxygen consumption (μmol/min).

*Statistically significant differences compared with basal state, $p < 0.05$.

†Statistically significant differences compared with basal state, $p < 0.01$.

‡Statistically significant differences between glutamate group and control group, $p < 0.05$.

§No sampling at 150 minutes.

higher in the glutamate group than in the control group at 30 minutes. Atrial filling pressures tended to be slightly lower in the glutamate group during the study period than in the control group (statistically significant for central venous pressure). There were no significant changes in myocardial oxygen uptake or coronary sinus blood flow during the study period.

Control group. In the control group, there were no significant hemodynamic changes during the study period. There were also no significant changes in myocardial oxygen uptake or coronary sinus blood flow.

Biochemical parameters. Detailed results of arterial levels of substrates and myocardial flux are given in Tables V and VI and Figs. 2 through 4.

Table V. *Arterial levels of substrates*

Time (min)	*Glutamate (μmol/L)*	*Alanine (μmol/L)*	*Lactate (mmol/L)*	*Glucose (mmol/L)*	*FFAs (mmol/L)*
0					
Glutamate	103 ± 10*	273 ± 21	1.05 ± 0.15	6.0 ± 0.1†	1.17 ± 0.04*
Control	162 ± 7	287 ± 21	1.03 ± 0.12	5.4 ± 0.3	0.62 ± 0.06
10					
Glutamate	172 ± 14‡	280 ± 22	1.02 ± 0.15‡	6.0 ± 0.1†	
Control	161 ± 9	259 ± 24‡	1.00 ± 0.11	5.3 ± 0.3‡	
20					
Glutamate	186 ± 18‡	273 ± 23	0.99 ± 0.14	6.0 ± 0.1§	
Control	157 ± 8	283 ± 20	1.00 ± 0.11	5.2 ± 0.2‖	
30					
Glutamate	189 ± 19‡	276 ± 23	0.97 ± 0.14‖	5.9 ± 0.1§	
Control	157 ± 8	271 ± 14‡	0.94 ± 0.09	5.2 ± 0.3¶	
60					
Glutamate	394 ± 20*‡	277 ± 27	0.97 ± 0.14	5.9 ± 0.1§	1.08 ± 0.06†
Control	160 ± 7	283 ± 13	0.90 ± 0.07	5.1 ± 0.2‡	0.84 ± 0.09‡
90					
Glutamate	129 ± 17†‖	275 ± 27	0.96 ± 0.13	5.9 ± 0.1*	0.98 ± 0.07‡**
Control	157 ± 8	256 ± 16‖	0.83 ± 0.06‖	5.0 ± 0.3¶	0.87 ± 0.09‡

Data are mean ± SEM for the basal state (0 min) and at 10, 20, 30, 60, and 90 minutes.
*Statistically significant differences between glutamate group and control group, $p < 0.001$.
†Statistically significant differences between glutamate group and control group, $p < 0.05$.
‡Statistically significant differences compared with basal state, $p < 0.01$.
§Statistically significant differences between glutamate group and control group, $p < 0.01$.
‖Statistically significant differences compared with basal state, $p < 0.05$.
¶Statistically significant differences compared with basal state, $p < 0.001$.
**Samples taken at 150 minutes.

Average myocardial uptakes of glutamate and corresponding arterial levels of glutamate during the study period are depicted in Fig. 2. The changes in myocardial flux of substrates during the study period are depicted in Fig. 3.

Glutamate

GLUTAMATE GROUP. During glutamate infusion, a significant increase in the myocardial uptake of glutamate was observed, with an early peak of 5.7 ± 1.2 μmol/min at 20 minutes. Arterial glutamate levels increased from 103 ± 10 μmol/L (basal state) to 394 ± 20 μmol/L at 60 minutes. During the first 30-minute period, there was a significant correlation between arterial levels ($r = 0.61$, $p < 0.001$) and arterial–coronary sinus differences. Thirty minutes after discontinuation of glutamate infusion, arterial levels had decreased to 129 ± 17 μmol/L.

CONTROL GROUP. In the basal state, the arterial level of glutamate and the myocardial uptake of glutamate were significantly higher in the control group than in the glutamate group. There were no changes in uptake in the control group during the study period.

Alanine

GLUTAMATE GROUP. In the basal state, there was a significant myocardial release of alanine in the glutamate group. A significant decrease in alanine release was observed at 30 minutes. Arterial levels of alanine remained unchanged during the study period.

