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Preoperative Nutritional Status Predicts the Severity of the Systemic Inflammatory Response Syndrome (SIRS) Following Major Vascular Surgery

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Objectives. *This study examined the relationship between pre-operative nutritional status and systemic inflammatory response syndrome (SIRS) or sepsis following major vascular surgery.*
Design and methods. *Subjects undergoing open AAA repair, EVAR or lower limb revascularisation were studied prospectively. Pre-operative nutrition was assessed clinically using Mini-Nutritional Assessment (MNA) and body composition was measured by dual energy X-ray absorptiometry (DEXA) scanning. SIRS severity was assessed for 5 post-operative days and sepsis noted within 30 days of surgery.*
Results. *Using MNA, neither SIRS severity nor sepsis occurrence differed significantly between 'well-nourished' subjects and those 'at risk of malnutrition'. Using DEXA, negative associations existed between body mass index and both SIRS score and SIRS duration. Fat free mass (FFM) was negatively associated with SIRS score and duration. Negative associations also existed between skeletal muscle mass (SMM) and SIRS score and duration. SMM was also negatively correlated with post-operative length of stay in hospital. There were no significant correlations between sepsis and any nutritional indices.*
Conclusions. *Lower pre-operative nutritional indices, indicating protein energy malnutrition, were associated with more severe systemic inflammatory responses following major vascular surgery.*

Keywords: Nutritional status; Postoperative complications; Sepsis; Abdominal aortic aneurysm; Vascular surgical procedures.

Introduction

Respiratory[1,2] and cardiac[2,3] co-morbidities have been clearly demonstrated to be associated with poor outcomes following open abdominal aortic aneurysm (AAA) repair. Whilst surgical revascularisation of the lower limb imposes less physiological stress than AAA repair, the necessity to adequately assess risk remains high. Furthermore, less invasive alternatives to bypass surgery[4] provide options for patients unsuitable for surgical revascularisation and therefore heightens the obligation to accurately assess surgical risk and to minimise this risk whenever possible.

The concepts of systemic inflammatory response syndrome (SIRS), sepsis, multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF),[5,6] usefully categorise the complex inflammatory processes that are experienced by patients subjected to major vascular surgery. However, it is currently difficult to predict those individuals who are likely to develop SIRS and sepsis in the post-operative period. An ability to predict and ultimately ameliorate, the post-operative occurrence of SIRS and sepsis is likely to positively impact upon post-operative morbidity and mortality rates.

Malnutrition refers to a continuum of inadequate nutritional status due to insufficient intake or exaggerated substrate loss.[7] The term protein-energy malnutrition (PEM) describes the form most frequently seen in clinical practice, in which there is a deficiency of carbohydrate, proteins and fats[8] leading to low body fat-free mass and fat mass.[9] Malnutrition has been shown to have an adverse effect on the clinical outcome of surgical patients.[10] In the setting of surgery for colorectal carcinoma, a strong relationship was demonstrated between poor pre-operative

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nutritional status, an exaggerated peri-operative activation of the cytokine network and subsequent poor clinical outcome.[11] Protein under-nutrition has also been suggested to be a major cause of decreased immune function in the elderly,[12] who largely make up the population subjected to major vascular surgical procedures. PEM occurs frequently in surgical patients, with a deterioration in nutritional status occurring over the course of hospitalisation.[13] The finding by Spark *et al*[14] that patients with chronic critical limb ischaemia exhibited significantly lower values of several nutritional markers compared with general surgical patients, supports the contention that impaired nutrition appears to be relatively common in patients presenting for major vascular surgery. Peri-operative starvation and the hypermetabolic stress response accompanying both surgical trauma and infective complications may compound the adverse metabolic and clinical consequences experienced by such patients.[8,15] Particularly relevant for the development of SIRS and sepsis are studies which have documented that poor nutritional status may predict the development of post-operative infective complications in a wide range of surgical procedures.[13,16]

The current study was designed to address whether poor preoperative nutritional status, assessed both anthropometrically and using imaging technologies, has the potential to predict the development and severity of post-operative SIRS and sepsis in patients following major vascular surgery.

