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Myocardial Injury and Systemic Fibrinolysis in Patients Undergoing Repair of Ruptured Abdominal Aortic Aneurysm: a Preliminary Report

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Background: *ruptured abdominal aortic aneurysm (AAA) is associated with inhibition of systemic fibrinolysis. Hypofibrinolysis is a risk factor for ischaemic myocardial injury, one of the commonest complications of ruptured AAA repair. Cardiac troponin I (cTnI) is one of the most sensitive and specific marker of myocardial injury currently available.*
Objective: *to examine, for the first time, the relationship between fibrinolytic activity and myocardial injury in patients operated for ruptured AAA.*
Methods: *twenty patients (18 men and 2 women of median age 74, range 65–86 years) undergoing repair of ruptured AAA were prospectively studied. Plasma tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1) activity were measured pre-operatively, immediately before and five minutes following aortic clamp release. Serum cTnI was measured pre-operatively, 6 and 24 h following clamp release.*
Results: *cTnI was detectable at one or more sample points in 13 (65%) patients, and in 7 out of 8 patients who suffered major cardiac complications. There was a significant negative correlation between pre-operative t-PA activity and cTnI before operation* ($r = -0.55$, $p = 0.01$) *and 6 h* ($r = -0.51$, $p = 0.02$) *after clamp release. There was a significant positive correlation between pre-operative PAI activity and cTnI before operation* ($r = +0.50$, $p = 0.03$), *6 h* ($r = +0.47$, $p = 0.04$) *and 24 h* ($r = +0.50$, $p = 0.03$) *after clamp release. There was no correlation between pre- and intra-operative hypotension or blood transfusion requirement and cTnI release.*
Conclusions: *hypofibrinolysis during ruptured AAA repair is associated with the development of peri-operative myocardial injury. The causal mechanisms underlying this state are not clear but treatment of this prothrombotic/hypofibrinolytic diathesis may help to limit myocardial cell necrosis.*

Key Words: Aortic aneurysm; Post-operative myocardial infarction; Troponin.

Introduction

Endothelial cell (EC) activation and injury lead to the release of tissue plasminogen activator (t-PA). t-PA converts plasminogen to active plasmin which, in turn, leads to the breakdown of fibrinogen and fibrin clot to fibrin degradation products. Plasminogen activator inhibitor 1 (PAI-1), the major natural inhibitor of t-PA, is produced by EC in response to stress. Previous work from this group has shown that ruptured abdominal aortic aneurysm (AAA) is associated with inhibition of systemic fibrinolysis, as demonstrated by elevated PAI-1 and reduced t-PA activity.[1]

The structural myocardial proteins, troponin I (cTnI) and T (cTnT), are extremely sensitive and specific biochemical markers for myocardial injury and are released early, 2 to 6 h, after myocardial cell necrosis.[2–4] In patients with acute chest pain they are highly specific markers for the early detection of myocardial cell necrosis and can predict the risk of acute myocardial infarction (AMI). They may also predict poor outcome in patients with unstable angina pectoris or minor myocardial injury.[5–8] The measurement of cTnI has been shown to have less cross reactivity with skeletal muscle troponin and as such may represent a more specific marker for cardiac injury as a lower detection limit may be assigned to this assay.[9]

Cardiac complications are the principal cause of mortality and major morbidity after aortic surgery.[10–12] There is considerable evidence to suggest that a hypofibrinolytic state is a causative factor in the development of occlusive coronary artery thrombosis and acute cardiac events in other patient groups.[13–15]

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The aim of this study was to examine whether the hypofibrinolytic state that occurs during ruptured AAA repair predisposes to the development of myocardial injury in the peri-operative period. This study examines fibrinolytic activity, assessed by plasma t-PA and PAI-1 activities, and myocardial injury, assessed by serum levels of cTnI, in patients undergoing repair of ruptured AAA.

Methods

Patient recruitment

Twenty patients (18 men and 2 women of median age 74, range 65–86 years) who underwent repair of ruptured infra-renal AAA, who survived for at least 24 h were prospectively studied. These were not consecutive patients as not every patient operated for ruptured AAA survived to reach the 24 h post-operative time point. Also not every patient could be studied due to consent being refused in some cases or an inability to sample blood, due to clinical considerations, in others. Ethical committee approval was gained for this study and written informed consent obtained from the patient, or where this was not possible initially, the study fully discussed with relatives until formal consent could be gained from the patient themselves. Seventeen patients had at least one documented episode of hypotension (systolic blood pressure less than 100 mmHg for longer than 15 min duration) prior to surgery. No patient had a history of liver disease or was taking oral anticoagulants. Nine patients were taking regular aspirin at the time of admission. Pre-, intra- and post-operative details were prospectively documented.

