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Glutamine Is Cardioprotective in Patients with Ischemic Heart Disease following Cardiopulmonary Bypass

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ABSTRACT

Background: The aim of the present study was to investigate the cardioprotective effects of the perioperative use of N(2)-L-alanyl-L-glutamine (GLN) in patients with ischemic heart disease (IHD) who undergo their operations under cardiopulmonary bypass (CPB).

Methods: This double-blind, placebo-controlled, randomized study included 50 patients who underwent cardiac surgery with CPB. Exclusion criteria were a left ventricular ejection fraction <50%, diabetes mellitus, <3 months since the onset of myocardial infarction, and emergency surgery. Patients in the study group (n = 25) received 0.4 g/kg GLN (Dipeptiven, 20% solution) per day. Patients in the control group (n = 25) were administered a placebo (0.9% NaCl). The primary end point was the dynamics of troponin I at the following stages: (1) prior to anesthesia, (2) 30 minutes after CPB, (3) 6 hours after CPB, (4) 24 hours after surgery, and (5) 48 hours after surgery. Secondary end points included measurements of hemodynamics with a Swan-Ganz catheter.

Results: On the first postoperative day after the surgery, the median troponin I level was significantly lower in the study group than in the placebo group: 1.280 ng/mL (interquartile range [IQR], 0.840-2.230 ng/mL) versus 2.410 ng/mL (IQR, 1.060-6.600 ng/mL) (P = .035). At 4 hours after cardiopulmonary bypass (CPB), the median cardiac index was higher in the patients in the study group: 2.58 L/min per m^2 (IQR, 2.34-2.91 L/min per m^2) versus 2.03 L/min per m^2 (IQR, 1.76-2.32 L/min per m^2) (P = .002). The median stroke index also was higher in the patients who received GLN: 32.8 mL/m^2 (IQR, 27.8-36.0 mL/m^2) versus 26.1 mL/m^2 (IQR, 22.6-31.8 mL/m^2) (P = .023). The median systemic vascular resistance index was significantly lower in the study group than in the placebo group: 1942 dyn·s/cm^5 per m^2 (IQR, 1828-2209 dyn·s/cm^5 per m^2) versus 2456 dyn·s/cm^5 per m^2 (IQR, 2400-3265 dyn·s/cm^5 per m^2) (P = .001).

Conclusion: Perioperative administration of GLN during the first 24 hours has cardioprotective effects in IHD patients following CPB. This technique enhances the troponin concentration at 24 hours after surgery and is associated with improved myocardial function.

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INTRODUCTION

Protection of the myocardium following ischemia and reperfusion injury is crucial in the perioperative management of patients after cardiopulmonary bypass (CPB). Despite improvements in surgical techniques, including the use of cardioplegia, anesthesia, and cardiac arrest, the risk of myocardial damage is directly associated with coronary microcirculation disturbances, apoptosis, and inflammation [Murphy 2004].

Glutamine is the most common essential amino acid in the body and exhibits a number of nonnutritive effects [Roth 2008]. Reduced plasma levels of glutamine are observed in various emergency conditions, including multiple trauma, sepsis [Roth 1982], and surgical interventions [Parry-Billings 1992]. In cardiac patients, intracellular myocardial glutamine concentrations are reduced regardless of the cardioplegic technique used [Suleiman 1997]. Moreover, low glutamine levels are associated with unfavorable clinical outcomes [Oudemans-van Straaten 2001].

Numerous experimental and clinical trials have demonstrated the cardioprotective effects of glutamine, including dose-dependent enhanced myocardial functional recovery following acute normothermal ischemia in the rat [Khogali 1998]. Glutamine has also been shown to reduce infarct size to approximately 39% in a rabbit model following ischemia/reperfusion injury [McGuinness 2008]. Glutamine treatment also increased load tolerance in patients with ischemic heart disease (IHD) [Khogali 2002].

Despite the varied experimental data showing the cardioprotective effects of glutamine, there is a lack of clinical trials with post-CPB patients. Therefore, the goal of the present study was to investigate the cardioprotective effects of the perioperative use of N(2)-L-alanyl-L-glutamine (GLN) in patients with IHD after CPB.