Subjects and Methods

Patient selection and recruitment

Patients scheduled to undergo elective open aortic abdominal aneurysm repair and endovascular abdominal aortic aneurysm repair (EVAR) at The Queen Elizabeth Hospital and the Royal Adelaide Hospital and those scheduled to undergo a major lower limb revascularisation procedure at The Queen Elizabeth Hospital were eligible for the study. The study was approved by the Ethics of Human Research Committees at both institutions according to the National Statement on Ethical Conduct in Research Involving Humans from the National Health and Medical Research Council of Australia.

Exclusion criteria were: Unwilling or unable to give informed consent; intervention associated with ischaemia-reperfusion injury within 3 months preceeding the study; and patients taking immunosuppressive medication, with the exception of an individual taking low dose corticosteroids (7.5mg prednisolone). Due to the relatively high frequency of local ulceration and gangrene in patients with critically ischaemic limbs (5/17), low grade pre-operative infection or local inflammation were not considered as criteria for exclusion in this cohort. Withdrawal criteria included major surgical intervention subsequent to the vascular repair or patient request.

Allocation of aortic aneurysm patients to open repair or EVAR was not randomised but determined by the surgical team prior to the study entry. Anatomical suitability for EVAR was a principal determinant of the chosen method of repair. All study participants underwent pre-operative assessment by a consultant anaesthetist, a general physician or a cardiologist, who identified patients as medically fit to proceed with surgery. The operative cohort included a total of 35 open AAA repairs, 16 EVAR and 17 lower limb revascularisation procedures for chronic limb ischaemia resulting from atherosclerosis. The severity of limb ischaemia varied. Six subjects had claudication, four had ischaemic rest pain and seven had minor tissue loss. None of the AAA repair procedures involved inflammatory aneurysms. Demographic details and relevant aspects of their medical histories were documented (Table 1). Co-morbidities were scored using the American Society of Anesthesiologists (ASA) Physical Status Classification as well as the Charlson Index.[17] All patients were continued on their pre-operative antiplatelet, anti-anginal and anti-hypertensive drugs as it would have been inappropriate and unethical to discontinue such therapies. The β-blockers administered were all cardioselective, being either atenolol or bisoprolol.

Table 1. Demographic and clinical characteristic of the 'open' aneurysm repair, EVAR and lower limb revascularisation cohorts

	Open AAA $n = 35$	EVAR $n = 16$	Lower limb revascularisation $n = 17$
Demographic			
Age	70.8 (7.2)	76.5 (6.8)	64.7 (14.6)
Male:Female ratio	30:5	16:0	13:4
Clinical			
ASAII	26%	19%	18%
ASAIII	60%	75%	76%
ASAIV	14%	6%	6%
Charlson Index Score	1.9 (0.9)	1.3 (0.9)	3.1 (1.7)
Diabetic	17%	7%	53%
β-Blocker therapy	86%	69%	41%
Post-operative length of stay	11.2 (3.8)	3.9 (1.6)	8.2 (0.6)

Means and standard deviations are shown unless otherwise indicated.

Surgical procedures

Open AAA repair was carried out in all cases using a standard transperitoneal approach. EVAR procedures were performed via bilateral groin incisions under general anaesthesia. In the 'lower limb' cohort, 15 subjects underwent infra-inguinal revascularisations and, in 2 patients, a supra-inguinal procedure was carried out. Spinal anaesthesia was used for 2 patients in the cohort and the remaining 15 patients underwent a general anaesthetic. Each anaesthetist used their own preference for anaesthetic and there was no set protocol for either general or spinal anaesthetic.

Post-operative assessment

Subjects were followed for the development of SIRS for the first five post-operative days. SIRS was defined according to the consensus definition established by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference in 1991.[18] The consensus statement uses four clinical criteria and identifies the presence of SIRS if two or more are present concurrently (Table 2). Sepsis was defined in a more recent consensus statement[19] as systemic inflammation (SIRS) in the presence of a known or suspected infective process. In the current study, the presence of sepsis within 30 post-operative days was identified either by a positive microbiological culture or on the basis of radiological investigations showing pulmonary consolidation.

