Cardiac metabolism and performance during L-glutamic acid infusion in postoperative cardiac failure

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Summary

1. Intravenous infusion of L-glutamic acid results in the augmentation of the cardiac output and an improvement of the circulation in patients with postoperative cardiac failure. This effect is not accompanied by increased myocardial oxygen demand.

2. Arterial plasma glutamate level rises 10-fold and arterial-coronary sinus plasma glutamate difference increases fivefold during intravenous L-glutamic acid infusion. This leads to cessation of ammonia release from the myocardium, probably due to augmentation of glutamine synthesis and to an increase in alanine formation coupled with a change from lactate release to lactate uptake by the myocardium.

3. The data obtained suggest that the beneficial effect of L-glutamic acid on depressed cardiac function in postoperative patients is related to changes in myocardial metabolism. Glutamic acid may be useful in treatment of circulatory and metabolic disturbances in cardiac failure.

Key words: cardiac function, exogenous glutamic acid, heart, myocardial metabolism, postoperative cardiac failure.

Introduction

Recent studies in different experimental models indicate that glutamic acid maintains the contractile function of ischaemic myocardium and facilitates its recovery during reperfusion [1, 2].

Glutamate added to blood or crystalloid potassium cardioplegic solution improves recovery of cardiac function after a period of global ischaemia [3, 4]. This beneficial effect is related to the replenishment of depleted high energy phosphates in myocardial cells [2-4]. Glutamic acid metabolism in ischaemic myocardium is closely connected with glycolysis and anaerobic ATP formation via substrate phosphorylation [1-5]. Glutamic acid is involved in the binding of free ammonia that accumulates in ischaemic and/or hypoxic myocardium [6, 7]. Ammonia excess can inhibit the oxidative decarboxylation of α-keto acids in the tricarboxylic acid cycle and decrease the intramitochondrial pool of pyridine nucleotides [8].

It is well known that, of all amino acids, only glutamic acid is extracted by the human heart and its uptake is increased in patients with coronary artery disease [9-11]. However, many aspects of the clinical application of glutamic acid remain unclear. The aim of our study was to find out whether the intravenous infusion of L-glutamic acid could improve cardiac performance in patients with low cardiac output syndrome after open-heart surgery.

Methods

Patients and instrumentation

Ten male patients (mean age 47.8 ± 4.6 years, mean weight 70.1 ± 9.9 kg) who had undergone recent open-heart surgery (Cardiac Surgery Department, U.S.S.R. Surgery Research Centre) were studied: aorto-coronary saphenous vein grafting (three or four grafts), six patients; mitral valve replacement with porcine xenoprosthesis, two patients; left ventricular aneurysm resection with septal defect closure and three aorto-coronary
grafts, one patient; ascending aorta and aortic valve replacement with allograft, one patient. Preoperatively each patient had signs of congestive heart failure.

A radial artery catheter, central venous catheter, Swan-Ganz catheter (Vygon) and left arterial catheter (in mitral valve surgery) were inserted during the operation. The aorta was cross-clamped for 60-105 min, and single dose Bretschneider-type potassium cold cardioplegic solution was infused. After the operation, under fluoroscopic control, a Teflon catheter (USCI) was placed in the coronary sinus. Intermittent positive pressure ventilation with air/oxygen (60:40, v/v) was used to maintain arterial blood gases within the normal range, and metabolic acidosis was corrected with sodium bicarbonate solution. In all patients the body temperature was 36-37°C (warming blanket and respiratory gas warmer were used). The catheters were connected to fluid-filled Statham transducers; pressure data were stored and displayed via a bedside computer (Hellige). Cardiac output was measured by thermodilution (Hoyer HZV-messer) in triplicate, and then averaged. Blood gases and acid-base status were estimated at 5 min intervals during the study (ABL-2, Radiometer). Before glutamic acid infusion blood pH was corrected within the normal range (7.40 ±0.03). Plasma osmolarity was assessed with an osmometer (Knauer) before and during infusion. Heart rate, cardiac output, mean arterial pressure, mean pulmonary artery pressure, mean right atrial pressure and pulmonary capillary wedge pressure (or left atrial pressure for patients with mitral valve dysfunction) were determined directly, cardiac and stroke indices were calculated (body surface area was estimated according to a height-weight nomogram). The systemic vascular resistance was calculated by the formula

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\text{Cardiac index} = \frac{\text{Mean arterial pressure} - \text{mean right atrial pressure}}{80} \times \text{cardiac output} \times \text{body surface area}
\]