MATERIALS AND METHODS

This double-blind, placebo-controlled, randomized study was approved by the Ethics Committee at our local hospital.

Table 1. Baseline Characteristics of the Patients*

	GLN Group (n = 25)	Control Group (n = 25)	*P*
Age, y	61 (54-63)	58 (57-62)	.593
Female sex, n	3 (12%, 2%-31%)	5 (20%, 7%-41%)	.702
Body mass index, kg/m^2	30.6 (30.1-34.2)	31.5 (28-34)	.628
NYHA class	2.5 (0.5)	2.5 (0.9)	1.000
Myocardial infarction, n	16 (64%, 42%-82%)	20 (80%, 59%-93%)	.345
Left ventricular ejection fraction, %	62.6 (5.4)	59.9 (8.2)	.173
EuroSCORE	3.36 (1.95)	3.64 (2.08)	.626
Coronary grafts, n			.735
1 Graft	1 (4%, 0.1%-20%)	2 (8%, 1%-26%)	
2 Grafts	9 (36%, 18%-57%)	7 (28%, 12%-49%)	
3 Grafts	15 (60%, 39%-79%)	16 (64%, 42%-82%)	
Endarterectomy, n	4 (16%, 4%-36%)	7 (28%, 12%-49%)	.496
Cardiopulmonary bypass time, min	55 (45-78)	52 (45-62)	.587
Aortic cross-clamp time, min	35 (28-47)	32 (27-43)	.449

*Results are presented as the mean (SD), the median (interquartile range), or the number of patients (percentage, 95% confidence interval). GLN indicates N(2)-L-alanyl-L-glutamine; NYHA, New York Heart Association.

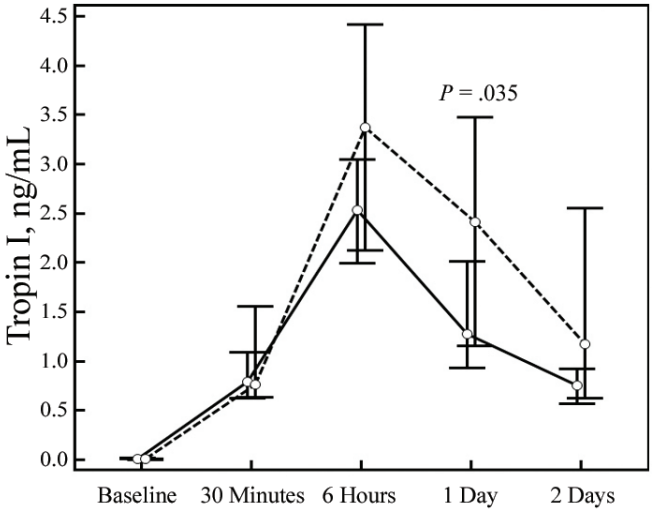

Figure 1. Troponin I concentrations in the N(2)-L-alanyl-L-glutamine (GLN) group (solid line) and the placebo group (dashed line) at baseline and at times after cardiopulmonary bypass. The increase in troponin I concentration was significantly less (*P* = .035) in patients who received GLN during the first postoperative day. Data are expressed as the median and the 95% confidence interval for the median.

Fifty patients with a diagnosis of IHD who underwent cardiac surgery with CPB between December 2009 and November 2010 were included in this study. Medical records were collected and organized in a standardized fashion with Excel (Microsoft, Redmond, WA, USA). Randomization was performed via sealed envelopes after written and informed consent was obtained from all patients. Exclusion criteria included the following: a left ventricular ejection fraction <50%, diabetes mellitus, <3 months since the onset of myocardial infarction, and emergency surgery. Patients in the study group (n = 25) received a 20% solution of GLN (Dipeptiven, 0.4 g/kg per day; Fresenius Kabi, Bad Homburg, Germany). Patients in the control group (n = 25) were administered a placebo (0.9% NaCl via a central venous catheter 24 hours after central vein catheterization). The infusion rate (in milliliters per hour) was calculated according to the following formula: (2 mL × body weight)/24. Solutions for infusion were prepared by an independent pharmacist. Pulmonary artery catheterization was performed with a Swan-Ganz catheter.