Operative methods

Ruptured AAA was defined by the presence of fresh retroperitoneal blood at operation. All operations were performed under general anaesthesia. Repair was performed through a transverse supra-umbilical incision with infra-renal aortic clamping. No patient was given systemic heparin. An aortic tube graft was inserted in 14 patients, an aorto-bi-iliac graft in 2 patients and an aorto-bifemoral graft in 4 patients.

Assay methods

Markers of fibrinolysis

Blood (3 ml) was collected in sodium citrate (0.106 mol/l) for estimation of PAI activity, 4.5 ml was collected into strong acid citrate (Stabilyte, Biopool, Umea, Sweden) for estimation of t-PA activity. PAI and t-PA activity levels were measured by chromogenic assay using an amidolytic method (Coatest PAI and Coatest t-PA, Chromogenix, Sweden).

Markers of myocardial injury

Blood (9 ml) was collected into clot activator serum tubes. Serum cTnI was measured by enzyme-linked immunosorbent assay (OPUS Troponin I, Dade Behring Inc, U.S.A.) using the fully automated OPUS II analyzer (Dade Behring Inc, U.S.A.). The lower limit of detection of the assay was 0.5 ng/ml and a value greater than or equal to this level was considered positive for myocardial injury.

Sample collection

Blood for t-PA and PAI activity was sampled from an indwelling arterial line immediately prior to the induction of anaesthesia (sample A), and immediately before (sample B) and five minutes (sample C) after aortic clamp release. Blood was sampled for cTnI I immediately prior to the induction of anaesthesia (sample A), and 6 h (sample B) and 24 h (sample C) after aortic clamp release. Samples were placed on ice and centrifuged within 30 min of collection at 3000 revolutions per min for 30 min at 4 °C. Plasma and serum were separated and stored at −80 °C for later batch analysis.

Definitions of major post-operative cardiac complications

These events were defined as follows: acute myocardial infarction (MI) in accordance with the World Health Organisation criteria that require two of the following three features to be present, ECG change, typical chest pain and cardiac enzyme rise;[16] congestive cardiac failure associated with chest X-ray evidence of pulmonary oedema; cardiac arrhythmias requiring therapeutic intervention; cardiac arrest or ventricular fibrillation and cardiac death.

Table 1. Tissue plasminogen activator (t-PA) activity and plasminogen activator inhibitor (PAI) activity in 20 patients operated for ruptured abdominal aortic aneurysm.

	Normal range	Sample	Median (range)
t-PA activity	0.2–2.0 IU/ml	A	0.24 (0.06–7.9)
		B	0.28 (0.08–7.6)
		C	0.36 (0.09–7.3)
PAI activity	<15 AU/ml	A	35.2 (2.6–39.4)
		B	38.2 (0.1–39.8)
		C	37.2 (0.1–39.5)

Key: Sample A = immediately before induction of anaesthesia, Sample B = immediately before release of the aortic clamp, Sample C = five minutes after aortic clamp release.

Statistical methods

As these data were not normally distributed, the Spearman rank test was used to correlate the levels of t-PA activity, PAI activity, systolic blood pressure pre and intra-operatively and blood transfusion requirement with cTnI levels. Where levels of cTnI were below the limit of detection of the assay, the minimum detection concentration was assigned to that sample (0.5 ng/ml), and statistical analysis performed using this definition.[17] A probability value of less than 0.05 was regarded as statistically significant.

Results

Fibrinolytic function and myocardial injury

The median (range) values for t-PA and PAI activity are shown in Table 1. cTnI was detectable in 24 of 60 (40%) samples and was positive for myocardial injury at 1 or more sample point in 13 (65%) patients. cTnI was detectable pre-operatively in 5 patients, at 6 h following clamp release in 7 patients and at 24 h in 12 patients. Twelve of the 13 patients with detectable cTnI were hypotensive before the operation. Eight (40%) patients had clinically apparent major post-operative cardiac complications (Table 2), and 7 of these patients had elevated cTnI. Six of the 12 patients with no major cardiac complications also had elevated cTnI levels.

There was a significant negative correlation between pre-operative t-PA activity and cTnI before operation ($r = -0.55$, $p = 0.01$) (Fig. 1) and 6 h ($r = -0.51$, $p = 0.02$) after aortic clamp release. There was a significant positive correlation between pre-operative PAI activity and cTnI before operation ($r = +0.50$, $p = 0.02$) (Fig. 2), 6 h ($r = +0.47$, $p = 0.04$) and 24 h ($r = +0.50$, $p = 0.03$) after aortic clamp release.