From 30 to 60 min after weaning from the cardiopulmonary bypass each patient revealed signs of low cardiac output syndrome: cardiac index 2.0-2.2 litres min⁻¹ m⁻²; mean left atrial, or pulmonary capillary wedge pressures 18-25 mmHg (2.4-3.3 kPa); mixed venous PO₂ 22-28 mmHg (2.9-3.7 kPa); mean arterial pressure 50-60 mmHg (6.6-7.9 kPa). Intravenous fluid and dopamine infusion (2-4 µg min⁻¹ kg⁻¹) helped to maintain the mean arterial pressure within the range 80-90 mmHg, to preserve the cardiac index (2.4-3.5 litres min⁻¹ m⁻²) and to keep the normal diuresis. Effect of glutamic acid infusion was studied after the stabilization of haemodynamic variables (4-10 postoperative hours).

**Study protocol**

At 15 min before glutamic acid infusion no fluids but dopamine were given. Glutamic acid solution (0.068 mol/l) was infused intravenously with an Infusomat pump (Braun Melsungen) at the rate of 2.0-3.7 mg min⁻¹ kg⁻¹ (0.014-0.025 mmol min⁻¹ kg⁻¹) during 15.3 ±3.0 min. Samples of arterial and coronary sinus blood were taken before the glutamic acid infusion, at 15 min during the infusion and 30 min after the infusion. Plasma glutamic acid concentration was determined every 3 min during infusion and every 15 min after it. Haemodynamic variables corresponding to peak plasma glutamate concentration were compared with preinfusion values. It was not possible to use a separate control group of patients because rapid infusion of 350-400 ml of any hypo-osmotic fluid having no specific cardiovascular effect may be dangerous for patients with cardiac failure. The patients therefore acted as their own controls.

**Analysis of metabolites**

Blood plasma was prepared by adding the blood to ice-cold heparinized tubes and immediate centrifuging at 3000 g for 15 min (4°C). Plasma proteins were precipitated by addition of an equal volume of cold perchloric acid (0.6 mol/l) and then centrifuged at 4000 g for 20 min (4°C). The supernatant was brought to pH 7.4 by potassium bicarbonate (1.16 mmol/l), placed on ice for 20 min and then centrifuged at 12000 g for 10 min (4°C) to sediment the potassium perchlorate precipitate. Plasma glutamate, glutamine, aspartate and alanine concentrations were determined by Liquimat-III amino acid analyser with fluorimetric cell FFM-31. Elution was carried out by Durrum lithium citrate buffers in a 0.4 cm x 30 cm column packed with Pierce DC-4A resin. The buffers were passed through a 0.9 cm x 12 cm pre-column packed with Pierce DC-3 resin to trap traces of ammonia. Norleucine served as an internal standard. Plasma lactate and ammonia were assayed spectrophotometrically (Yanako UO-2000) by using lactate dehydrogenase [12] and the ammonia-free glutamate dehydrogenase [13].

**Calculations and statistics**

All the values are expressed as means ± standard error of the mean. Haemodynamic variables were evaluated in each patient by Student's t-test for
paired data (two-tailed). The statistical significance of biochemical data was estimated by Student's t-test for unpaired data. A value of $P < 0.05$ was considered significant.

**Results**

**Circulatory effects**

Haemodynamic data before and after glutamic acid infusion are presented in Table 1. It is apparent that initially (during dopamine infusion) all the patients met criteria of cardiac failure: moderately high heart rate, low stroke index, increased mean pulmonary artery pressure and pulmonary capillary wedge pressure (or mean left atrial pressure). Mean arterial pressure was maintained at $89 \pm 4$ mmHg by dopamine infusion. Mixed venous $P_{O_2}$ was $32.5 \pm 1.87$ mmHg ($4.0 \pm 0.2$ kPa), mixed venous $O_2$ saturation was $54.5 \pm 2.3\%$, arterial blood pH was $7.38 \pm 0.01$; arterial blood $P_{O_2}$ and $O_2$ saturation were maintained within the normal range (100–120 mmHg and 95–100%, respectively) by mechanical ventilation. Glutamic acid infusion at a rate of 20–25 ml/min was associated with increase in cardiac and stroke indices. Simultaneously heart rate, pulmonary capillary wedge pressure (or mean left atrial pressure) and mean pulmonary artery pressure decreased. Mean arterial pressure and mean right atrial pressure remained stable during infusion. The systemic vascular resistance decreased from $2073 \pm 303$ to $1628 \pm 183$ dynes s$^{-1}$ cm$^{-5}$ ($P < 0.05$).