Demographic data and perioperative and postoperative follow-up characteristics were analyzed. All patients were evaluated according to the EuroSCORE risk-stratification model. The primary end point was the dynamics of troponin I. Blood sampling was performed to obtain serum at the following times: (1) prior to anesthesia, (2) 30 minutes after CPB, (3) 6 hours after CPB, (4) 24 hours after surgery, and (5) 48 hours after surgery. Blood samples were immediately centrifuged and kept frozen (–80°C) prior to testing. Troponin I levels were measured with an enzyme immunoassay kit (Troponin I ELISA; Biomerica, Irvine, CA, USA) and assessed via an automated analyzer (ELx808 Absorbance Microplate Reader; BioTek, Winooski, VT, USA).

Secondary end points included the following hemodynamic variables: heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, pulmonary artery wedge pressure, cardiac index, stroke index, and systemic vascular resistance index (SVRI). These measurements were taken at the following times: (1) after anesthesia induction, (2) immediately before the institution of CPB, (3) 5 minutes after CPB, (4) 30 minutes after CPB, (5) 2 hours after CPB, (6) 4 hours after CPB, (7) 6 hours after CPB, and (8) 24 hours after surgery.

We also analyzed several other postoperative follow-up characteristics, including mortality, ventilation time, frequency of inotropic support, readmission to the intensive care unit (ICU), and durations of ICU and hospital stays. Mortality was defined as death in the hospital. Ventilation time was defined as the period between admission to the postoperative unit and extubation. Inotropic support was defined as a requirement for infusion of an inotrope or vasopressor (dopamine, adrenaline, dobutamine, noradrenaline, Mesatone) equivalent to dopamine dosages (>5 μg/kg per minute) or their combination not less than 6 hours after surgery.

CPB and coronary artery bypass grafting were performed in all of the patient operations. Surgeries were performed with standard anesthesia procedures and techniques. Patients received benzodiazepine premedication and beta-blockers until the day of the surgery. Induction was performed with midazolam, fentanyl, and pipecuronium bromide. Anesthesia before and after CPB was maintained by sevoflurane inhalation in combination with fentanyl. Propofol was used