Pre- and intra-operative hypotension and myocardial injury

No correlation was found between the lowest documented systolic blood pressure either pre or intra operatively and cTnI release during the first 24 h.

Blood transfusion requirements and myocardial injury

No correlation was found between the packed cell blood transfusion requirements of the patient either intra or post operatively and cTnI release during the first 24 h.

Discussion

The present study has shown, for the first time, an association between pre-operative inhibition of systemic fibrinolysis, as demonstrated by elevated PAI-1 and reduced t-PA activity, and peri-operative myocardial injury, as demonstrated by cTnI release, in patients undergoing repair of ruptured AAA.

In patients undergoing major vascular surgery, cTnI offers major advantages over other standard biochemical markers of myocardial injury. Unlike the myocardial iso-enzyme of creatine kinase (CK-MB), cTnI is not increased due to skeletal muscle injury so spurious results as a result of surgical trauma are not obtained.[9] Given this potential usefulness, there are very few published series that have examined the use of troponin in the diagnosis of PMI in non-cardiac vascular surgical patients. Adams *et al*. reported on 108 patients of whom 96 had undergone major vascular surgery.[18] Eight patients suffered a PMI as defined by echocardiographic detection of segmental wall defects. Of these, all had an associated cTnI rise, but only 6 had a CK-MB rise. A further 19 patients had a CK-MB rise with no echocardiographic changes, only one of whom had a cTnI rise. They concluded that cTnI is of most benefit in avoiding the false negative diagnosis of cardiac injury with a raised CK-MB, but with no echocardiographic evidence of wall damage. Metzler studied 67 patients undergoing a variety of major abdominal, vascular and orthopaedic operations.[19] With serial measurement over a 7 day period, 13 patients (20%) had an increase in both cTnT and cTnI. 8 patients had significant cardiac events and relatively higher (>0.2 $\mu g/l^{-1}$) cTnT levels. They concluded that the degree of cTn elevation reflects the severity of injury and also suggested that elevations of both cTnT and cTnI are necessary for diagnosis.

Table 2. Post-operative cardiac complications and cardiac troponin I (cTnI I) levels in 20 patients operated for ruptured abdominal aortic aneurysm.

Patient	Cardiac complications	Cardiac troponin I (ng/ml)		
		Sample A	Sample B	Sample C
1	Arrhythmia	ND	ND	2.6
2	None	3.6	0.9	0.6
3	None	ND	27.6	50.9
4	MI, arrhythmia, CCF	ND	24.9	106
5	CCF	1.1	7.4	16.5
6	Arrhythmia, CCF	1.3	71.1	110
7*	None	0.6	0.6	ND
7*	None	0.6	0.6	ND
8*	Arrhythmia, CCF	ND	ND	ND
9	CCF	ND	ND	0.5
10	None	6.8	5.5	2.9
11*	None	ND	ND	ND
12*	Arrhythmia	ND	ND	0.7
13*	None	ND	ND	0.9
14	None	ND	ND	ND
15	None	ND	ND	ND
16*	Arrhythmia	ND	ND	1.0
17	None	ND	ND	1.7
18	None	ND	ND	ND
19	None	ND	ND	ND
20	None	ND	ND	ND

Key: Sample A = immediately before induction of anaesthesia, Sample B = 6 h after aortic clamp release, Sample C = 24 h after aortic clamp release, MI-myocardial infarction, CCF = congestive cardiac failure, ND = not detectable, * = died.

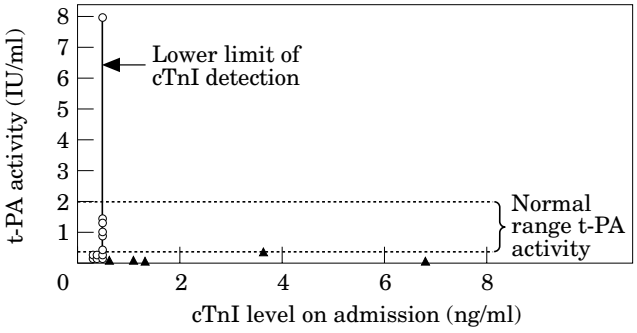

Fig. 1. The relationship between tPA and cTnI levels preoperatively (*Spearman rank correlation). (▲) cTnI rise; (○) no cTnI rise. $r = -0.55$, $p = 0.01$.

