Altered protein metabolism following coronary artery bypass graft (CABG) surgery

Giuseppe CASO*, James A. VOSSWINKEL*, Peter J. GARLICK†, Mohamed K. BARRY*, Thomas V. BILFINGER* and Margaret A. MCNURLAN*

*Department of Surgery, Stony Brook University Medical Center, Stony Brook, NY 11794-8191, U.S.A., and †Department of Animal Sciences, University of Illinois, Urbana, IL 61801, U.S.A.

ABSTRACT

The aim of the present study was to investigate the acute effect of CABG (coronary artery bypass graft) surgery on the rates of synthesis of muscle protein, the positive acute-phase protein fibrinogen and the negative acute-phase protein albumin. Synthesis rates of muscle protein, fibrinogen and albumin were measured simultaneously before and 4 h after the end of surgery from the incorporation of L-[$^2H_5$]phenylalanine (given at 43 mg/kg of body weight) in 12 patients undergoing CABG surgery. Surgery was performed either with the use of extracorporeal circulation with cardiopulmonary bypass (on-pump; $n = 5$) or with the beating heart procedure without cardiopulmonary bypass (off-pump; $n = 7$). Post-surgical muscle protein fractional synthesis rates were decreased by 36 ± 6.5% compared with pre-surgical values (1.59 ± 0.10 compared with 0.97 ± 0.08%/day respectively; $P < 0.001$). In contrast, the synthesis rates of both fibrinogen (36 ± 4 compared with 100 ± 11 mg · day^{-1} · kg^{-1} of body weight; $P < 0.0001$) and albumin (123 ± 12 compared with 178 ± 19 mg · day^{-1} · kg^{-1} of body weight; $P < 0.001$) were both significantly increased after surgery. No significant differences were found between surgery performed with or without cardiopulmonary bypass. In conclusion, the results demonstrate that CABG surgery has a profound effect on protein metabolism, with a differential response of protein synthesis in muscle and liver.

INTRODUCTION

Surgical trauma is accompanied by accelerated protein catabolism with mobilization of amino acids [1]. Following surgery, the rate of protein synthesis is reduced in skeletal muscle [2–4], so amino acids are available for the synthesis of acute-phase proteins, such as fibrinogen. There is evidence that fibrinogen synthesis is elevated in injured patients [5,6], but the specific response of fibrinogen synthesis to surgical trauma has not been investigated. The effect of cardiac surgery on the synthesis of albumin, a negative-phase protein, has also not been clearly delineated. Although measurements in patients during elective cholecystectomy suggest a decrease [7,8], the response of albumin synthesis in the post-operative period has not been characterized.

Given that over 400000 CABG (coronary artery bypass graft) surgeries are performed annually in the U.S.A. [9], the aim of the present study was to assess the acute impact of CABG surgery on the synthesis of muscle and the acute-phase liver proteins fibrinogen and albumin. Synthesis rates of muscle protein and the plasma proteins fibrinogen and albumin were measured simultaneously before and 4 h following CABG surgery

Key words: albumin, cardiopulmonary bypass, coronary artery bypass graft (CABG), fibrinogen, muscle protein synthesis, stable isotope.

Abbreviations: AUC, area under the curve; BCAA, branched-chain amino acid; BMI, body mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; EAA, essential amino acid; EF, ejection fraction; FSR, fractional synthesis rate; IL-6, interleukin-6; NEAA, non-essential amino acid.

Correspondence: Dr Giuseppe Caso (email Giuseppe.Caso@stonybrook.edu).

from the incorporation of L-[$^2H_5$]phenylalanine [10–12]. The present study also aimed to assess whether CABG surgery with or without the use of CPB (cardiopulmonary bypass) had any differential effects on the metabolic response of protein synthesis to surgical trauma.

MATERIALS AND METHODS

Subjects and experimental design

A total of 12 patients with coronary artery disease and undergoing coronary revascularization participated in the study. All patients had unstable angina and were admitted to Stony Brook University Medical Center to undergo cardiac catheterization, followed by CABG for coronary stenosis $>50\%$. All patients were haemodynamically stable pre-operatively and were not affected by acute or chronic renal disease (creatinine plasma concentration <1.7 mg/dl) or had biochemical evidence of liver dysfunction. None of the patients were being treated or had a previous history of congestive heart failure. The average pre-operative EF (ejection fraction) was $49.1 \pm 2.3\%$.

In five patients, CABG surgery was performed with CPB (on-pump; $n=5$) whereas, in seven, surgery was performed with the 'beating heart' approach without the use of CPB (off-pump; $n=7$).

Anaesthesia consisted of a mixed technique using inhalational agents and fentanyl. Coronary revascularization was performed through a standard midline sternotomy in both groups. Standard aortic cannulation was used. Myocardial preservation was carried out with the application of antegrade and retrograde blood cardioplegia, and a cross-clamping of the aorta was used. Proximal anastomoses were constructed with the use of a side-biting clamp. Moderate hypothermia was used, the temperature ranging between 28 and 32 °C in the on-pump group. For the off-pump group, the temperature was maintained as close to 37.5 °C as possible. The Guidant^R stabilizer system was used in all off-pump cases.