Table 2. Hemodynamic Measurements*

			Time after CPB						
	n	Baseline	Before CPB	5 min	30 min	2 h	4 h	6 h	Postoperative day 1
HR, beats/min									
GLN	25	54 (48-60)	61 (57-70)	70 (68-82)	71 (70-79)	80 (77-89)	80 (70-89)	82 (71-89)	80 (76-91)
Control	25	52 (49-65)	69 (56-74)	75 (69-91)	80 (70-92)	80 (68-96)	73 (62-94)	76 (66-91)	82 (67-88)
MAP, mm Hg									
GLN	25	77 (75-81)	87 (75-92)	79 (68-85)	78 (69-81)	80 (73-89)	77 (72-81)	79 (68-82)	81 (74-91)
Control	25	78 (67-92)	82 (79-90)	76 (70-87)	78 (72-81)	78 (63-86)	73 (67-82)	76 (67-83)	83 (77-91)
CVP, mm Hg									
GLN	25	9 (7-12)	7 (6-10)	11 (7-12)	10 (9-11)	9 (6-11)	12 (11-12)	10 (8-12)	12 (8-14)
Control	25	10 (7-12)	8 (7-9)	8 (7-9)	8 (7-11)	9 (6-11)	10 (6-13)	10 (6-11)	9 (5-12)
PAP, mm Hg									
GLN	25	16 (14-19)	17 (13-19)	20 (18-21)	18 (16-19)	16 (15-20)	19 (17-22)	18 (16-20)	22 (20-25)
Control	25	17 (14-18)	16 (15-19)	19 (16-22)	19 (16-22)	17 (14-19)	18 (14-21)	19 (15-20)	22 (17-24)
PWP, mm Hg									
GLN	25	13 (11-15)	11 (9-16)	14 (13-16)	13 (11-15)	11 (10-13)	13 (11-15)	12 (10-14)	14 (13-16)
Control	25	11 (10-13)	14 (10-14)	14 (12-14)	14 (10-15)	11 (9-13)	11 (8-14)	12 (8-15)	13 (9-16)
Cardiac index, L/min per m^2									
GLN	25	1.7 (1.4-1.9)	2.1 (1.6-2.6)	3.1 (2.7-3.4)	2.2 (2.1-2.7)	2.2 (2.1-2.5)	2.6 (2.3-2.9)	2.6 (2.1-2.7)	2.3 (1.8-2.7)
Control	25	1.7 (1.4-1.9)	1.9 (1.7-2.5)	2.9 (2.6-3.2)	2.3 (1.9-2.6)	1.9 (1.6-2.4)	2.0 (1.8-2.3)	2.1 (2.0-2.4)	2.26 (1.9-2.4)
							P = .002*		
SI, mL/m^2									
GLN	25	31.4 (27.1-36.1)	34.3 (31.0-37.4)	43.7 (35.7-46.6)	29.6 (26.9-38.4)	27.9 (24.0-32.6)	32.8 (27.8-36.0)	32.6 (28.3-34.7)	28.2 (22.8-30.9)
Control	25	30.9 (25.1-38.3)	31.4 (26.4-34.3)	35.9 (31.8-41.4)	27.4 (24.3-30.7)	26.3 (21.4-28.6)	26.1 (22.6-31.8)	27.0 (25.5-36.0)	28.1 (24.9-31.6)
							P = .023*		
SVRI, dyn·s/cm^5 per m^2									
GLN	25	3295 (2760-3878)	2575 (2314-3498)	1815 (1565-1917)	2339 (2047-2746)	2285 (1973-2903)	1942 (1828-2209)	2020 (1806-2574)	2261 (2161-2905)
Control	25	3140 (2591-4184)	3097 (2312-3478)	1895 (1629-2132)	2474 (2027-2718)	2854 (2376-3032)	2456 (2400-3265)	2490 (2160-2790)	2751 (2455-2867)
							P = .001*		

*Results are presented as the median (interquartile range). *P* values for significant differences between the 2 groups (Mann-Whitney *U* test) are indicated in boldface. CPB indicates cardiopulmonary bypass; HR, heart rate; GLN, N(2)-L-alanyl-L-glutamine; MAP, mean arterial pressure; CVP, central venous pressure; PAP, pulmonary artery pressure; PWP, pulmonary wedge pressure; SI, stroke index; SVRI, systemic vascular resistance index.

during CPB. A full medial sternotomy was performed in all patients, and CPB at systemic heparinization was begun after cannulation of the right atrium and ascending aorta. The normothermic (35.5°C-36.5°C) CPB flow rate was maintained at 2.5 L/min per m^2, and the systemic pressure was kept between 60 and 90 mm Hg. Myocardial protection was achieved with antegrade crystalloid cardioplegia solution at 4°C. All patients were admitted to the ICU following surgery. Ventilator weaning was performed when the patient had stable hemodynamics, no hemorrhagic signs, and adequate homeostatic rates.

Parametric quantitative data are presented as the mean (SD); nonparametric data are presented as the median (interquartile range [IQR]). Quantitative characteristics are described as the number (percentage); for binary characteristics, a 95% confidence interval was used.