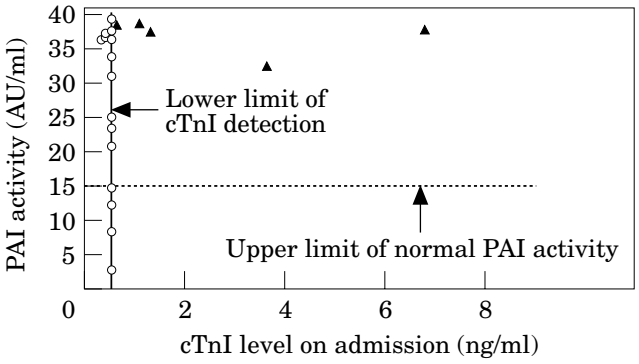

Fig. 2. The relationship between PAI-1 and cTnI levels on admission to hospital (*Spearman rank correlation). (▲) cTnI rise; (○) no cTnI rise. $r = 0.50$, $p = 0.03$.

Lee *et al*. studied cTnT in 1175 patients undergoing major non-cardiac vascular surgery.[20] cTnT was elevated in 87% of patients with a CK/CK-MB rise and ECG changes diagnostic of PMI. This compares with 16% of patients who had no evidence of PMI. In those patients who had other cardiac complications, cTnT was elevated in 62%, compared with 15% of those with no complications. These data indicate that cTnT had a similar performance for the diagnosis of definite MI as CK/CK-MB but a better correlation with major cardiac complications where no definite infarction could be identified. They concede however that asymptomatic cTnT rise was common and that some 90% of patients with a rise suffered no apparent major cardiac complications. This suggests the following possibilities: a lack of specificity of cTnT for cardiac injury; a lack of specificity for the antibodies against cTnT used in their assay or sub-clinical myocardial micro-infarction that could not be detected other means. This question of the significance of an asymptomatic rise in troponin is addressed by a later study from the same group.[21] In this study, they examined an asymptomatic group of 772 patients undergoing major surgery, of whom 92 (12%) and 211 (27%) suffered a cTnT or CK/CK-MB rise respectively. They conclude that cTnT rise was associated with a higher relative risk of cardiac complications at 6 months follow up. cTnT rise was also correlated with in-hospital congestive failure, new cardiac arrhythmia or a raised CK/CK-MB suggesting

that micro-infarction with cTnT release may have been the cause of these events.

In a study by Neill *et al*. of 80 patients undergoing major vascular or orthopaedic surgery cTnT, cTnI and CK/CK-MB were examined.[22] Silent myocardial ischaemia was found in 21 patients and elevations occurred in 4, 6 and 17 of these patients for cTnT, cTnI and CK/CK-MB respectively. This study calculated the relative odds risk for major adverse cardiac events and found that, in keeping with the previous studies by Metzler and Lee, cTnT was a useful prospective marker for both major and minor cardiovascular complications.[19,20]

In this study, cTnI was elevated at one or more sample point in 13 (65%) patients, and in 7 of 8 patients who had clinically apparent major cardiac complications. It is possible that the elevated cTnI levels in the 6 patients with no clinically apparent cardiac complications indicate micro infarction as has been previously described and this occurrence may put patients at a subsequent higher risk of late cardiac events.[20]

We have found that there was an association between high PAI activity and low t-PA activity and biochemical evidence of myocardial injury. It is relevant, therefore, to speculate about the possible causal mechanisms underlying this observation. Patients with peripheral arterial disease have a high prevalence of coronary artery disease.[11,23] Rupture of coronary artery plaque leading to thrombosis generally results in transmural ischaemia and a Q-wave infarction on electrocardiography.[8] By contrast, post-operative MI is often of the non-Q wave type and is frequently heralded by periods of ST segment depression indicating myocardial ischaemia.[24,25] Hypofibrinolysis may predispose to both types of infarction by promoting acute thrombosis of a critical stenosis within a main coronary artery and/or sludging of the myocardial microcirculation.

In conclusion, these novel data demonstrate that the hypofibrinolytic state which occurs during ruptured AAA repair is closely linked to the development of post-operative myocardial injury through, as yet, unknown mechanisms. This observation may be of direct clinical value if early rises in cTnI can be used to predict subsequent cardiac complications and/or the treatment of the prothrombotic diathesis can be used to prevent or limit the extent of myocardial necrosis.[26] These questions are currently the subject of on-going studies.