The severity of SIRS was scored prospectively on the first five post-operative days by a daily inspection of the clinical records. According to the consensus definition,[18] the presence of one criterion does not constitute SIRS, hence a score of 0 was assigned. When either 2, 3 or 4 criteria were present simultaneously, a severity score of 1, 2, or 3 was given. If the SIRS score fluctuated over the 24h period, the maximum score was assigned for that day. A cumulative SIRS score was determined for each subject by adding all daily scores. SIRS duration was determined by adding the number of days on which SIRS was present, irrespective of whether these days were consecutive.

Table 2. (ACCP/SCCM) definition of Systemic Inflammatory Response syndrome (SIRS)[18]

Two or more of the following criteria in the setting of known or suspected causes of endothelial inflammation:

- A temperature of $>38\,^{\circ}C$ or $<36\,^{\circ}C$
- A heart rates of >90 beats per minute
- A respiratory rate of >20 breaths per minute or $PaCO_2 <32$ mm Hg
- A white blood cell count of $>12.0\times10^9/L$, $<4.0\times10^9/L$ or $>10\%$ immature neutrophils (band forms)

APACHE II scores[20] for all patients were recorded daily for the first five post-operative days or until discharge from hospital, if occurring before 5 days. The maximum Apache score was employed as a measure of post-operative morbidity. Length of stay in the Intensive Care Unit and total post-operative length of stay in hospital were also recorded.

Assessment of nutritional status

Pre-operative nutritional status was assessed using the Mini-nutritional assessment (MNA), administered in the pre-operative period by the study investigators. The MNA is a practitioner-administered tool designed to provide a single, rapid assessment of nutritional status in elderly patients. This 18 item tool is comprised of anthropometric assessments (measurement of body mass index (BMI), mid-arm and calf circumference and weight loss); a general assessment, consisting of six questions related to lifestyle, mobility and medications; a dietary assessment and a self-assessment component, measuring the subject's self-perception of their health and nutrition. An overall score (maximum 30 points) is calculated which classifies the patients as either well nourished (a score of ≥24 points), at risk of malnutrition, indicating borderline nutritional status (17–23.5 points) or malnourished (<17 points).[21]

Whole body composition analysis was performed pre-operatively by dual energy X ray absorptiometry (DEXA) scanning using GE-lunar Prodigy Vision densitometers (GE Medical Systems Lunar Corporation, Wisconsin, USA) in the Department of Nuclear Medicine and Bone Densitometry, The Royal Adelaide Hospital or in the Osteoporosis Centre, Departments of Endocrinology and Nuclear Medicine, The Queen Elizabeth Hospital. The two densitometers were cross calibrated using a phantom.

Five DEXA-derived measures of total body composition, fat mass (FM), fat-free mass (FFM), fat mass index (FMI), fat-free mass index (FFMI) and estimated skeletal muscle mass (SMM) were determined for each subject. Total body FM (kg) was obtained directly from DEXA data reports, whilst FFM (kg) was calculated from reported data as described by Hansen *et al.*[22] The height-normalised indices (FMI and FFMI in kg/m^2) were calculated by dividing FM and FFM respectively by height squared, according to the method of VanItallie *et al.*[23] Total body SMM (kg) was calculated from the sum of total arm and total leg fat-free soft tissue mass (FFST) values, using the following formula, as described by Hansen *et al.*,[22] SMM = 1.333(arm FFST + leg FFST).

Statistical analyses

With the exception of the mini-nutritional assessment, cumulative SIRS score and length of ICU stay, all other variables were normally distributed. To determine differences between the three surgical cohorts with respect to clinical and demographic factors and SIRS and sepsis measures, the following statistical procedures were used:- i) Pearson product moment correlations, ii) one-way analysis of variance with Scheffe post-hoc comparisons and chi-square test for all normally distributed continuous and categorical variables. For non-normally distributed variables, the Mann-Whitney U test for comparisons between two groups and the Kruskal-Wallis Test for comparisons between more than two groups were used. To determine associations between all measures of nutritional status and SIRS and sepsis measures, the data were pooled due to the small number of patients in each surgical group and surgical procedure controlled for in the analysis using partial correlations and one-way analysis of variance with procedure entered as a covariate. All analyses were performed using SPSS version 14.

