Cardiopulmonary Bypass and Plasma Taurine

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We measured the changes in plasma concentrations of taurine and cystine after cardiopulmonary bypass in 14 patients undergoing valve replacement or coronary-aorta bypass grafting. The total concentration of all amino acids in the plasma decreased during the operations, and then recovered gradually towards its preoperative value. The concentrations of taurine and cystine remained unchanged at the end of the operations, and then started to decrease through the second post-operative day. The administration of reduced glutathione 2.4–9.0g prior to cardiopulmonary bypass in two patients failed to lessen the post-operative decrease in cystine and taurine concentrations in the plasma. Because favorable effects of taurine supplementation on the ischemic myocardium have been reported, the administration of taurine might be of value to avoid the depression of cardiac functions after cardiopulmonary bypass.

The myocardium is usually rich in taurine, but levels of taurine have been shown to be low in the ischemic myocardium[1]. The administration of taurine is known to have a positive inotropic effect and an antiarrhythmic effect[2]. Taurine is also reported to reverse the negative inotropic effect of diltiazem or propranolol[2]. A direct link between decreased taurine levels in the myocardium and decreased myocardial mechanical functions has been proposed, based on experiments using cats on low-taurine diet[3]. The cats manifest dilated cardiomyopathy, and supplementary taurine results in normalization of the left ventricular functions. The underlying mechanisms for taurine's effects on the myocardium have not been elucidated; taurine is thought to have regulatory roles in calcium homeostasis and in osmolarity[4,5]. Myocardial ischemia during cardiopulmonary bypass (CPB) surgery followed by low output syndrome is still a major problem in cardiac surgery. We measured the changes in plasma concentrations of taurine and cystine, an oxidized form of cysteine which is a precursor of taurine, in patients undergoing cardiac surgery using CPB. We also examined the effect of an intravenous infusion of reduced glutathione on plasma concentrations of taurine and cystine.

Methods

We measured the plasma concentrations of amino acids in 14 adult

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Table 1. Plasma concentrations of all amino acids, taurine and cystine before and after cardiopulmonary bypass surgery

		Before operation	End of operation	the 1st post-operative day	the 2nd post-operative day
All amino acids	($mg \cdot dl^{-1}$)	35.7 ± 7.6	22.7 ± 6.8*	27.9 ± 8.0*	29.7 ± 7.7
Taurine	($mg \cdot dl^{-1}$)	1.0 ± 0.3	1.0 ± 0.4	0.8 ± 0.4	0.6 ± 0.2*
Cystine	($mg \cdot dl^{-1}$)	2.0 ± 0.8	2.1 ± 0.7	1.2 ± 0.5*	1.2 ± 0.5*

Mean ± SD

Asterisks indicate $P < 0.05$ versus corresponding pre-operative values.

patients (9 male and 5 female) undergoing valve replacement (10 patients) and coronary-aorta bypass grafting (CABG, 4 patients). All patients (62.2 ± 7.9 years old) were in NYHA II and III categories, and were free from evident liver damage. All were required to fast overnight for 10h before surgery. Anesthesia was induced by an intravenous administration of diazepam and fentanyl, and was maintained with fentanyl (about 81 ± 18 $\mu g \cdot kg^{-1}$). Endotracheal intubation was facilitated by an intravenous administration of pancuronium or vecuronium. A membrane-type, pulsatile cardiopulmonary bypass apparatus primed with half saline containing glucose was used, and mild hypothermia of 27°C at a rectal temperature was induced during the bypass. The pump flow was maintained about 2.1 $l \cdot min^{-1} \cdot m^{-2}$, and the acid-base balance was controlled according to α-statt regulation. Cell saver and hemofiltration were used during the operations. The hearts were arrested by a solution containing KCl 20 mM, glucose 25 $g \cdot l^{-1}$ and insulin 5 $IU \cdot l^{-1}$. The duration of the bypass was 3.4 ± 1.0h. No amino acid solution was used during the entire course of the study. For fuel, glucose was given intravenously at a rate of 0.1–0.2 $g \cdot kg^{-1} \cdot h^{-1}$ until the second post-operative day. Insulin was administered intravenously, if necessary, to maintain blood glucose concentrations below 300 $mg \cdot dl^{-1}$. In another part of the study, two patients undergoing CABG were given reduced glutathione (GSH) prior to CPB. Nine and 2.4g of GSH (200 and 60 $mg \cdot kg^{-1}$) were given intravenously in case 1 and in case 2, respectively.