CONTROL GROUP. In the basal state, there was a significant release of alanine in the control group. A significant decrease in alanine release was observed at 20 minutes. Arterial levels of alanine in the control group decreased during the study period (statistically significant at 10, 30, and 90 minutes).

Lactate

GLUTAMATE GROUP. Myocardial uptake of lactate increased from 4.9 ± 2.0 μmol/min (basal state) to 14.1 ± 4.4 μmol/min after 60 minutes of glutamate infusion. Arterial levels of lactate decreased (statistically significant at 10 and 30 minutes), and the fractional uptake of lactate increased from 3.5% ± 1.2% (basal state) to 8.7% ± 2.2% at 60 minutes (Fig. 4).

CONTROL GROUP. In the basal state, myocardial uptake of lactate was significantly higher in the control group than in the glutamate group. In contrast to the glutamate group, myocardial uptake decreased significantly during the study period. Arterial levels decreased during the study period (statistically significant at 90 minutes).

Table VI. *Myocardial flux of substrates (μmol/min)*

Time (min)	*Glutamate*	*Alanine*	*Lactate*	*Glucose*	*FFA*
0					
Glutamate	0.7 ± 0.2*†	−3.2 ± 0.8‡	4.9 ± 2.0*§	17.8 ± 6.3*	17.1 ± 2.2‡‖
Control	4.7 ± 1.3¶	−3.5 ± 1.1‡	18.9 ± 5.4‡	10.2 ± 4.8*	9.6 ± 2.5‡
10					
Glutamate	3.1 ± 0.5‡**	−2.0 ± 1.0*	4.2 ± 1.4‡‖	13.5 ± 9.4	
Control	5.1 ± 1.8¶	−6.2 ± 2.3*	16.6 ± 5.6‡	7.9 ± 12.4	
20					
Glutamate	5.7 ± 1.2‡**	−2.0 ± 0.8*	6.3 ± 3.6‖	14.0 ± 9.7	
Control	5.4 ± 1.9‡	−0.8 ± 2.8††	19.0 ± 6.3‡	11.8 ± 17.1	
30					
Glutamate	4.2 ± 1.0‡**	−2.0 ± 1.1*††	5.2 ± 2.7*	5.0 ± 12.7	
Control	4.2 ± 1.6‡	−4.4 ± 1.6‡	12.6 ± 4.1‡††	5.4 ± 11.1	
60					
Glutamate	4.4 ± 1.0* **	−2.8 ± 1.1*	14.1 ± 4.4‡††	13.7 ± 13.2	16.7 ± 3.8‡
Control	3.6 ± 1.0‡	−3.4 ± 1.2‡	10.8 ± 3.7‡††	7.3 ± 3.7*	14.4 ± 5.0‡
90					
Glutamate	1.8 ± 0.4‡**	−3.1 ± 0.6‡	10.2 ± 3.4‡††	11.1 ± 5.9*	20.0 ± 8.7‡ ‡‡
Control	3.2 ± 0.8¶	−4.9 ± 1.2‡	5.2 ± 2.8*††	−1.0 ± 6.4	14.2 ± 2.8‡

Data are mean ± SEM for basal state (0 min) and at 10, 20, 30, 60, and 90 minutes.
*Statistically significant uptake or release, $p < 0.05$.
†Statistically significant differences between glutamate group and control group, $p < 0.001$.
‡Statistically significant uptake or release, $p < 0.01$.
§Statistically significant differences between glutamate group and control group, $p < 0.01$.
‖Statistically significant differences between glutamate group and control group, $p < 0.05$.
¶Statistically significant uptake or release, $p < 0.001$.
**Indicate statistically significant differences compared with basal state, $p < 0.01$.
††Indicate statistically significant differences compared with basal state, $p < 0.05$.
‡‡Samples taken at 150 minutes.

Glucose

GLUTAMATE GROUP. In the basal state, there was a significant myocardial uptake of glucose (17.8 ± 6.3 μmol/min). There was no significant change in uptake during the study period. Arterial levels remained unchanged.

CONTROL GROUP. In the basal state, there was a significant myocardial uptake of glucose (10.2 ± 4.8 μmol/min). There was no significant change in uptake during study period. Arterial glucose levels in the basal state were significantly lower in the control group than in the glutamate group, and there was a decrease in arterial glucose levels during the study period.