Results

Clinical details of the operative cohorts

Demographic details of the three cohorts are provided in Table 1. Patients undergoing lower limb revascularisation were significantly younger, [F (2, 65) = 6.4, $P = .003$] and had more comorbidities, [F (2, 65) = 10.2, $P < .001$] than patients undergoing EVAR. Patient groups also differed significantly with respect to use of beta blockers (X^2 (2) = 11.1, $P = .004$) and postoperative length of stay [F (2, 65) = 25.8, $P \leq .0001$]. Patient groups were otherwise comparable with respect to other clinical and demographic factors such as gender and ASA.

Incidence of post-operative SIRS and Sepsis

The incidence of SIRS and sepsis in the three cohorts are illustrated in Fig. 1A. SIRS was detected on at least one day in 91% of subjects after open AAA repair, in 44% after EVAR and in 71% of subjects after revascularisation for chronic lower limb ischaemia (χ^2 (2) = 13.5, $P = .001$). Incidence of sepsis was 49% in the 'open AAA repair' cohort, 6% in the EVAR and 12% in the lower limb cohorts and was also significantly associated with procedure type (χ^2 (2) = 12.9, $P = .002$). Three patients in the 'open AAA repair' cohort died within the first four post-operative days.

Fig. 1B illustrates the comparison of cumulative SIRS scores in the three operative cohorts, indicative of the severity of SIRS. SIRS scores were significantly higher in the 'open repair' cohort than in the EVAR cohort ($P = .020$). There was no significant difference in cumulative SIRS scores between either the open and lower limb or the EVAR and lower limb cohorts. Mean SIRS duration (Fig. 1C) was significantly higher in subjects undergoing open AAA repair compared to the other cohorts [F (2,65) = 8.2, $P = 0.001$].

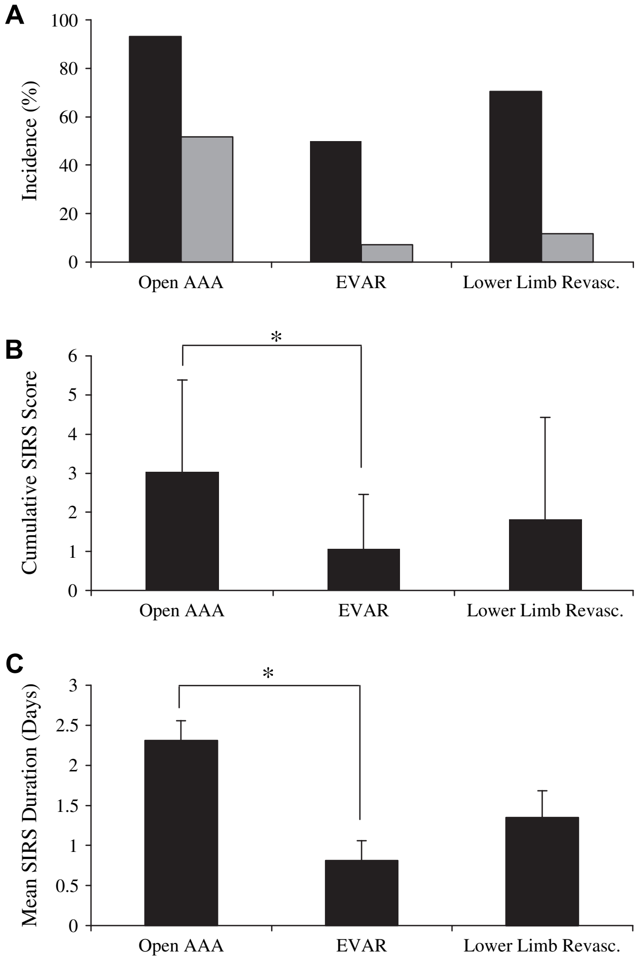

Fig. 1. Incidence and severity of SIRS and sepsis in the three operative cohorts. A: Percentage incidence of post-operative SIRS (black bars) and sepsis (hatched bars) in the three operative cohorts. B: Mean cumulative SIRS scores in the three operative cohorts. *$p = 0.02$. C: Mean duration of SIRS in the three operative cohorts. Values are Means ± SEM. *$p = 0.05$.