Synthesis of muscle protein, fibrinogen and albumin was measured in all patients before and 4 h after completion of surgery with a flooding dose of L-[$^2H_5$]phenylalanine, as described previously (e.g. [10–13]). The first measurement was carried out post-absorptively on the morning of the surgery. Two lines were inserted into contralateral forearm veins, one to be used for injection of isotopically labelled amino acid and the other one for blood sampling. After taking a baseline blood sample, a sterile solution containing unlabelled L-phenylalanine (Ajinomoto) plus L-[$^2H_5$]phenylalanine (43 mg/kg of body weight; 10 mol %; Cambridge Isotope Laboratories) was injected over 10 min. Blood samples were then taken over 90 min to determine the enrichment of unlabelled phenylalanine and that of fibrinogen and albumin in plasma. At 90 min, following local anaesthesia, a biopsy of the vastus lateralis muscle was taken under sterile conditions using a trucut biopsy needle (Temno; Bauer Medicals). The measurement was repeated 4 h after surgery. The protocol of the second measurement was similar, except that a baseline muscle biopsy was also taken before isotope injection to assess the background enrichment of muscle protein, and that the enrichment of the injected solution was increased from 10 to 20 mol %.

Muscle biopsies were immediately frozen in liquid nitrogen and kept at -70 °C until analysis. Plasma and serum samples were aliquoted and stored at -70 °C until analysis.

In addition to assessment of the synthesis of muscle protein, fibrinogen and albumin, the plasma volume was also determined both before and after surgery with Indocyanine Green [14]. Indocyanine Green (IC-Green; Akorn Inc.) was given as a bolus injection 30 min after the administration of the labelled phenylalanine, followed by serial blood sampling to measure the concentration of Indocyanine Green in plasma. Plasma volume was calculated as described previously [14].

All subjects gave written informed consent, and the protocol was approved by the Stony Brook University Institutional Review Board.

Analytical methods

Enrichment of muscle protein, albumin and fibrinogen

Muscle protein synthesis rates were determined from the enrichment of the muscle-protein-bound phenylalanine following acid hydrolysis and plasma unlabelled phenylalanine, as described previously [12,13].

Fibrinogen was isolated from plasma by sequential ammonium sulfate precipitation, followed by solubilization in sodium citrate [11]. Albumin was isolated from plasma samples after precipitation with trichloroacetic acid, followed by differential solubility in ethanol, as described previously [10,15,16]. The purity of the isolated albumin was confirmed by SDS/PAGE (10 % gel) and visualized by Coomassie Blue staining, as shown in Figure 1.

Protein enrichments were determined following acid hydrolysis by monitoring ions with m/z 106 ($m+2$) and 109 ($m+5$) of the n-heptafluorobutyryl derivative of β-phenylethylamine on a MD800 GCMS (gas chromatograph mass spectrometer) (Fisons Instruments), operated under electron impact conditions and in spit mode [12,13,17].

Enrichment of plasma phenylalanine

Plasma unlabelled phenylalanine was purified by cation-exchange chromatography and derivatized to the tertiary butyldimethylsilyl derivative. Following electron impact, the ions at m/z 336 and 341 were monitored (MD800 GCMS) [13,17].

Calculations

The rate of muscle protein synthesis [FSR (fractional synthesis rate)], expressed as a proportion of muscle

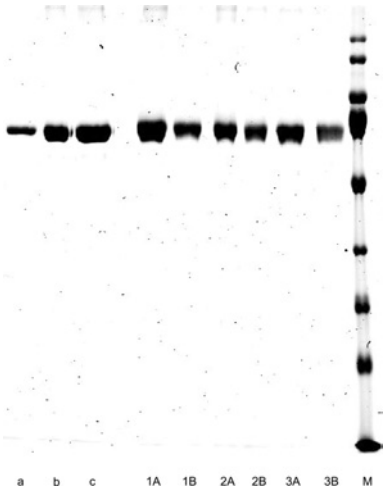

Figure 1 Coomassie Blue staining of albumin standards and albumin isolated from the plasma of three study subjects before (A) and after (B) surgery

Proteins were stained with Coomassie Blue following separation by SDS/PAGE. Lanes a–c, albumin standards of 1, 2.5 and 5 μg respectively; lane M, molecular-mass markers.

protein, was calculated with the formula [12,13,17]:

$$\text{FSR}\,(\%/\text{day}) = (\text{Ep1} - \text{Ep0})/\text{A} \times 100$$

where Ep1−Ep0 is the increase in enrichment in protein, and A indicates the AUC (area under the curve) of the plasma unlabelled phenylalanine enrichment (precursor pool) over the 90 min incorporation time.

The FSRs of fibrinogen and albumin, expressed as a proportion of their respective intravascular protein pools, were calculated similarly from the increase in the protein-bound phenylalanine enrichment (between 50 and 90 min) and the AUC of the corresponding unlabelled plasma phenylalanine enrichment by time curve [10,11,15,16].