Triple product (heart rate $\times$ systolic arterial pressure $\times$ mean left atrial pressure), often used in cardiac surgery [14] for evaluation of left ventricular energy consumption and oxygen demand, was high initially during dopamine infusion (normal value up to 150 000 (mmHg)$^2$·beat/min) but decreased after glutamic acid administration. Improved left ventricular function (Fig. 1) was presumably associated with the lower myocardial wall stress and lowered oxygen demand.

Increased cardiac performance was accompanied with slight venous $P_{O_2}$ and $O_2$ saturation increase up to $36.0 \pm 2.7$ mmHg ($4.8 \pm 0.4$ kPa) and $59.1 \pm 3.5\%$, respectively ($P < 0.05$), indicating better oxygenation and perfusion of peripheral tissues.

It should be noted that glutamic acid intravenous infusion did not cause acidosis: the mean arterial pH was $7.38 \pm 0.02$. None of the patients had blood pH lower than 7.33 either during or after infusion. No significant changes in plasma osmolality were observed during glutamic acid infusion, the mean value being $320 \pm 25$ mosmol/l.
FIG. 1. Improvement of left ventricular performance under the effect of intravenous glutamic acid infusion in patients with postoperative low cardiac output syndrome (10 patients). LAP, Left atrial pressure.

**Metabolism of amino acids, ammonia and lactate**

The initial arterial plasma glutamic acid concentration was close to the normal value (0.076 ± 0.014 and 0.067 ± 0.026 [11] μmol/ml, respectively). Intravenous infusion of glutamic acid solution provided a rapid elevation of plasma glutamate level. At 10 min after the onset of the infusion the plasma concentration of glutamate rose to 1.24 ± 0.14 μmol/ml and was stable until the infusion was stopped, then sharply decreased. Before infusion the arterial–coronary sinus plasma glutamate difference was 0.030 ± 0.012 μmol/ml, indicating a slight uptake of endogenous glutamate, but during glutamic acid infusion it increased fivefold up to 0.175 ± 0.068 μmol/ml (Fig. 2).

In a normal subject arterial and venous plasma ammonium concentration ranges from 20.5 to 60.5 nmol/ml [15, 16]. However, the initial plasma ammonium levels in our patients were much higher (Table 2). In the majority of patients a negative value of the arterial–coronary sinus difference for ammonium was observed, indicating a release of ammonia excess from the failing heart. Glutamic acid administration resulted in a significant decrease of coronary sinus plasma ammonium levels with arterial plasma ammonium concentration unchanged. Thus, ammonia release changed to ammonia uptake during glutamic acid infusion. Simultaneously, increased glutamine release from the heart was observed; the negative arterial–coronary sinus plasma glutamine difference increased threefold during glutamic acid infusion.

Similar shifts in ammonia and glutamine metabolism remained at 30 min after glutamic acid infusion (Table 2).

There were no significant changes in plasma aspartate concentration during glutamic acid infusion, and the negative arterial–coronary sinus difference for alanine increased threefold as compared with the initial value (Table 2). Plasma lactate concentrations in arterial and cardiac venous blood were markedly higher than normal values (both about 0.7 ± 0.1 μmol/ml [11]) before glutamic acid infusion. During this period a tendency towards lactate release from the hearts was observed in all but one patient, the mean plasma arterial–coronary sinus difference being 0.08 ± 0.06 μmol/ml. At 15 min of infusion the mean arterial–coronary sinus difference of lactate became significantly positive (0.06 ± 0.03 μmol/ml) and subsequently increased (to 0.14 ± 0.06 μmol/ml) by the end of the study, regardless of the decreased plasma glutamic acid level.

**Discussion**

As appears from the above results, intravenous glutamic acid infusion results in improvement of cardiac function in patients with cardiac failure after open-heart surgery. This effect is manifested in enhanced cardiac performance. Experimental data [17] revealed cardiac output increase during glutamic acid infusion with no contractility changes. Hyper-osmolar glutamic acid solution was considered to be the cause of plasma volume increase and improvement in cardiac performance. Unlike previous work [17], we infused the hypo-
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osmolar glutamic acid solution at a lower rate and observed neither increased plasma osmolarity nor rise in right atrial pressure. Therefore, improvement of the circulation does not seem to be related to expanded intravascular volume and increased ventricular preload. It is more likely to be linked to a direct effect of glutamic acid on myocardial metabolism. This relationship can be partially confirmed by more pronounced effects of glutamic acid on the failing heart than on an intact heart [17].