FFAs

GLUTAMATE GROUP. A significant myocardial uptake of FFAs (17.1 ± 2.2 μmol/min) was observed in the basal state in the glutamate group. There was no significant change during the study period. The arterial level of FFAs decreased from 1.17 ± 0.04 mmol/L (basal state) to 1.08 ± 0.06 mmol/L at 60 minutes ($p = 0.052$) and to 0.98 ± 0.07 at 150 minutes ($p < 0.01$).

CONTROL GROUP. A significant myocardial uptake of FFAs (9.6 ± 2.5 μmol/min) was observed in the basal state in the control group. There was no significant change during the study period. The arterial level of FFAs increased from 0.62 ± 0.06 mmol/L (basal state) to 0.84 ± 0.09 mmol/L at 60 minutes and 0.87 ± 0.09 at 90 minutes. Despite this increase, the arterial level was significantly lower in the control group than in the glutamate group in the basal state and at 60 minutes.

Discussion

The main finding of this study is that glutamate infusion early after coronary operations was associated with increased myocardial uptake of glutamate and improved myocardial extraction of lactate. The results are compatible with an improvement in myocardial oxidative metabolism and were associated with improved myocardial performance. Intravenous metabolic support with glutamate may therefore provide a means of improving metabolic and functional recovery of the heart after coronary operations.

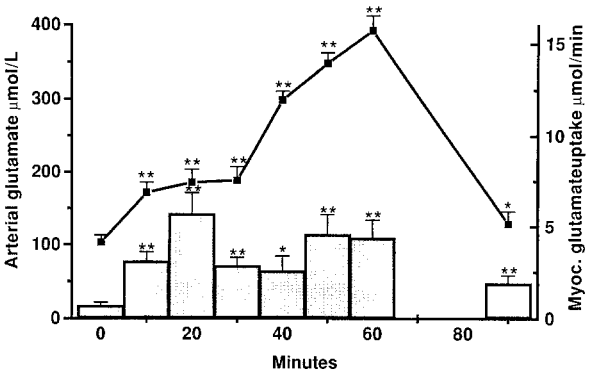

Fig. 2. Myocardial glutamate uptake (µmol/min; *bars*) and arterial glutamate level (µmol/L; *straight line with squares*) according to whole blood analyses (mean ± SEM). *Asterisks* indicate statistically significant differences from basal state, with *single asterisk* representing $p < 0.05$ and *double asterisk* representing $p < 0.01$.

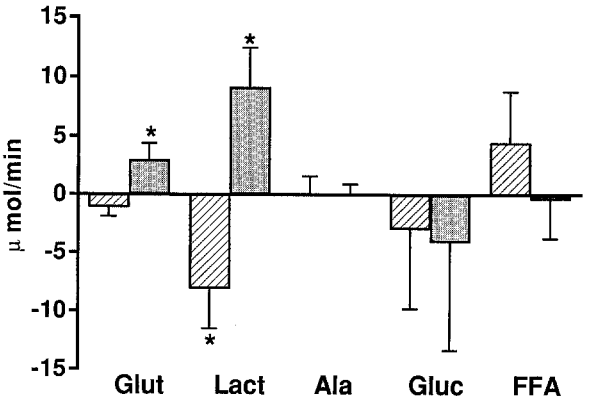

Fig. 3. Change in myocardial flux of substrates in control *(hatched bars)* and glutamate *(gray bars)* groups from the basal state to 60 minutes (mean ± SEM). *Glut,* Glutamate; *Lact,* lactate; *Ala,* alanine; *Gluc,* glucose; *FFA,* free fatty acids. *Asterisks* indicate statistically significant differences from basal state, with *single asterisk* representing $p < 0.05$.

Some aspects of study design deserve to be considered. The study was neither blind nor randomized because data on the impact of glutamate administration on arterial levels, myocardial glutamate uptake, and adverse effects were limited when the study was planned. The descriptive nature of the study was therefore emphasized. More important, early detection of any signs suggestive of adverse effects was considered mandatory. The main purpose of the control group was to provide information about metabolic and hemodynamic changes occurring spontaneously during the study period. Although the inclusion criteria were strict, some minor differences between the glutamate and control groups were observed. Obviously, randomization might have avoided these differences. Despite these limitations, we suggest that the results are relevant. They agree with basic science data and available data from human studies and therefore may serve as encouragement for future randomized studies and provide approximate guidelines with respect to the choice of dosages for these studies.