The ASRs (absolute synthesis rates) of albumin and fibrinogen (i.e. the total amount of protein synthesized/day) were calculated by multiplying the FSR by the intravascular mass of either fibrinogen or albumin. Intravascular mass of either fibrinogen or albumin were obtained from the plasma volume and plasma concentrations of the respective proteins.

Other analytical procedures

Plasma fibrinogen, albumin, IL-6 (interleukin-6) and amino acid concentrations were measured in baseline samples collected before and 4 h after the end of surgery. Fibrinogen concentrations were determined using an ACL Advance/Futura coagulometer (Instrumentation Laboratory) [18]. Albumin concentrations were measured with an automated Bromocresol Green method [19]. IL-6 was assayed by ELISA (Linco Research), and plasma amino acid concentrations were measured by HPLC, as described previously [12,20].

Table 1 Anthropometric and intra-operative characteristics of all the patients, or when grouped depending on whether surgery was performed with (on-pump) or without (off-pump) CPB

Values are means ± S.E.M. ACC, aortic cross-clamping; n/a, not applicable.

	All ($n = 12$)	On-pump ($n = 5$)	Off-pump ($n = 7$)
Age (years)	60 ± 3	65 ± 6	55 ± 3
Height (m)	1.76 ± 0.02	1.80 ± 0.03	1.72 ± 0.02
Weight (kg)	91 ± 4	92 ± 7	90 ± 4
BMI (kg/m^2)	29.5 ± 1.1	28.3 ± 1.9	30.4 ± 1.3
Gender (n) (male/female)	11/1	5/0	6/1
Preoperative EF (%)	49.1 ± 2.3	53 ± 1.2	46.4 ± 4.4
Duration of surgery (min)	212 ± 14	226 ± 24	203 ± 18
ACC duration (min)	n/a	98 ± 19	n/a
CPB duration (min)	n/a	132 ± 20	n/a
Grafts (n)	3.3 ± 0.3	3.4 ± 0.2	3.1 ± 0.4

Statistics

Values are expressed as means ± S.E.M. Comparisons between basal and post-surgical values in the same subject were analysed using a paired Student's t test. Comparisons between changes in values in patients operated with (on-pump) or without (off-pump) the use of CPB were performed using two-tailed unpaired Student's t tests. $P < 0.05$ was taken to be statistically significant.

RESULTS

The anthropometric and intra-operative characteristics of all of the patients ($n = 12$), including when subdivided depending on whether individuals underwent surgery with (on-pump; $n = 5$) or without the use of CPB (off-pump; $n = 7$), are shown in Table 1. The patients in the two groups were comparable for age and BMI (body mass index). There was no significant difference in the pre-operative EF, number of grafts each patient received or in the overall duration of the surgical procedure in the on-pump and off-pump groups. No patients required prolonged mechanical ventilation in the post-operative period, or developed an infection or any other significant complication. The post-surgical length of the hospital stay was 5.2 ± 0.3 days, which was comparable in the two groups.

The plasma concentration of IL-6 was undetectable in the pre-surgical samples in seven patients (three in the on-pump and four in the off-pump groups), but increased significantly 4 h after surgery (Table 2). No difference was detected in the post-surgical increase between the on-pump and off-pump groups (Table 2).

The plasma concentrations of NEAAs [non-essential amino acids (alanine, aspartate, asparagine, cysteine, glutamate, glutamine, glycine, serine and tyrosine)], EAAs [essential amino acids (histidine, isoleucine, leucine,

Table 2 Plasma fibrinogen, albumin, IL-6 and amino acid concentrations before and after surgery in all of the patients, or when grouped depending on whether surgery was performed with (on-pump) or without (off-pump) CPB

Values are means ± S.E.M. *$P < 0.05$ compared with pre-surgical values. †Change in concentration after surgery was significantly different from the on-pump group.

	All		On-pump		Off-pump	
	Pre	Post	Pre	Post	Pre	Post
Fibrinogen (g/l)	5.95 ± 0.50	5.04 ± 0.33*	6.26 ± 1.04	4.74 ± 0.52*	5.71 ± 0.51	5.25 ± 0.45
Albumin (g/l)	37.7 ± 0.8	31.7 ± 1.4*	36.4 ± 1.4	28.2 ± 1.7*	38.6 ± 0.8	34.1 ± 1.5*†
IL-6 (ng/l)	9.6 ± 3	107 ± 31*	7.5 ± 3.1	83 ± 37	11 ± 5	123 ± 48*
NEAAs (μmol/l)	1689 ± 67	1397 ± 70*	1681 ± 110	1395 ± 101	1694 ± 90	1375 ± 92
EAAs (μmol/l)	1060 ± 52	780 ± 36*	1070 ± 70	825 ± 62*	1056 ± 71	766 ± 41*
BCAAs (μmol/l)	426 ± 22	331 ± 17*	436 ± 24	361 ± 62*	430 ± 35	330 ± 24*