Blood samples were taken through radial arterial cannulas, and amino acid concentrations in plasma were determined by the ninhydrin method after separation by high performance liquid chromatography using a Hitachi L-8500 amino acid analyzer (Hitachi, Tokyo, Japan). Because cysteine is oxidized to cystine spontaneously, the total amount of cysteine and cystine was obtained through this assay. Results are expressed as mean ± S.D. Statistical analysis of the data was performed using ANOVA. $P < 0.05$ was considered statistically significant.

Results

The total concentration of all amino acids in the plasma decreased during the operations, and then recovered gradually towards its pre-operataive value (table 1). The concentrations of taurine and cystine remained unchanged at the end of the operations, and then started to decrease through the second post-operative day. The plasma taurine concentrations in a patient who required cardiac support with intra-aortic baloon pumping were 0.24 $mg \cdot dl^{-1}$ at the 2nd and the 3rd

Table 2. Plasma taurine and cystine concentrations in patients given intravenous GSH

	Before operation	End of operation	the 1st post-operative day	the 2nd post-operative day
Case 1 (GSH 9.0g)				
Taurine ($mg \cdot dl^{-1}$)	2.1	0.9	0.5	0.7
Cystine ($mg \cdot dl^{-1}$)	1.9	3.7	0.8	1.6
Case 2 (GSH 2.4g)				
Taurine ($mg \cdot dl^{-1}$)	1.2	1.2	0.8	0.7
Cystine ($mg \cdot dl^{-1}$)	2.9	3.4	1.3	2.0

post-operative day, the lowest values observed in this examination. There was no difference in the pre-operative concentrations of plasma taurine between those patients with and without ischemic heart diseases (not shown).

In another part of the study, two patients were given GSH prior to CPB (table 2). Nine and 2.4g of GSH were administered intravenously in case 1 and in case 2, respectively. Although the plasma cystine concentrations at the end of surgery seemed to be higher than the pre-operative values in these two patients, there were no differences in the plasma concentrations of taurine and cystine at the 1st and the 2nd post-operative day between the patients who were and were not given GSH.

Discussion

Taurine concentrations in plasma were shown to decrease through 2POD after cardiac surgery using CPB, while total amino acid concentrations were gradually recovering towards its pre-operative value. Cystine, an oxidized form of cysteine which is a precursor of taurine, also decreased through the 2nd post-operative day. The ranges of plasma taurine and cystine concentrations in fasting, normal adults are 0.15–2.35 and 0.40–1.39 $mg \cdot dl^{-1}$, respectively. In contrast, Lombardini and Bricker did not find any changes in the plasma taurine concentrations until the 2nd post-operative day after CABG[6]. They, however, observed a post-operative increase of 50 to 80% in taurine concentrations in whole blood, and speculated that cellular components of the blood sequestered plasma taurine. A possible sequestration of plasma taurine was also reported in patients with an acute myocardial infarction, whose plasma taurine remained unchanged in spite of the increased taurine concentrations in whole blood[7]. Because human leukocytes and platelets, but not erythrocytes, contain taurine at high concentrations, blood cells seem to be able to sequester plasma taurine[8]. It might be possible that the activated leukocytes require much more taurine to scavenge chlorinated oxidants[8]. The involvement of leukocytes in the pathogenesis of reperfusion injury in the myocardium has been established[9,10]. At the end of the operations, the plasma concentrations of taurine and cystine remained unchanged, although the total concentration of all amino acids reached its minimum value. This suggests a possible influx of taurine and cystine into plasma at this time. A sequestration of plasma taurine into blood cells, whether it does occur or not, does not seem the sole mechanism for the post-operative progressive decline in the plasma taurine and