Use of beta-blockers was investigated initially as a possible confounder, however, no significant associations were found between the incidence of SIRS and the use of beta-blockers.

Nutritional status classified by the mini nutritional assessment (MNA)

Of the 31 subjects in the 'open repair' cohort whose nutritional status was classified using the MNA, 24 were classified as 'well-nourished', 6 were classified as 'at risk of malnutrition' and only one was categorised as being 'malnourished'. Since the latter category was represented by a single subject who died shortly after skin closure, this category was not included in the statistical analyses. It is noteworthy, however, that all three subjects who died within the study period were classified as either 'at risk of malnutrition' or 'malnourished'. The nutritional status of 16 EVAR patients was classified using the MNA. Of these subjects, 15 were classified as 'well nourished' and only one was classified as being 'at risk of malnutrition'. Nine members of the 'lower limb' cohort were categorised as 'well nourished' whilst the remaining 8 were 'at risk of malnutrition' according to the MNA. No significant associations were found between measures of cumulative SIRS, SIRS duration, incidence of SIRS or Sepsis and those categorised as either 'well nourished' or 'at risk of malnutrition' according to the MNA.

Anthropometric measures of body composition

Measures of BMI were obtained from 64 of the 68 patients in the study and DEXA-derived measures of body composition from 44 of the 68 participants. Partial correlations are shown in Table 3. After controlling for surgical procedure, BMI was not significantly associated with cumulative SIRS scores or SIRS duration. Correlations between each of the five DEXA-derived measures of body composition with SIRS outcomes are also shown in Table 3, again controlling for surgical procedure. Fat free mass (FFM) was correlated negatively with SIRS score ($r = -.38$, $P = .01$) and SIRS duration ($r = -.39$, $P = .01$). Similarly, negative associations were also detected between skeletal muscle mass (SMM) and both SIRS score ($r = -.38$, $P = .01$) and SIRS duration ($r = -.41$, $P = .007$).

No significant differences in mean BMI or DEXA derived measures were found between those who developed sepsis compared with those who did not (Table 4).

Table 3. Partial correlations between anthropometric measures of body composition and SIRS measures

Anthropometric Measures	SIRS (cumulative)	SIRS (duration)
Body-Mass Index (BMI)	−.23	−.29 (*P* = .06)
Fat-free Mass (FFM)	−.38 (*P* = .01)	−.39 (*P* = .01)
Fat-free Mass Index (FFMI)	−.29 (*P* = .06)	−.31 (*P* = .05)
Fat Mass (FM)	−.13	−.21
Fat Mass Index (FMI)	−.06	−.13
SMM	−.38 (*P* = .01)	−.41 (*P* =.007)

Association between nutritional status and general post-operative morbidity

Table 5 reports the partial correlations between DEXA-derived measures of body composition and BMI and measures of general post-operative morbidity. There was a significant inverse association between SMM and length of stay in hospital ($r = -.32$, $P = .04$). All other correlations between measures of body composition, including MNA and measures of post-operative morbidity were not statistically significant.

Discussion

Reports of the incidence of SIRS associated with major vascular surgery are limited. In a study examining the inflammatory responses to EVAR compared with the conventional open method of AAA repair, Sweeney *et al*.[24] reported a 33% incidence of SIRS in an open AAA repair cohort. The only other published data on the incidence of SIRS following major vascular surgery appears in two papers from the Department of Surgery, University of Leicester,[25,26] which reported an incidence of SIRS of 89% following open AAA surgery which is very similar to the 91% found in the current study.

As predicted, the incidence of SIRS in EVAR patients was markedly lower than in those undergoing

Table 4. Means and standard deviations for anthropometric measures of nutritional status and the development of sepsis

	Sepsis		
	Present	Absent	*P* value
Sample Size, Body Mass Index	*n* = 18	*n* = 41	
BMI	26.1 (4.8)	27.4 (4.0)	0.44
Sample Size, DEXA measures	*n* = 13	*n* = 31	
FFM	52.2 (10.5)	56.4 (8.8)	0.39
FFMI	18.8 (2.6)	19.3 (2.0)	0.69
FM	21.3 (9.8)	22.6 (9.3)	0.94
FMI	7.7 (3.7)	7.8 (3.2)	0.78
SMM	26.4 (5.7)	29.9 (5.7)	0.21

There were no significant differences between any body composition indices and the presence or absence of sepsis.