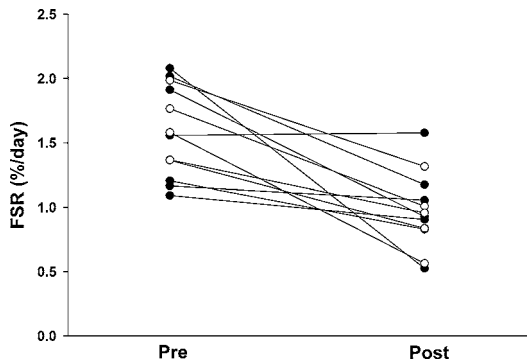

Figure 2 Individual changes in muscle protein FSRs before and after CABG surgery performed with (on-pump) or without (off-pump) CPB

(●) With CPB ($n = 5$); (○) without CPB ($n = 7$).

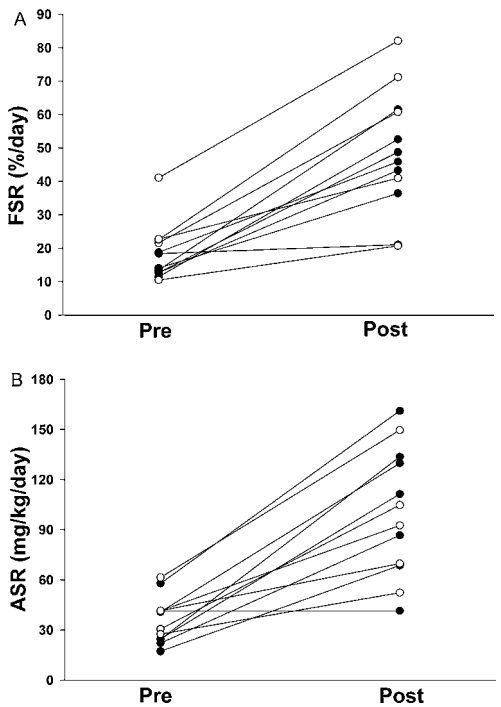

Figure 3 Individual changes in fibrinogen FSRs (A) and ASRs (B) before and after CABG surgery performed with (on-pump) or without (off-pump) CPB

(●) With CPB ($n = 5$); (○) without CPB ($n = 7$).

lysine, methionine, phenylalanine, threonine, tryptophan and valine)] and BCAAs [branched-chain amino acids (leucine, isoleucine and valine)] were decreased 17 ($P < 0.02$), 26 ($P < 0.001$) and 22 % ($P < 0.02$) respectively, following surgery (Table 2). The fall in plasma amino acid concentration was comparable in the on-pump and off-pump groups (Table 2).

Muscle protein synthesis

Rates of muscle protein synthesis (FSRs) decreased significantly following surgery (Figure 2). At 4 h after surgery, muscle FSR was 36 ± 6 % lower compared with pre-surgical values [1.59 ± 0.10 compared with 0.97 ± 0.08 %/day ($n = 12$); $P < 0.001$]. The muscle FSR decreased from 1.61 ± 0.12 to 0.94 ± 0.12 %/day in the on-pump group ($P < 0.005$), and from 1.58 ± 0.16 to 1.00 ± 0.12 %/day in the off-pump group ($P < 0.05$). No difference was detected in the depressive effect between the two surgical procedure (−42 ± 6 compared with −32 ± 10 %; P value was not significant).

Plasma protein synthesis

Plasma fibrinogen concentrations were significantly lower after surgery ($P < 0.02$; $n = 12$; Table 2). The magnitude of the decrease in concentration tended to be greater in the patients who underwent surgery with CPB (−20 ± 8 in the on-pump CPB compared with −9 ± 3 % in the off-pump CPB groups), although this difference did not reach statistical significance ($P = 0.1$; Table 2). The synthesis of fibrinogen was increased after surgery (Figure 3). When expressed as the FSR, fibrinogen synthesis was stimulated 186 ± 32 % [18.3 ± 2.4 compared with 48.8 ± 5.3 %/day ($n = 12$); $P < 0.005$; Figure 3A]. Fibrinogen FSR increased 135 ± 27 % (23.7 ± 4.9 compared with 55.1 ± 10.9 %/day; $P < 0.02$) in the on-pump group and by 223 ± 47 % (14.5 ± 1.1 compared with

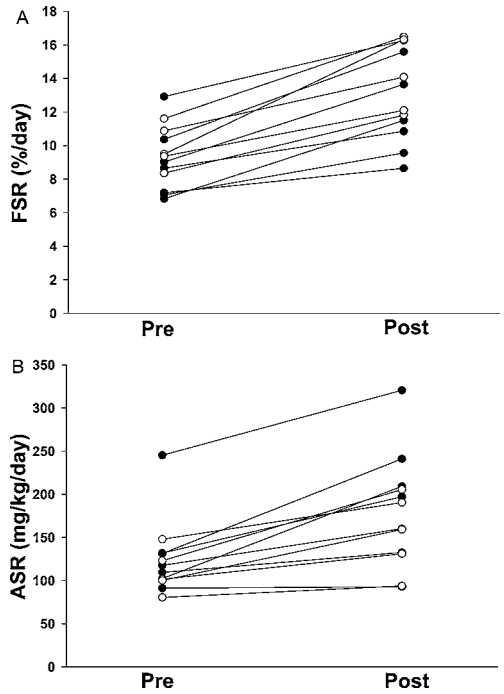

Figure 4 Individual changes in albumin FSRs (A) and ASRs (B) before and after CABG surgery performed with (on-pump) or without (off-pump) CPB

(●) With CPB ($n = 5$); (○) without CPB ($n = 7$).