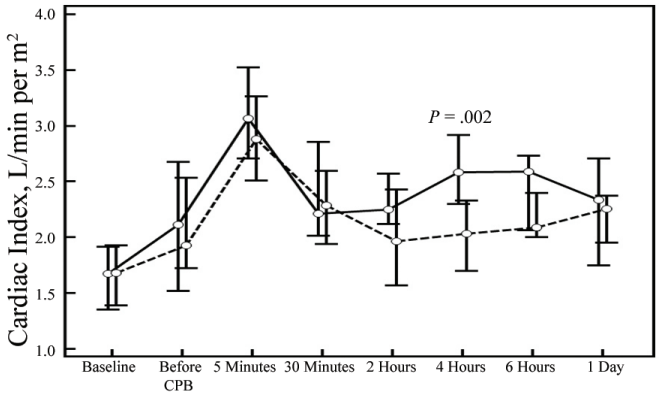

Figure 2. Cardiac index values in the N(2)-L-alanyl-L-glutamine (GLN) group (solid line) and the placebo group (dashed line) at baseline and at various times after cardiopulmonary bypass. The cardiac index was significantly higher (P = .002) in patients who received GLN at 4 hours after cardiopulmonary bypass. Data are expressed as the median and the 95% confidence interval for the median.

Comparative analyses of parametric characteristics were performed via the independent-samples Student t test. Comparative analyses of nonparametric characteristics were performed with the Mann-Whitney U test. Comparative analyses of qualitative characteristics were performed with the Fisher exact test. The criterion for statistical significance for all statistical analyses was a type I error equal to .05. Null hypotheses were rejected if the probability (P) did not exceed the type I error. Statistical analyses were conducted according to standard methods [Zar 2010] with Stata software (version 11.1; StataCorp, College Station, TX, USA).

RESULTS

The patients in the 2 groups were comparable with respect to the following baseline characteristics: sex, age, and initial severity of cardiovascular pathology (Table 1). The baseline troponin I concentrations in the 2 groups were not significantly different. Significant increases in the troponin I concentration were observed in both groups at various times. Following surgery, the median troponin I level was 0.788 ng/mL (IQR, 0.590-1.230 ng/mL) in the study group and 0.760 ng/mL (IQR, 0.580-1.740) in the placebo group (P = .854). The highest troponin I levels were observed at 6 hours after CPB: median, 2.535 ng/mL (IQR, 1.880-3.355 ng/mL) in the study group and 3.375 ng/mL (IQR, 1.945-4.890 ng/mL) in the placebo group (P = .257). Significant batch-to-batch variations were observed 24 hours after surgery. At this stage, the median troponin I level was significantly lower in the study group than in the placebo group: 1.280 ng/mL (IQR, 0.840-2.230 ng/mL) versus 2.410 ng/mL (IQR, 1.060-6.600 ng/mL) (P = .035). By 48 hours after surgery, the difference between the 2 groups in the troponin I concentration was not statistically significant (Figure 1).

The patients in the study group maintained higher rates of myocardial function (Table 2). Four hours after CPB, the median cardiac index was higher in the patients in the study group: 2.58 L/min per m^2 (IQR, 2.34-2.91 L/min per m^2) versus 2.03 L/min per m^2 (IQR, 1.76-2.32 L/min per m^2) (P = .002, Figure 2). Similarly, the median stroke index was higher in the patients receiving GLN: 32.8 mL/m^2 (IQR, 27.8-36.0 mL/m^2) versus 26.1 mL/m^2 (IQR, 22.6-31.8 mL/m^2) (P = .023). The median SVRI, however, was significantly lower in the study group than in the placebo group: 1942 dyn·s/cm^5 per m^2 (IQR, 1828-2209 dyn·s/cm^5 per m^2) versus 2456 dyn·s/cm^5 per m^2 (IQR, 2400-3265 dyn·s/cm^5 per m^2) (P = .001).

Table 3. Postoperative Complications and Clinical Course*

	GLN Group (n = 25)	Control Group (n = 25)	P
Ventilation time, h	5 (4-7)	6 (5-8)	.776
Inotropic support, n	5 (20%, 7%-41%)	4 (16%, 4%-36%)	1.000
Readmission to ICU, n	0	4 (16%, 4%-36%)	.109
ICU stay, d	1 (1-2)	1 (1-2)	.621

*Results are presented as the median (interquartile range) or the number of patients (percentage, 95% confidence interval). GLN indicates N(2)-L-alanyl-L-glutamine; ICU, intensive care unit.