cystine concentrations in our patients. An increased demand for taurine in the ischemic myocardium can also account for our observations. The other possibility is an increase in urinary excretion of taurine. The shortage of nutritional intake until the 2nd post-operative day might also affect the taurine and cystine concentrations in plasma. The post-operative recovery of total amino acid concentration in plasma was probably due to the accelerated breakdown of muscle proteins induced by surgical stress and nutritional deficiency. Taurine and cysteine might have roles other than fuels, or might have a different turnover rate. A simple hemodilution due to CPB prime seemed to be ruled out because of its progressive decline through the 2nd post-operative day.

In the ischemic myocardium, taurine concentrations have been shown to be low[1]. Furthermore, the administration of taurine has been shown to improve cardiac functions in animals with induced myocardial ischemia[1] and in patients with congestive heart failure[11]. These facts and our results suggest the possibility that low concentrations of plasma taurine after CPB suppress cardiac functions, and that supplementary taurine, and also cysteine or GSH, improve the low output state after CPB and reduce the requirement for catecholamines which cause arrhythmias and damage the myocardium. Taurine and cysteine are also expected to reduce reperfusion injury in the heart due to their free radical scavenging properties[12].

GSH, γ-glutamyl-cysteinyl-glycine, plays important roles in protection against free radical injury as well as in detoxification of xenobiotics. The administration of GSH has been expected to ameliorate reperfusion injury in the myocardium, and Amano et al. demonstrated that GSH at a dose of 200 $mg \cdot kg^{-1}$ has been shown to reduce CPB-induced myocardial injury judged by creatine phosphokinase and mitochondrial aspartate aminotransferase activities in sera[13]. The administration of GSH was associated with an increase in the plasma concentrations of its constituent amino acid, cysteine (table 2); the increased supply of cysteine was expected to increase the plasma taurine concentration. However, no such increase occurred in our patients who were given GSH. It may be that the dosage of GSH used might have been insufficient to replenish supplies of taurine. A continuous infusion rather than a single bolus administration of GSH may be necessary to maintain the plasma concentrations of cysteine to facilitate its utilization. The effects of GSH administration on cardiac functions after CPB and on plasma taurine concentrations should be further investigated.

The therapeutic effects of branched chain amino acids on myocardial dysfunctions induced by ischemia have been demonstrated in animal experiments[14]. An addition of glutamate to cardioplegic solution and an intravenous infusion of glutamate have been shown to improve cardiac functions in patients undergoing CABG and in those with post-operative cardiac failure, respectively[15,16]. Ornithine, aspartate and arginine also enhance the recovery of ischemic myocardium in the rabbit[14]. The beneficial effects of these amino acids on the myocardium may be due to their abilities to serve as fuels, to promote protein synthesis and to inhibit protein degradation. Although the exact dynamic changes in these amino acids in plasma and in the myocardium after cardiac surgery using CPB have not been elucidated, maintaining the plasma concentrations of amino acids during peri-operative periods seems essential to reduce the risk of heart failure and to promote early discharge.

The effects of supplementary taurine or GSH in patients undergoing cardiac surgery seem to be worth while studying in more detail. Although the plasma amino acid concentrations do not necessarily reflect intracellular aminio acid concentrations, Franconi et al. reported a linear relationship between extracellular and intracellular taurine concentrations in guinea pig ventricular strips[5]. Because the rate of turnover of taurine in the heart was reported to be very slow[17], a pre-operative oral administration of taurine might be required to maintain taurine concentrations in the myocardium which is likely to become ischemic.

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