44.0 ± 4.9 %/day; $P < 0.005$) in the off-pump group. Similarly, when fibrinogen was expressed as an ASR, synthesis was stimulated 204 ± 37 % in the post-operative period [35.9 ± 4.0 compared with 100.1 ± 11 mg · day^{-1} · kg^{-1} of body weight ($n = 12$); $P < 0.005$; Figure 3A]. The Fibrinogen ASR increased from 40.5 ± 5.9 to 93.8 ± 16.6 mg · day^{-1} · kg^{-1} of body weight ($P < 0.02$) after the on-pump procedure and from 32.6 ± 5.5 compared with 104.7 ± 15.7 mg · day^{-1} · kg^{-1} of body weight ($P < 0.01$) after the off-pump procedure. The percentage stimulation of fibrinogen synthesis was not significantly different following the on-pump and off-pump procedures, although there was a tendency for the increase in ASR to be higher in the off-pump group (+255 ± 54 compared with +133 ± 30 %; $P = 0.1$).

Plasma albumin concentrations decreased from 37.7 ± 0.8 to 31.7 ± 1.4 g/l following surgery ($P < 0.005$; Table 2), and declined more in the on-pump than in the off-pump group (−23 ± 3 compared with −12 ± 3 % respectively; $P < 0.02$; Table 2). However, despite a decrease in the plasma concentration of albumin, the synthesis of albumin was significantly increased in the post-surgical period (Figure 4). When expressed as the FSR, the synthesis of albumin increased 41 ± 5 % [9.31 ± 0.5 compared with 13.07 ± 0.8 %/day ($n = 12$); $P < 0.001$; Figure 4A]. The albumin FSR increased 43 ± 8 % in the on-pump group (from 9.94 ± 0.6 to 14.16 ± 1.0 %/day; $P < 0.005$) and 40 ± 7 % in the off-pump group (from 8.86 ± 0.8 to 12.29 ± 1.1 %/day; $P < 0.005$), with no significant difference between the patients undergoing the two surgical procedures. When expressed as the ASR, albumin synthesis also significantly increased from 123 ± 12 to 178 ± 19 mg · day^{-1} · kg^{-1} of body weight ($n = 12$; $P < 0.001$; Figure 4B). The albumin ASR was stimulated from 111 ± 12 to 156 ± 20 mg · day^{-1} · kg^{-1} of body weight in the on-pump group ($P < 0.05$) and from 132 ± 20 to 193 ± 28 mg · day^{-1} · kg^{-1} of body weight in the off-pump group ($P < 0.05$). The increase in albumin ASR following the two procedures was comparable (+40 ± 10 compared with +47 ± 14 %; P value was not significant).

DISCUSSION

The present study demonstrates that muscle protein synthesis is acutely inhibited following CABG surgery. At 4 h after completion of surgery, muscle protein synthesis rates were 36 ± 6 % lower than pre-operative values ($P < 0.001$; $n = 12$). In contrast with the decreased effect on muscle, surgery was accompanied by a significant stimulation of synthesis of both fibrinogen and albumin. These findings demonstrate that CABG surgery has a profound effect on protein metabolism, with a differential response of protein synthesis in muscle and liver.

The decrease in the rate of muscle protein synthesis observed after CABG surgery is consistent with previous studies demonstrating that surgical trauma has a negative impact on protein synthesis in human muscle. Essen et al. [3] showed that muscle protein synthesis is approx. 30 % lower than pre-operative values immediately after open cholecystectomy, and a similar degree of inhibition has been demonstrated 1 day following the same procedure [4]. It is noteworthy that the degree of inhibitory effect on muscle protein synthesis after cholecystectomy [3] is comparable with that observed in the present study, despite the difference in surgery. The similarity of the metabolic response of muscle to the two surgical procedures may suggest that the decreased response of muscle protein synthesis immediately following surgery is not related to the characteristics and severity of the surgery. This observation is similar to findings of Essén et al. [2], showing that the decline in muscle protein synthesis 1 day after minimally invasive laparoscopic cholecystectomy was comparable with that observed after the more invasive open cholecystectomy procedure. Although the acute response of muscle protein synthesis to surgery may be similar despite different surgical procedures, it is possible that the recovery of muscle protein synthesis may be more rapid after less traumatic procedures. Further studies are required to determine if this is the case.

