Serum Myoglobin and Renal Morbidity and Mortality following Thoracic and Thoraco-Abdominal Aortic Repair: Does Rhabdomyolysis Play a Role?


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Abstract  Objectives: The intractability of renal dysfunction following thoracic and thoraco-abdominal aortic repair leads us to believe that the accepted mechanisms of renal injury — ischaemia and embolism — are incompletely explanatory. We studied postoperative myoglobinaemia and renal dysfunction following aortic surgery.

Methods: Between September 2006 and February 2008, we studied serum myoglobin in 109 patients requiring thoracic/thoraco-abdominal repair for three postoperative days. Forty-two of the 109 (38%) patients were female. The median age was 67 years (range 23–84 years). As we have focussed more attention on renal function, our independent renal consultants have dialysed more aggressively. We divided dialysis into: (1) creatinine indication, (2) non-creatinine indication and (3) no dialysis.

Results: Thirteen of the 109 (12%) patients met creatinine indication for dialysis (>4 mg/dL) and an additional 28 (26%) were dialysed for other reasons. Overall mortality was 12 out of 109 (11%) cases: 11 out of 41 (27%) in dialysed patients and one out of 68 (1.5%) in nondialysed patients. Mortality did not differ between the indications for dialysis. Predictors of mortality were baseline glomerular filtration rate (GFR), postoperative myoglobin and dialysis. The only predictor of dialysis was postoperative myoglobin.

Conclusion: A strong relationship between postoperative serum myoglobin and renal failure suggests a rhabdomyolysis-like contributing aetiology following thoraco-abdominal aortic repair. We postulate a novel mechanism of renal injury for which mitigation strategies should be developed.

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Over the course of the two decades that thoraco-abdominal aortic repair has been performed in large numbers, great improvements have been made in many postoperative complications, notably the dreaded complication of postoperative neurological deficits (paraplegia and paraparaparesis). Neurological deficit rates have fallen by more than 80% in experienced centres, from more than 16% to less than 2% overall.1,2 These improvements have resulted from the development of adjuncts for use in surgery and from advances in intra-operative anaesthesia and postoperative care.3

A problem that has been less responsive to prevention efforts is postoperative renal dysfunction, which, although widely variable in incidence in many small reports, has remained fairly constant in larger studies despite the use of different methods to protect the kidneys.4–6 In our centre and others, numerous mechanical and pharmacological treatments have been tried, but overall renal failure rates have not changed greatly over time.7–9 The aetiology of renal failure in this setting has long been thought to be ischaemic, due either to interrupted blood flow during aortic clamping or to embolic processes that result from manipulation of the vessels. Since renal dysfunction remains a significant source of morbidity that is difficult to reverse once established, improvements in preventive care are critical. The lack of responsiveness of renal dysfunction to interventions that ought to work for the presumed ischaemic/embolic aetiologies has caused us to broaden our search for potential causes of renal morbidity beyond those classically postulated.10

Proteins released into the circulation by muscular injury or insult have been known for many years to produce renal failure following crush or burn injuries, extreme exercise, lengthy medical intensive care hospitalisation and some types of surgery.11–14 Termed as rhabdomyolysis, this protein release can be precipitated by direct muscular trauma (crush, incision, etc.) or by ischaemia (compartment syndrome, blood-flow interruption, etc.). We postulated that a potential mechanism of renal insult following aortic repair might include the perioperative release of myoglobins from skeletal muscle.

We recently described a cohort of patients for whom we did not have myoglobin data but did have information on functional muscle ischaemia.10 In that study, we observed that patients who lost somatosensory evoked-potential (SSEP) signals in the leg after cannulation of the ipsilateral femoral artery for distal aortic perfusion had increased risk (SSEP) signals in the leg after cannulation of the ipsilateral femoral artery for distal aortic perfusion had increased risk that patients who lost somatosensory evoked-potential (SSEP) signals in the leg after cannulation of the ipsilateral femoral artery for distal aortic perfusion had increased risk of postoperative renal failure. This effect persisted despite adjustment for other established renal risk factors such as glomerular filtration rate (GFR), age, gender and ischaemic time. The findings, although indirect, were consistent with our suspicion that muscular ischaemia might be important in the aetiology of postoperative renal dysfunction. We, therefore, undertook the present study to develop additional information regarding this hypothesis.