No significant differences between the 2 groups with respect to postoperative follow-up or mortality were observed (Table 3).

DISCUSSION

Perioperative administration of 0.4 g/kg GLN per day contributes to a reduction in myocardial damage in patients who undergo coronary artery bypass grafting with CPB. Lower troponin I concentrations in patients receiving GLN are associated with higher rates of myocardial function (cardiac index, stroke index) and lower vascular tone (SVRI).

Numerous mechanisms for the cardioprotective effects of glutamine have been described. Glutamine is an indirect precursor of glutathione (GSH) and is involved in antioxidant protection [Roth 2002] by increasing the ratio of reduced to oxidized GSH [Khogali 1998]. The correlation between the perioperative use of glutamine and plasma GSH concentrations in patients after CPB has previously been shown [Engel 2009].

Moreover, in cases of ischemia/reperfusion injury, glutamine increases the myocardial ATP/ADP ratio and prevents intracellular lactate accumulation [Wischmeyer 2003]. Glutamine is essential for glutamine–fructose-6-phosphate amidotransferase (GFAT) in regulating glucose metabolism during the hexosamine biosynthesis pathway. Up-regulated glucose metabolism through the hexosamine biosynthesis pathway increases O-linked N-acetyl-glucosamine (O-GlcNAc) actions on nucleocytoplasmic proteins and has been shown to be cardioprotective [Liu 2007]. O-GlcNAc modulates the actions of insulin, mitogen-activated protein kinase, and protein kinase C [Vosseller 2002]. All of these pathways are involved in ischemic cardioprotection [Murphy 2004].

The cardioprotective effects of glutamine also include the induction of heat shock protein (HSP) expression (HSP-70) by activating heat shock factor 1 [Morrison 2006]. Hayashi et

al [2002] observed that preoperative administration of glutamine in rats undergoing CPB induced HSP-70 expression and reduced the inflammatory response by stimulating nitric oxide synthase activity. All of these mechanisms are involved in the cardioprotective effects of glutamine; however, further prospective clinical studies are warranted.

Increased troponin I concentrations are evident in patients who undergo operations with CPB. Inadequate myocardial protection, surgical interventions, and reperfusion are the most significant among these mechanisms [Takeda 2002]. A close correlation between the troponin I concentration and mortality during the postoperative follow-up has been recognized [Lurati Buse 2010]. In the present study, lower troponin I levels in patients who received GLN were associated with more positive values with respect to central hemodynamic characteristics. The absence of significant batch-to-batch variation in heart rate compared with improvements in the cardiac index, the stroke index, and SVRI in the patients who received GLN provides evidence of the improved inotropic myocardial function in this group.

The present study has numerous limitations that must be addressed. There was no opportunity to identify clinical differences during the follow-up period because of the small number of patients. We did not study all of the mechanisms involved in the cardioprotective effects of GLN. Thus, it may be interesting to evaluate whether a correlation exists between GLN administration and myocardial HSP expression at various stages of the perioperative period; however, such studies are difficult to perform in the clinical setting. Moreover, we administered GLN parenterally during the first 24 hours following surgery. Thus, this study did not answer the question of the feasibility of using GLN during the preoperative period and did not address methods of drug administration. Furthermore, because we excluded compromised patients with diabetes mellitus and those with a decreased left ventricular ejection fraction from the present study, these data cannot be extrapolated to these categories of patients. Our study involved only uncomplicated IHD patients who underwent their operations with a short period of CPB. Because the degree of myocardial damage is directly related to the length of CPB, further investigations into the cardioprotective effects of GLN in more severe cases could be interesting.

In conclusion, perioperative administration of GLN during the first 24 hours has cardioprotective effects in IHD patients following CPB. This technique enhances the troponin I concentration at 24 hours after surgery and is associated with improved myocardial function.

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REFERENCES

Engel JM, Mühling J, Kwapisz M, Heidt M. 2009. Glutamine administration in patients undergoing cardiac surgery and the influence on blood glutathione levels. Acta Anaesthesiol Scand 53:1317-23.