Traditionally, CABG surgery is performed with the circulation maintained on CPB, allowing the heart to be stopped for the placement of the coronary artery grafts. Although facilitating bypass grafts, CPB is associated with a systemic inflammatory response which can increase tissue damage and contribute to post-operative morbidity (i.e. [21–23]). A study by Löfberg et al. [24] showed that muscle protein synthesis was significantly decreased in healthy volunteers following haemodialysis, suggesting that exposure of blood to foreign surfaces may have a detrimental effect on protein metabolism. The use of CPB during CABG surgery may therefore contribute additive catabolic effects on protein metabolism. However, in the present study, the conventional and beating heart surgeries had a similar overall acute impact on muscle, and no detectable difference was observed in the degree of inhibition of muscle protein synthesis either with or without CPB (-42 ± 6 compared with -32 ± 10 % respectively). In the present study, the measurements were carried out 4 h after surgery and only assessed the acute response to surgery. The study did not address the question of whether the beating heart procedure would minimize the catabolic response in muscle later in the post-operative period, thus reducing the overall loss of muscle protein following surgery.

In contrast with the decrease in the rate of muscle protein synthesis observed in the present study, the synthesis of fibrinogen was increased after CABG surgery. Fibrinogen synthesis rates were stimulated considerably 4 h after surgery to 204 % of pre-operative values (Figure 3). Elevated synthesis of fibrinogen has been demonstrated previously in animals following acute inflammation [25] and in patients after trauma [5,6]. The stimulation of hepatic synthesis of fibrinogen and other acute-phase proteins is mediated by cytokines and contributes to the increase in the plasma concentrations of these proteins following trauma and inflammation [26,27]. Among the cytokines, IL-6 appears to be a major regulator of fibrinogen synthesis during the acute-phase response, an effect mediated by enhancing transcription of mRNA for fibrinogen [28,29]. The dramatic stimulation of fibrinogen synthesis rates detected in the present study may result from the inflammatory and acute-phase response to the surgical trauma and triggered, in part, by the release of IL-6, which was also found to be significantly elevated 4 h after CABG surgery (Table 2).

As with other kinds of surgical trauma, CABG is accompanied by a stimulation of the immuno/inflammatory response, and the plasma concentration of many cytokines and markers of inflammation increase in a timely fashion following surgery [21–23,30,31]. The use of CPB during CABG can itself contribute to activation of the immune system, and several studies have indicated that the immuno/inflammatory response is attenuated following the 'beating heart' procedure [31–35]. However, in the present study, no difference was detected in the plasma concentrations of the immuno/inflammatory marker IL-6 between the on-pump and off-pump groups. These findings suggest that the acute-phase response following the two procedures was probably comparable, at least at the time of measurement, in these patient populations, which led to similar increases in the synthesis of fibrinogen between the on-pump and off-pump groups.

Albumin is considered a negative acute-phase protein, i.e. the plasma concentration of albumin is decreased by trauma [26,27], and Barle et al. [7,8] have shown that both the rates of synthesis of albumin and total liver proteins are decreased during elective laparoscopic cholecystectomy. In one of these studies, Barle et al. [7] measured albumin synthesis within 1 h from the start of surgery. In the present study, conducted approx. 8.5 h after the start of the surgical procedure, the synthesis of albumin was not decreased, but rather was increased significantly (Figure 4). Although it is possible that the contrasting response of albumin synthesis in the two studies may be related to the different surgical procedures, taken together these two studies suggest that there may be a biphasic response in albumin synthesis to surgical trauma, with an immediate decrease in synthesis, followed by a subsequent stimulation. The stimulation of albumin synthesis following surgery is consistent with human studies with different types of catabolic states resulting from endotoxin administration [36], head trauma [5] and critical illness [37]. Another study by Barle et al. [38] showed that during laparoscopic cholecystectomy albumin synthesis is higher in patients with acute cholecystitis compared with those undergoing elective cholecystectomy without acute inflammatory response, suggesting that inflammation also contributes to an increase in albumin synthesis. It can therefore be hypothesized that following surgery albumin synthesis rates are initially decreased, but are then subsequently stimulated when an immuno/inflammatory response to surgical trauma develops. The magnitude and time course of the stimulatory effect on albumin synthesis may depend on the type of surgery and the extent of the acute-phase reaction elicited. In the present study, the increase in albumin synthesis was already observed 4 h after the end of the surgical procedure, in association with a detectable acute-phase response (i.e. increase in plasma IL-6 levels). In addition, the stimulation of albumin synthesis was comparable in patients who underwent surgery with or without CPB (Figure 4).

The increase in albumin synthesis occurred at the same time as plasma albumin concentrations were decreased (Table 2), implying that the decrease in albumin concentration following trauma and injury does not reflect a decrease in synthetic rates, but mainly reflects an enhanced rate of transcapillary escape of albumin [27,39].