Table 5. Partial correlations between anthropometric measures of nutrition and measures of morbidity

	Maximum Apache score	Postoperative LOS (days)	Intensive care LOS (hours)
BMI	−.04	−.15	.08
FFM	−.18	−.19	−.30 (P = .06)
FFMI	.03	−.15	−.12
FM	.10	−.07	.09
FMI	.18	−.04	.15
SMM	−.22	−.32 (P = .04)	−.23

an open AAA repair, with only 44% of EVAR patients developing SIRS compared to 91% in the open cohort. There was similarly a much lower incidence of sepsis following EVAR (6%) than open repair (49%). It is well recognised that EVAR is associated with less early post-operative morbidity than elective open AAA repair. Sweeney and co-workers[24] reported a 12% incidence of SIRS following EVAR compared to 33% after open repair. A previous study from the current authors also demonstrated a reduced endocrine stress response in EVAR patients compared to those undergoing open repair.[27] Although pre-operative inflammatory markers such as hsCRP were not measured in the current study, none of the subjects fulfilled the criteria for SIRS and sepsis preoperatively. In support of only minimal pre-operative inflammation in the subjects, preoperative plasma cytokine levels, including interleukin-6 and tumour necrosis-alpha, were measured as part of another study. Cytokines were mostly undetectable or very low in all subjects (manuscript in preparation).

The MNA, employed in this study is a validated and widely used clinical measure of nutrition in an elderly population and has been shown to have a sensitivity of 96%, a specificity of 89% and a predictive value of 97%.[21] This nutritional assessment tool was therefore considered appropriate to the largely elderly candidates for major vascular surgery who comprise the cohorts included in the study.

FM, FFM and SMM were selected as markers of nutritional status for the current study on the basis of considerable evidence demonstrating loss of these component tissues with under-nutrition and, in particular, with protein energy malnutrition (PEM).[9] A significant inverse association between the DEXA-derived body composition measures, FFM and SMM, and post-operative SIRS severity was identified by this study, indicating that a lower pre-operative lean body mass and more precisely, a lower total skeletal muscle mass, may predispose to more severe SIRS following major vascular interventions. While body composition analysis by DEXA is not yet employed beyond the research setting, these findings strongly support the suggestion that patients with PEM may be at particular risk of more severe post-operative SIRS. In contrast an association between MNA and post-operative SIRS severity was not detected, possibly suggesting that MNA, which generates categorical rather than numerical data, does not have sufficient sensitivity to detect the significant associations that were demonstrated using DEXA scanning.

The inability to identify an association between nutritional markers and post-operative sepsis in this study does not discount the potential role of nutritional status in sepsis susceptibility. Rather it may reflect the fact that the relationship is complex and not readily identified in a clinical cohort study comprised of a modest number of subjects.

A number of limitations should be acknowledged for this study. Sample size is modest and therefore the analysis was limited to pooled operative cohorts only. With a larger sample, differences that could be attributed to different procedures may have been determined. Use of more definitive measures of recovery, such as time to extubation and specific complications, could also be used in future studies. However, these measures would be very different between the procedural groups and the analysis would only be possible with a much larger sample size, as comparisons within each group would be needed. In future studies, it may be preferable to concentrate on one high-risk procedure such as open AAA repair where SIRS and sepsis is more frequent, thereby increasing the likelihood of detecting associations between nutritional indices and operative outcomes.

The current study has provided evidence that SIRS is more prevalent and of greater severity in vascular surgical subjects who present with pre-operative protein energy depletion. The results of this study therefore raise the question whether pre- or peri-operative nutritional supplementation of malnourished patients or those at risk of malnutrition may reduce the incidence and severity of post-operative SIRS and sepsis.

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