There are no reasons to suggest a direct vasodilatory effect of the glutamic acid infusion since the mean arterial pressure remained stable during the whole study. Presumably, cardiac performance improvement may cause a certain fall in systemic vascular resistance.

In our study the increase of glutamic acid uptake by the heart during infusion was associated with certain changes in myocardial metabolism. In fact, activated anaerobic metabolism resulted in a release of lactate, ammonia and alanine from the hearts of patients with postoperative cardiac failure (Table 2). However, glutamic acid infusion increased the myocardial glutamine synthesis, which led to cessation of ammonia diffusion from the hearts. This metabolic rearrangement seems to be beneficial since ammonia can inhibit energy formation in myocardial cells [8]. Coupling of glutamic acid metabolism with glycolysis and Kreb's cycle reactions is accomplished by alanine aminotransferase and aspartate aminotransferase [5].

The increase of alanine formation during the infusion confirms the participation of glutamic acid transamination with pyruvate in the mechanism of its action [1, 2, 18].

A lack of increase in the coronary sinus plasma aspartic acid concentration cannot exclude the possibility of aspartate formation within the myocardial cells from the exogenous glutamic acid. This is explained by a lower ability of aspartate for diffusion from myocardium as compared with alanine or glutamine, and its intensive metabolism in the heart [19]. It should be noted that in ischaemia the alanine aminotransferase reaction shunts pyruvate derived from glycolysis to alanine, thus decreasing lactate accumulation [20]. A shift in lactate metabolism towards its uptake by the heart under the influence of glutamic acid can be due to use of pyruvate both in alanine synthesis and the pyruvate dehydrogenase reaction. The increase of lactate uptake observed after glutamic acid infusion, when alanine release decreased to the initial value, confirms an activation of anaerobic metabolism in the heart, i.e. pyruvate utilization in the latter reaction.

It remains obscure whether or not glutamic acid infusion maintains higher levels of myocardial ATP and phosphocreatine, although this effect was observed in animal studies [1–4]. The present data show that the improvement of cardiac function is associated with an effect of glutamic acid on intermediary myocardial metabolism. This conclusion agrees with the following experimental results: (a) similar changes in metabolism and contractility were observed during perfusion of isolated rat and rabbit hearts [1, 2, 4]; (b) circulatory changes caused by neurohumoral mechan-

| TABLE 2. Changes in plasma metabolite concentrations induced by glutamic acid infusion (n = 10) |
| Compound | Conc. before infusion | Change in concn. | 15 min of infusion | 30 min after infusion |
| Ammonia (nmol/ml) | a 160 ± 21 | 157 ± 20 | 148 ± 18 |
| | v 174 ± 25 | 128 ± 16* | 138 ± 15* |
| | a-v -14 ± 10 | 29 ± 12* | 10 ± 8 |
| Glutamine (nmol/ml) | a 528 ± 21 | 680 ± 38* | 607 ± 28 |
| | v 553 ± 16 | 758 ± 49† | 660 ± 29 |
| | a-v -25 ± 12 | -78 ± 19* | -53 ± 14 |
| Alanine (nmol/ml) | a 292 ± 16 | 380 ± 21* | 330 ± 19 |
| | v 307 ± 18 | 425 ± 23† | 353 ± 22 |
| | a-v -15 ± 8 | -45 ± 10* | -23 ± 9 |
| Lactate (μmol/ml) | a 4.03 ± 0.25 | 3.89 ± 0.17 | 3.40 ± 0.24 |
| | v 4.11 ± 0.06 | 3.83 ± 0.18 | 3.26 ± 0.20* |
| | a-v -0.08 ± 0.06 | 0.06 ± 0.03* | 0.14 ± 0.06* |
isms were found only after direct cerebral or intra-thecal glutamic acid administration [21]; (c) the neurohumoral effect of glutamate is a part of baroreceptor-mediated circulatory responses [22, 23]; however, the described effect was manifested via improvement of cardiac metabolism and performance. Thus, elevation of plasma glutamate level may cause some improvement of the circulatory performance. However, a rapid metabolism of exogenous glutamic acid can be provided by prolonged infusion. One can assume that more pronounced protective action of glutamate results in a sharp decrease in glutamate level after the end of infusion. One can release from the myocardium to their uptake may be of particular importance for cardiac performance. However, a rapid metabolism of exogenous glutamic acid results in a sharp decrease in glutamate level after the end of infusion. One can assume that more pronounced protective action of glutamic acid can be provided by prolonged infusion of the amino acid of a higher concentration at a lower rate, or by direct glutamic acid infusion into coronary circulation.

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References