In summary, the results of the present study demonstrate that CABG surgery has a profound effect on tissue protein metabolism acutely, with an opposite response in skeletal muscle and liver export proteins. In particular, muscle protein synthesis is decreased, whereas the hepatic synthesis of both acute-phase protein fibrinogen and albumin are significantly stimulated 4 h following surgery. The present study did not detect any difference in the magnitude of the metabolic response of muscle or liver protein synthesis whether CABG surgery was performed with or without CPB. However, further studies are needed to better characterize the time course response of muscle and liver protein metabolism to surgical trauma and to ascertain whether the off-pump procedure has any advantage in minimizing the loss of muscle protein during the post-operative period.

ACKNOWLEDGMENTS

This work was supported, in part, by the Center Grant No. MO1-RR-10710 and grant No. DK54991 from the National Institutes of Health. The expert technical assistance of G. Casella and Y. Hong, and the scientific advice of Dr Lisa M. Ballou are gratefully acknowledged. We also thank the nursing staff at the General Clinical Research Center (GCRC) and the Cardiac Intensive Care Unit at the Stony Brook University Medical Center.

REFERENCES

1 Garlick, P. J. and Wernerman, J. (1997) Protein metabolism in injury. Scientific Foundations of Trauma (Cooper, G. J., Dudley, H. A. F., Gann, D. S., Little, R. A. and Maynard, R. L., eds.), pp. 690–727, Butterworth Heineman, Oxford
2 Essén, P., Thorell, A., McNurlan, M. A. et al. (1995) Laparoscopic cholecystectomy does not prevent the postoperative protein catabolic response in muscle. Ann. Surg. **222**, 36–42
3 Essén, P., McNurlan, M. A., Wernerman, J., Vinnars, E. and Garlick, P. J. (1992) Uncomplicated surgery, but not general anesthesia, decreases muscle protein synthesis. Am. J. Physiol. **262**, E253–E260
4 Tjäder, I., Essén, P., Thörne, A., Garlick, P. J., Wernerman, J. and McNurlan, M. A. (1996) Muscle protein synthesis rate decreases 24 hours after abdominal surgery irrespective of total parenteral nutrition. JPEN, J. Parenter. Enteral Nutr. **20**, 135–138
5 Mansoor, O., Cayol, M., Gachon, P. et al. (1997) Albumin and fibrinogen syntheses increase while muscle protein synthesis decreases in head-injured patients. Am. J. Physiol. **273**, E898–E902
6 Thompson, C., Blumenstock, F. A., Saba, T. M. et al. (1989) Plasma fibronectin synthesis in normal and injured humans as determined by stable isotope incorporation. J. Clin. Invest. **84**, 1226–1235
7 Barle, H., Hallstrom, L., Essen, P. et al. (2004) The synthesis rate of albumin decreases during laparoscopic surgery. Clin. Physiol Funct. Imaging **24**, 91–95
8 Barle, H., Nyberg, B., Ramel, S. et al. (1999) Inhibition of liver protein synthesis during laparoscopic surgery. Am. J. Physiol. **277**, E591–E596
9 Thom, T., Haase, N., Rosamond, W. et al. (2006) Heart Disease and Stroke Statistics–2006 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation **113**, e85–e151
10 Caso, G., Scalfi, L., Marra, M. et al. (2000) Albumin synthesis is diminished in men consuming a predominantly vegetarian diet. J. Nutr. **130**, 528–533
11 Hunter, K. A., Garlick, P. J., Broom, I., Anderson, S. E. and McNurlan, M. A. (2001) Effects of smoking and abstention from smoking on fibrinogen synthesis in humans. Clin. Sci. **100**, 459–465
12 Caso, G., Garlick, P. J., Ballou, L. M., Vosswinkel, J. A., Gelato, M. C. and McNurlan, M. A. (2006) The increase in human muscle protein synthesis induced by food intake is similar when assessed with the constant infusion and flooding techniques. J. Nutr. **136**, 1504–1510
13 McNurlan, M. A., Garlick, P. J., Steigbigel, R. T. et al. (1997) Responsiveness of muscle protein synthesis to growth hormone administration in HIV-infected individuals declines with severity of disease. J. Clin. Invest. **100**, 2125–2132
14 Menth-Meier, S. E., Imoberdorf, R., Regli, B., Kipfer, B., Turgay, M. and Ballmer, P. E. (2001) Determination of plasma volume by indocyanine green: validation of the method and use in patients after cardiopulmonary bypass. Intensive Care Med. **27**, 925–929
15 Ballmer, P. E., McNurlan, M. A., Milne, E. et al. (1990) Measurement of albumin synthesis in humans: a new approach employing stable isotopes. Am. J. Physiol. **259**, E797–E803
16 Hunter, K. A., Ballmer, P. E., Anderson, S. E., Broom, J. and Garlick, P. J. (1995) Acute stimulation of albumin synthesis rate with oral meal feeding in healthy subjects measured with [ring-$^2H_5$]phenylalanine. Clin. Sci. **88**, 235–242
17 Caso, G., Ford, G. C., Nair, K. S., Garlick, P. J. and McNurlan, M. A. (2002) Aminoacyl-tRNA enrichment after a flood of labeled phenylalanine: insulin effect on muscle protein synthesis. Am. J. Physiol. Endocrinol. Metab. **282**, E1029–E1038
18 Tan, V., Doyle, C. J. and Budzynski, A. Z. (1995) Comparison of the kinetic fibrinogen assay with the von Clauss method and the clot recovery method in plasma of patients with conditions affecting fibrinogen coagulability. Am. J. Clin. Pathol. **104**, 455–462
19 Doumas, B. T., Watson, W. and Biggs, H. G. (1971) Albumin standards and the measurement of serum albumin with bromocresol green. Clin. Chim. Acta **31**, 87–96
20 Caso, G., Ford, G. C., Nair, K. S., Vosswinkel, J. A., Garlick, P. J. and McNurlan, M. A. (2001) Increased concentration of tracee affects estimates of muscle protein synthesis. Am. J. Physiol. Endocrinol. Metab. **280**, E937–E946
21 Hall, R. I., Smith, M. S. and Rocker, G. (1997) The systemic inflammatory response to cardiopulmonary bypass: pathophysiological, therapeutic, and pharmacological considerations. Anesth. Analg. **85**, 766–782
22 Wan, S., LeClerc, J. L. and Vincent, J. L. (1997) Cytokine responses to cardiopulmonary bypass: lessons learned from cardiac transplantation. Ann. Thorac. Surg. **63**, 269–276
23 Edmunds, Jr, L. H. (1998) Inflammatory response to cardiopulmonary bypass. Ann. Thorac. Surg. **66**, S12–S16
24 Lofberg, E., Essen, P., McNurlan, M. et al. (2000) Effect of hemodialysis on protein synthesis. Clin. Nephrol. **54**, 284–294
25 Jahoor, F., Wykes, L., Del Rosario, M., Frazer, M. and Reeds, P. J. (1999) Chronic protein undernutrition and an acute inflammatory stimulus elicit different protein kinetic responses in plasma but not in muscle of piglets. J. Nutr. **129**, 693–699
26 Fleck, A., Colley, C. M. and Myers, M. A. (1985) Liver export proteins and trauma. Br. Med. Bull. **41**, 265–273
27 Fleck, A. (1989) Clinical and nutritional aspects of changes in acute-phase proteins during inflammation. Proc. Nutr. Soc. **48**, 347–354
28 Geiger, T., Andus, T., Klapproth, J., Hirano, T., Kishimoto, T. and Heinrich, P. C. (1988) Induction of rat acute-phase proteins by interleukin 6 *in vivo*. Eur. J. Immunol. **18**, 717–721
29 Heinrich, P. C., Castell, J. V. and Andus, T. (1990) Interleukin-6 and the acute phase response. Biochem. J. **265**, 621–636