Impaired myocardial utilization of oxygen has been demonstrated early after ischemia.[5, 13, 14] In animals, amino acids, particularly glutamate and aspartate, are important in the recovery of myocardial oxidative metabolism after ischemia.[5, 15] These observations also seem relevant for human beings, according to studies performed in association with cardiac operations.[2, 4] Moreover, a high fractional uptake of glutamate has been demonstrated early after coronary operations, indicating that substrate availability may be limiting for the uptake of glutamate during the first hours of reperfusion.[4] It has therefore been suggested that exogenous administration of glutamate could enhance metabolic and possibly functional recovery of the heart.[1]

In this study, a significant increase in the myocardial uptake of glutamate was observed during glutamate infusion, with an early peak at 20 minutes. Although myocardial uptake of glutamate correlated with the arterial level during the first half hour, an increase in arterial (whole blood) levels more than twofold or threefold was not associated with a further increment in myocardial glutamate uptake. The results suggest that myocardial glutamate uptake is dependent not only on arterial levels but probably also on myocardial requirements. Data obtained at peak uptake of glutamate (unpublished data) suggest that an infusion rate of 30 to 40 $mg \cdot kg^{-1} \cdot hour^{-1}$ may be sufficient to adequately enhance myocardial glutamate uptake, at least after routine CABG operations. The precise mechanisms governing myocardial glutamate uptake in the heart are not known at present. The roles of carrier proteins and different transport systems for amino acids in various tissues has received increasing attention during the last decade. Recently published data point out the pH dependence of L-glutamate transport in sarcolemmal vesicles from rat heart.[16] Acidosis in ischemic heart regions may therefore explain the increased uptake of glutamate in isch-

emic and postischemic hearts. A high turnover of glutamate in the human body is suggested by the rapid decrease of arterial levels after discontinuation of glutamate infusion.

The arterial FFA level was reduced during the study period in the glutamate group, whereas arterial level increased in the control group. Reduction of arterial FFA levels is considered desirable for the postischemic heart[17]; however, the change in this study was small. Reduced FFA levels have been reported previously during glutamate administration as a result of increased insulin secretion.[18] In normal subjects, maximal reduction of plasma FFA levels may appear at plasma insulin levels as low as 30 mU/L, which correspond to the reported increment in insulin during glutamate infusion.[17, 18] After CABG operations, however, only a minor impact on arterial FFA levels has been reported at these insulin levels, and no effect on myocardial uptake of substrates may be expected.[17, 19] In agreement with this, there was no change in the net uptake of the major substrates (FFAs and glucose) during glutamate infusion.

The myocardial uptake of lactate, however, increased almost threefold during glutamate infusion. Lactate uptake is normally dependent on arterial levels.[20] The increase in lactate uptake was not the result of increased arterial levels, however; on the contrary, the arterial levels of lactate decreased somewhat, whereas the fractional uptake of lactate increased significantly from 3.5% to 8.7% during glutamate infusion (Fig. 4). These results are compatible with an improved myocardial utilization of lactate. The methods used in this study do not allow a precise assessment of the metabolic fate of lactate; in the human heart, however, the metabolic pathways after conversion of lactate to pyruvate are limited to either (1) transamination to alanine, (2) oxidation in the Krebs cycle after oxidative decarboxylation by pyruvate dehydrogenase, and possibly (3) pyruvate carboxylation to form oxaloacetate, thereby regenerating Krebs cycle intermediates.[21] Because alanine release tended to decrease in this study, an increased transamination of pyruvate is unlikely. We therefore suggest that glutamate infusion was associated with an improved oxidation of lactate. These findings agree with animal experimental data, which demonstrate improved recovery of myocardial oxidative metabolism after ischemia by substrate enhancement with glutamate.[5]

It may be argued that the net myocardial uptake of lactate observed in the basal state is incompatible

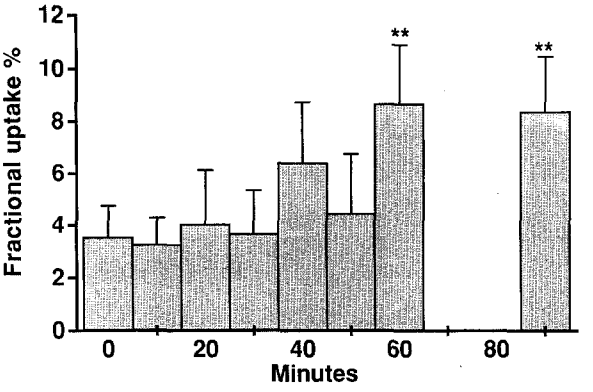

Fig. 4. Fractional (%) uptake of lactate in glutamate group (mean ± SEM). *Asterisks* indicate statistically significant differences from basal state, with *single asterisk* representing $p < 0.05$ and *double asterisk* representing $p < 0.01$.