Hayashi Y, Sawa Y, Fukuyama N, Nakazawa H, Matsuda H. 2002. Preoperative glutamine administration induces heat-shock protein 70 expression and attenuates cardiopulmonary bypass-induced inflammatory response by regulating nitric oxide synthase activity. Circulation 106:2601-7.

Khogali SE, Harper AA, Lyall JA, Rennie MJ. 1998. Effects of L-glutamine on post-ischaemic cardiac function: protection and rescue. J Mol Cell Cardiol 30:819-27.

Khogali SE, Pringle SD, Weryk BV, Rennie MJ. 2002. Is glutamine beneficial in ischemic heart disease? Nutrition 18:123-6.

Liu J, Marchase RB, Chatham JC. 2007. Glutamine-induced protection of isolated rat heart from ischemia/reperfusion injury is mediated via the hexosamine biosynthesis pathway and increased protein O-GlcNAc levels. J Mol Cell Cardiol 42:177-85.

Lurati Buse GA, Koller MT, Grapow M, Bolliger D, Seeberger M, Filipovic M. 2010. The prognostic value of troponin release after adult cardiac surgery—a metaanalysis. Eur J Cardiothorac Surg 37:399-406.

McGuinness J, Neilan TG, Cummins R, Sharkasi A, Bouchier-Hayes D, Redmond JM. 2009. Intravenous glutamine enhances COX-2 activity giving cardioprotection. J Surg Res 152:140-7.

Morrison AL, Dinges M, Singleton KD, Odoms K, Wong HR, Wischmeyer PE. 2006. Glutamine's protection against cellular injury is dependent on heat shock factor-1. Am J Physiol Cell Physiol 290:C1625-32.

Murphy E. 2004. Primary and secondary signaling pathways in early preconditioning that converge on the mitochondria to produce cardioprotection. Circ Res 94:7-16.

Murphy GJ, Angelini GD. 2004. Side effects of cardiopulmonary bypass: What is the reality? J Card Surg 19:481-8.

Oudemans-van Straaten HM, Bosman RJ, Treskes M, van der Spoel HJ, Zandstra DF. 2001. Plasma glutamine depletion and patient outcome in acute ICU admissions. Intensive Care Med 27:84-90.

Parry-Billings M, Baigrie RJ, Lamont PM, Morris PJ, Newsholme EA. 1992. Effects of major and minor surgery on plasma glutamine and cytokine levels. Arch Surg 127:1237-40.

Roth E, Funovics J, Muhlbacher F, et al. 1982. Metabolic disorders in severe abdominal sepsis: glutamine deficiency in skeletal muscle. Clin Nutr 1:25-41.

Roth E, Oehler R, Manhart N, et al. 2002. Regulative potential of glutamine—relation to glutathione metabolism. Nutrition 18:217-21.

Roth E. 2008. Nonnutritive effects of glutamine. J Nutr 138:2025S-31S.

Suleiman MS, Moffatt AC, Dihmis WC, et al. 1997. Effect of ischaemia and reperfusion on the intracellular concentration of taurine and glutamine in the hearts of patients undergoing coronary artery surgery. Biochim Biophys Acta 1324:223-31.

Takeda S, Nakanishi K, Ikezaki H, et al. 2002. Cardiac marker responses to coronary artery bypass graft surgery with cardiopulmonary bypass and aortic cross-clamping. J Cardiothorac Vasc Anesth 16:421-5.

Vosseller K, Sakabe K, Wells L, Hart GW. 2002. Diverse regulation of protein function by O-GlcNAc: a nuclear and cytoplasmic carbohydrate posttranslational modification. Curr Opin Chem Biol 6:851-7.

Wischmeyer PE, Van den Hoek TL, Li C, et al. 2003. Glutamine preserves cardiomyocyte viability and enhances recovery of contractile function after ischemia-reperfusion injury. J Parenter Enteral Nutr 27:116-22.

Zar JH. 2010. Biostatistical analysis. Upper Saddle River, NJ: Pearson Prentice-Hall. 960 p.