30 Fransen, E., Maessen, J., Dentener, M., Senden, N., Geskes, G. and Buurman, W. (1998) Systemic inflammation present in patients undergoing CABG without extracorporeal circulation. Chest **113**, 1290–1295
31 Diegeler, A., Doll, N., Rauch, T. et al. (2000) Humoral immune response during coronary artery bypass grafting: A comparison of limited approach, 'off-pump' technique, and conventional cardiopulmonary bypass. Circulation **102**, III95-II100
32 Wan, S., Izzat, M. B., Lee, T. W., Wan, I. Y., Tang, N. L. and Yim, A. P. (1999) Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. Ann. Thorac. Surg. **68**, 52–56
33 Schulze, C., Conrad, N., Schutz, A. et al. (2000) Reduced expression of systemic proinflammatory cytokines after off-pump versus conventional coronary artery bypass grafting. Thorac. Cardiovasc. Surg. **48**, 364–369
34 Ascione, R., Caputo, M. and Angelini, G. D. (2003) Off-pump coronary artery bypass grafting: not a flash in the pan. Ann. Thorac. Surg. **75**, 306–313
35 Wan, I. Y., Arifi, A. A., Wan, S. et al. (2004) Beating heart revascularization with or without cardiopulmonary bypass: evaluation of inflammatory response in a prospective randomized study. J. Thorac. Cardiovasc. Surg. **127**, 1624–1631
36 Barle, H., Januszkiewicz, A., Hallstrom, L. et al. (2002) Albumin synthesis in humans increases immediately following the administration of endotoxin. Clin. Sci. **103**, 525–531
37 Barle, H., Gamrin, L., Essen, P., McNurlan, M. A., Garlick, P. J. and Wernerman, J. (2001) Growth hormone does not affect albumin synthesis in the critically ill. Intensive Care Med. **27**, 836–843
38 Barle, H., Hammarqvist, F., Westman, B. et al. (2006) Synthesis rates of total liver protein and albumin are both increased in patients with an acute inflammatory response. Clin. Sci. **110**, 93–99
39 Fleck, A., Raines, G., Hawker, F. et al. (1985) Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet **i**, 781–784

Received 2 August 2007/26 September 2007; accepted 22 October 2007
Published as Immediate Publication 22 October 2007, doi:10.1042/CS20070278