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References

1 Adam DJ, Ludlam CA, Ruckley CV, Bradbury AW. Coagulation and fibrinolysis in patients undergoing operation for ruptured and nonruptured infrarenal aortic aneurysms. *J Vasc Surg* 1999; **30**: 641–650.
2 Mair J, Dienstl F, Puschendorf B. Cardiac troponin T in the diagnosis of myocardial injury. *Crit Rev Clin Lab Sci* 1992; **29**: 31–57.
3 Mair J, Genser N, Morandell D *et al.* Cardiac troponin I in the diagnosis of myocardial injury and infarction. *Clin Chim Acta* 1996; **245**: 19–38.
4 Adams JE, III, Bodor GS, Davila-Roman VG *et al.* Cardiac troponin I a marker with high specificity for cardiac injury. *Circulation* 1993; **88**: 101–106.
5 Hamm CW, Goldmann B, Heeschen C *et al.* Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T of troponin I. *N Engl J Med* 1997; **337**: 1648–1653.
6 Hamm CW, Ravkilde J, Gerhardt W *et al.* The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992; **327**: 146–150.
7 Heeschen C, Hamm CW, Goldmann B *et al.* Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofaban. *Lancet* 1999; **354**: 1757–1762.
8 Antman EM, Tanasijevic MJ, Thompson B *et al.* Cardiac specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; **335**: 1342–1349.
9 Bodor G, Porterfield D, Voss EM, Smith S, Apple FS. Cardiac Troponin I is not expressed in fetal and healthy or diseased adult human skeletal muscle. *Clin Chem* 1997; **41**: 1710–1715.
10 Seegobin RD, Wilmshurst TH, Johnston J *et al.* Early postoperative myocardial morbidity in patients with coronary artery disease undergoing major non-cardiac surgery: correlation with perioperative ischaemia. *Can J Anaes* 1991; **38**: 1012–1022.
11 Galland RB. Mortality following elective infrarenal aortic reconstruction: a Joint Vascular Research Group study. *Br J Surg* 1998; **85**: 633–636.
12 Soreside O, Grimsgaard CHR, Myre HO, Solheim K. Time and cause of death for 301 patients operated on for abdominal aortic aneurysm. *Age Ageing* 1982; **11**: 256–260.
13 Juhan-Vague I, Pyke SDM, Alessi MC, Jespersen J, Thompson SG. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *Circulation* 1996; **94**: 2057–2063.
14 Held C, Hjemdahl P, Rehnqvist N *et al.* Fibrinolytic variables and cardiovascular prognosis in patients with stable angina pectoris treated with verapamil or metoprolol. *Circulation* 1997; **95**: 2380–2386.
15 Juhan-Vague I, Alessi MC. Plasminogen activator inhibitor-1 and atherothrombosis. *Thromb Haemost* 1993; **70**: 000–138.
16 WHO. Report of the Joint International Society and federation of Cardiology/World Health Organisation Task Force and Standardisation of Clinical Nomenclature and criteria for diagnosis of ischaemic heart. *Circulation* 1979; **59**: 607–608.
17 De Beaux A, Goldie AS, Ross JA, Carter DC, Fearon KCH. Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis. *Br J Surg* 2001; **83**: 349–353.
18 Adams JE, III, Sigard GA, Allen BT *et al.* Diagnosis of perioperative myocardial infarction with measurment of cardiac troponin I. *N Engl J Med* 1994; **330**: 670–674.
19 Metzler H, Gries M, Rehak P *et al.* Perioperative myocardial cell injury: the role of troponins. *Br J Anaes* 1997; **78**: 386–390.

20 Lee TH, Thomas EJ, Ludwig LE *et al.* Troponin T as a marker for myocardial ischemia in patients undergoing major noncardiac surgery. *Am J Cardiol* 1996; **77**: 1031–1036.
21 Lopez-Jimenez J, Goldman L, Sacks DB *et al.* Prognostic value of cardiac troponin T after noncardiac surgery: 6 month follow up. *J Am Coll Cardiol* 1997; **29**: 1241–1245.
22 Neill F, Sear JW, French G *et al.* Increases in serum concentrations of cardiac proteins and the prediction of early postoperative cardiovascular complications in non cardiac surgery patients. *Anesthesiology* 2000; **55**: 641–647.
23 L'Italien GJ, Cambria RP, Cutler BS. Comparative early and late cardiac morbidity among patients requiring different vascular surgical procedures. *J Vasc Surg* 1995; **21**: 935–944.
24 Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW. Myocardial infarction after noncardiac surgery [see comments]. *Anesthesiology* 1998; **88**: 572–578.
25 Landesberg G, Luria MH, Cotev S *et al.* Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery [see comments]. *Lancet* 1993; **341**: 715–719.
26 Thompson JF, Mullee MA, Bell PRF. Intraoperative heparinisation, blood loss and myocardial infarction during aortic aneurysm surgery: a Joint Vascular Research Group study. *European Journal of Vascular and Endovascular Surgery* 1996; **12**: 86–90.

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