with defective oxidative metabolism. The myocardial protection provided by antegrade crystalloid cardioplegia, however, may vary considerably in different regions of the heart. This implies that disturbances of oxidative metabolism may also vary considerably regionally. The coronary-sinus catheter technique, however, reflects global left ventricular metabolism.[6] Low levels of lactate extraction in the early reperfusion period thus may represent the net result of continued lactate release from poorly protected regions and lactate utilization in well-protected regions. The improved lactate utilization during glutamate infusion may be the result of regionally improved oxidative metabolism in poorly protected parts of the heart.[22] Analogously, the increase in global myocardial oxygen consumption observed during glutamate infusion, although not statistically significant, may be compatible with regionally improved oxidative metabolism.

The major hemodynamic effects of glutamate infusion were increases in left ventricular stroke work and mean arterial blood pressure, compatible with improved myocardial performance. The impact of intravenous glutamate on myocardial metabolism and myocardial performance agree with data from animal experiments in which L-glutamate was used as a cardioplegic additive.[5] In contrast to clinical experience with amino acid–enhanced blood cardioplegia (unpublished data), we did not observe any signs of vasodilation. To explain this discrepancy, the higher arterial levels of glutamate (and aspartate) after amino acid–enhanced blood cardioplegia,[23] other components of the cardioplegic solution

and conditions caused by cardiopulmonary bypass must be considered. Because the increase in cardiac index was not primarily an effect of vasodilation, it is also evident that the limited employment of vasodilators to prevent postoperative hypertension has minor impact on the hemodynamic results. The positive hemodynamic impact of glutamate in this study provides further support for the suggested link between metabolic and hemodynamic function.[1, 24, 25]

In human beings, positive metabolic and hemodynamic effects of glutamate were demonstrated by Pisarenko, Lepilin, and Ivanov[26] in patients treated with dopamine because of heart failure after cardiac operations. These patients differed from those in our study by their poorer hemodynamic condition, a more severe degree of metabolic derangement, and more pronounced metabolic and hemodynamic responses to glutamate. The metabolic and hemodynamic impact of glutamate may therefore be related to the magnitude of metabolic derangement before treatment.

Timing of intervention and patient selection are factors that could influence the impact of metabolic treatment. This study was started 1 to 2 hours after completion of the operation because previous studies performed during this period demonstrated myocardial metabolic abnormalities that seemed accessible to glutamate treatment.[4] The patients in the glutamate group, however, demonstrated myocardial metabolic alterations that were minor compared with these studies. This discrepancy is probably explained by the shorter aortic crossclamp times, the lesser extent of coronary artery disease, and the employment of a superior degree of sedation and muscle relaxation in this study. Metabolic derangement was even less pronounced in the control group, and it is uncertain whether these patients would have benefited from glutamate administration at this stage. Further studies should focus on glutamate administration during early reperfusion in patients undergoing more extensive operations, patients at high risk, and patients with postoperative heart failure.

Our results suggest that patients undergoing routine CABG with short aortic crossclamp times may still benefit from glutamate, however, so the role of glutamate administration as a clinical routine also deserves further investigation. In this respect, intravenous glutamate administration offers an alternative to amino acid enhancement of cardioplegic solutions. It is unlikely, however, that additional intravenous amino acid administration would provide further benefit during early reperfusion in patients receiving amino acid–enhanced cardioplegia. On the other hand, preoperative and postoperative ischemia may now be more important determinants of clinical outcome in coronary operations as a result of current standards of myocardial protection.[27, 28] Because glutamate is reported to improve myocardial tolerance to ischemia in patients with coronary problems,[29] intravenous glutamate administration offers the prospect of improving myocardial protection during the preoperative and postoperative periods of CABG. These and other issues discussed here should be addressed in prospective, randomized studies.

This study suggests that intravenous glutamate infusion can enhance myocardial uptake of glutamate and improve metabolic and hemodynamic recovery of the heart early after coronary operations. Randomized studies are needed to confirm these results and to explore the therapeutic and prophylactic potentials of the intravenous administration of amino acids.

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