This report describes our observations regarding the clinical course of myoglobinemia following thoracic and thoraco-abdominal aortic repair, in further support of our hypothesis that rhabdomyolysis may play a role in the aetiology of acute renal dysfunction in this clinical setting. We also evaluate the effects of renal morbidity on subsequent mortality.

Methods

Between August 2006 and February 2008, we performed repairs of the thoraco-abdominal aorta in 109 consecutive patients, who were included in the cohort if they did not have clinical renal failure preoperatively (i.e., were not on dialysis preoperatively) and if they had serum myoglobin data available preoperatively and for most of the first three postoperative days. All patients were followed under our institutional review board (IRB)-approved clinical research/quality-improvement database protocol. The median age of the population was 67 years (range: 23–84); of the 109 patients, 42 (39%) were female and 67 (61%) were male. In our laboratory, the upper limit of normal for the serum myoglobin was 85 ng ml\(^{-1}\). Though we did not define a level of serum myoglobin at which rhabdomyolysis was determined to have occurred in our study, this value has been described in the literature as being in the neighbourhood of 1000–5000 ng ml\(^{-1}\).15–17

Postoperative renal dysfunction was defined as an increase in serum creatinine of 1 mg dl\(^{-1}\) day\(^{-1}\) for two consecutive days beyond the baseline, a clinical diagnosis of acute renal failure or need for haemodialysis. This definition corresponds to ‘I’ and ‘above’ in the risk, injury, failure, loss and end-stage kidney (RIFLE) criteria for renal outcome.18 The need for dialysis was determined by our independent renal consultants. Our recent, increased focus on renal function has led our consultants to intervene earlier now, than in the past, with dialysis or temporary haemofiltration. Historically, our consultants used a serum creatinine threshold of 4 mg dl\(^{-1}\) as the primary indication for renal replacement therapy. Today, continuously increasing creatinine, markedly decreased urine output or increasing volume load are also considered to be relative indications. We, therefore, stratified renal replacement intervention as: (1) classical indication (serum creatinine > 4 mg dl\(^{-1}\)), (2) other indication and (3) no renal replacement prescribed.

Thoraco-abdominal aortic aneurysms (TAAAs) were described as type I, II, III, IV and V. Descending thoracic aortic aneurysms (DTAAs) were described as extent A, B and C. Due to the limited sample size, for purposes of analysis, the extent classifications were categorised into two groups: those with visceral aneurysm extent (TAAA II, III and IV, which involve the renal artery orifices) and all the rest (TAAA I and V, and DTAAs).

Data were analysed by univariate contingency table methods, with 2 × 2 tables for dichotomous variables and 4 × 2 tables arrayed over quartiles for continuous data. Continuous logistic regression analysis was also conducted for association of univariate continuous variables with postoperative renal dysfunction. Odds ratios shown for continuous variables represent the change in odds associated with a one-unit change in the continuous variable. Multivariable analysis was conducted by multiple logistic regression. The time course of change in serum myoglobin, as well as the time-by-group interaction for renal dysfunction, was estimated using repeated measures analysis of variance. Serum myoglobin data were log-transformed for the statistical analysis to meet the normality assumptions required by multiple regression analysis and repeated measures analysis of variance.
All multivariable regression analyses proceeded rationally with combinations of best subsets, automated step-wise and manual forward-selection techniques. Computations were performed using SAS, version 9.1.3, Service Pack 4 (SAS Institute, Inc., Cary, NC, USA).

Surgical Methods

All patients underwent endotracheal anaesthesia using a double-lumen endotracheal tube to control the lungs independently. A cerebrospinal fluid (CSF) drainage catheter was inserted by the anaesthesiologist and actively managed to keep the CSF pressure near 10 mmHg. The patients were placed in the thoraco-abdominal position with tilt of the left groin to gain access to the femoral artery.

Following entry of the chest by thoraco-abdominal incision, distal aortic perfusion was initiated by cannulating the left atrium or the left pulmonary vein and using a centrifugal pump (Biomedicus, Medtronic, Minneapolis, MN, USA) and an in-line heat exchanger into the femoral artery. Subsequently to our recent finding that direct cannulation of the femoral artery is associated with loss of the SSEP signal in the cannulated leg, we modified our technique to use a side-arm graft. By sewing a short end-to-side graft to the left common femoral artery and cannulating the graft rather than the artery, we are able to maintain blood flow to the leg distal to the cannulation site (Fig. 1). Aortic repair proceeded in a sequential manner, with proximal anastomosis and re-attachment of intercostal arteries performed, followed by restoration of anterograde pulsatile circulation to the intercostal arteries. After intercostal artery re-implantation, the infra-renal aorta was clamped and opened. The coeliac, superior mesenteric and both renal arteries were identified, and the orifices were cannulated for perfusion. We used tepid blood, cold blood or cold lactated Ringer’s solution to the kidneys, with thermal monitoring of the left kidney and maintenance of the temperature below 20 °C. Following re-attachment of the visceral arteries, the perfusing catheters were removed and pulsatile flow restored to the visceral arteries. Finally, the distal aortic anastomosis was completed. Decannulation and closure of the incision concluded the procedure. Postoperatively, the patients were taken to the intensive care unit, with CSF pressure maintained at 10 mmHg for 3 days.

Results

Thirteen of 109 (12%) patients met creatinine indication for dialysis (>4 mg dl⁻¹) and an additional 28 (26%) received renal replacement therapy for other reasons. Postoperative renal replacement therapy rates and their relationship to demographic and clinical variables are shown in Table 1. The only significant predictor of dialysis was postoperative myoglobin.

Among the total cohort, mean preoperative serum myoglobin was 55 ng ml⁻¹, which is within normal limits in our laboratory. Immediately postoperatively, upon admission to the intensive care unit, mean serum myoglobin was 1331 ng ml⁻¹. This progressed over the following three postoperative days to 2290 on postoperative day 1, 2611 on day 2 and 1739 on day 3. Among those who developed renal dysfunction postoperatively, preoperative value of serum myoglobin was 59, followed by postoperative values of 1494, 3484, 5226 and 4026 on postoperative days 0–3. This is in stark contrast to patients who did not develop renal dysfunction, whose serum myoglobins were 52 at baseline, and 1238, 1501, 1092 and 399 on days 0–3. All comparisons between renal dysfunction groups beyond day 0 were significant at \( p < 0.0001 \) (Fig. 2). The relationship between peak myoglobin and three-category dialysis status is shown in Fig. 3. Of the 41 patients who received renal replacement therapy in the hospital, 15 (37%) were weaned prior to discharge. We were unable to identify any predictors of weaning.

Overall mortality was 12 out of 109 (11%) and was 11 out of 41 (27%) in dialysed patients and 1 out of 68 (1.5%) in non-dialysed patients (\( p < 0.0001 \)). Mortality did not differ between the two indications for dialysis. Univariate
The greatest impact has been on TAAA extent II, where neurological deficit rates have dropped from over 30% to under 5%.1,3

The most important as yet unsolved morbidity problem for TAAA and DTAA repair is renal failure. Renal failure has shown a clear association with mortality in many studies and is, therefore, an extremely important target for intervention.5,8,19 We have used mechanical methods, perfusion of warm, tepid or cold blood into the coeliac, superior mesenteric and both renal arteries and crystalloid to cool the kidneys below 15 °C, as well as other methods using prostaglandin 1 or 2 to protect the kidneys. Many of these have been described in the literature, and all have produced variable results that are difficult to interpret in light of the generally small numbers of cases reported and the heterogeneity in renal outcome definition.5,7,20

The aetiology of renal failure in this setting is almost certainly multifactorial. While the prevailing theory is that renal failure is caused predominantly by ischaemia or embolism in this setting, our data demonstrate a strong potential for an additional mechanism of renal insult. In clinical situations where rhabdomyolysis is common, especially those such as burn and compartment syndrome, renal failure associated with myoglobinaemia is well described. It has traditionally been thought that serum myoglobin forms casts in the renal tubules which cause blockage and renal failure. More recently, hypotheses related to haem-protein toxicity and lipid peroxidation have been advanced, but the mechanisms of injury due to these factors remain unclear.16,17,23

Although surgically associated rhabdomyolysis has been reported in trauma and urological surgery, nothing has
appeared in the literature showing an association between renal failure and postoperative serum myoglobin in TAAA repair. One plausible source of skeletal muscle ischaemia might be leg cannulation for distal aortic perfusion. As traditionally implemented with direct cannulation, the arterial runoff to the distal femoral artery has been subject to reduced arterial flow distal to the cannulation site. Lacking a history of direct myoglobin measures, we recently published an investigation of the relationship between functional leg ischaemia as measured by loss of SSEP signals in the leg and the risk of renal failure. In that study, we detected increased risk of renal failure associated with loss of the cannulated-leg evoked potentials, and the association persisted despite adjustment for numerous other known predictors of postoperative renal dysfunction. That finding led us to alter our cannulation technique to include the use of a side-arm graft that permits continued perfusion of the leg downstream of the cannulation site. As no overlap exists between the patients included in the previous study and the present one, we are unable to evaluate the relationship between ischaemic SSEP changes and myoglobin response.

We did not attempt to identify direct muscular insult or injury in this group of patients, particularly given the difficulty of assessing muscular symptoms beyond gross movement and sensation during the first three postoperative days in this population of patients who are often still sedated during this time period. While few other sources of myoglobin are currently known besides skeletal muscle, the evidence for occurrence of 'textbook' rhabdomyolysis beyond documented myoglobinaemia is admittedly circumstantial in these patients. Incision size is a potential source, and though we did not measure this directly, it is correlated with the extent of the repaired aneurysm. We were unable to demonstrate any association between the extent of the repair and serum myoglobin concentration. Bertrand et al. described lumbar muscular rhabdomyolysis in a cohort of 224 patients undergoing abdominal aortic surgery. They diagnosed rhabdomyolysis in 20 cases (9%) using serum creatine kinase (CK) levels. These authors found an increased incidence of rhabdomyolysis with obesity. We looked at this in detail, using analyses of body mass main effects as well as interaction effects with cross-clamp and pump-run times. We were unable to identify any relationship between serum myoglobin values and obesity or procedural times. This is a potentially important mechanism, however, and we are currently evaluating patterns of evoked-potential change in an attempt to identify potential skeletal muscle ischaemia.

A further consideration is the possibility that pre-existing peripheral vascular disease might increase the risk for rhabdomyolysis during aortic surgery. We work up symptomatic peripheral disease, but tend to focus on the major problem at hand and do not do complete peripheral workups on patients without complaints. Our inability to demonstrate a relationship between peripheral disease and myoglobin could result partly from under-diagnosis of clinically silent peripheral disease.

This study has shown that the peak level for these markers occurs on postoperative day 2 and that the mean serum myoglobin in the renal dysfunction group remains above the clinically important level of 1000 ng ml$^{-1}$ for 3 days after surgery. Our results document a compelling relationship between rise in serum myoglobin and postoperative renal dysfunction, with event rates on the order of 90% in the highest myoglobin quartile by postoperative day 3.

While the association is striking, what the therapeutic implications of this finding indicate are less clear. Prevention of rhabdomyolysis should be the first priority. Prophylactic volume expansion has been reported as one of the few effective pre-treatments, and we currently do this in all our thoraco-abdominal patients.

![Figure 2](image1) Time course of serum myoglobin. Day 1 is the day before surgery. Day 0 is day of surgery, and days 1–3 are postoperative days 1–3. The solid line indicates patients with renal failure and dashed line indicates patients without. Rhabdomyolysis is described in the literature as occurring at myoglobin levels of 1000–5000 ng ml$^{-1}$. Upper limit of normal range for our laboratory is 85 ng ml$^{-1}$.

![Figure 3](image2) Highest postoperative myoglobin versus dialysis status. Creatinine >4 mg dl$^{-1}$ is traditional indication for dialysis. Other Haemodialysis (HD) is other indication for renal replacement. No HD is no use of renal replacement therapy.
As for treatment of rhabdomyolysis once it occurs, flushing of the kidneys via volume expansion is the first-line therapy\textsuperscript{12,13,16,23} and is probably the only therapeutic modality that is uncontroversial (assuming volume expansion is judicious). Alkalisation through the use of bicarbonate is controversial, but may reduce formation of myoglobin crystals and lipid peroxidation. Mannitol has historically been used and has been helpful in cases of rhabdomyolysis induced by compartment syndrome, but its role in surgical cases is less clear.

Future research is needed to better characterise the clinical course, risk factor interactions and risk/benefit of treatment. Additional mechanistic studies are also needed to improve understanding of pathophysiology and to assist in the development of therapeutic targets.

Conflict of Interest Statement

The authors have no commercial relationships pertinent to the work reported in this manuscript.

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