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Cardiac troponin release is associated with biomarkers of inflammation and ventricular dilatation during critical illness

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ABSTRACT

Introduction: Troponin release is common during critical illness. We hypothesized that there was an association between cardiac troponin T (cTnT) and biomarkers of systemic inflammation and ventricular dilatation.

Methods: In an observational prospective cohort study, we enrolled consecutive adult patients admitted for non-cardiac reasons to the Intensive Care Unit (ICU) in 2 tertiary care centers. We measured cTnT, C-reactive protein (CRP), Interleukin-6 (IL-6), procalcitonin (PCT) and N-terminal pro brain natriuretic peptide (NT-proBNP) daily in the first week, and on alternate days in the second week. Using a peak cTnT cut-off ≥15ng/L and concomitant changes on electrocardiogram (ECG), patients were categorised as "definite myocardial infarction (MI)", "possible MI", "cTnT rise only" or "no cTnT rise". Within each group, associations between CRP, IL-6, PCT, NT-proBNP and cTnT were investigated using mixed effect models.

Results: 172 patients were included in the analysis of whom 84% had a cTnT rise ≥15ng/L. 21 patients (12%) had a definite MI, 51 (30%) had a possible MI and 73 (42%) had a cTnT rise only. At time of peak cTnT, 71% of patients were septic and 67% were on vasopressors.

Multivariable analysis showed a significant association between cTnT and IL-6 in all patients with a cTnT rise independent of age, gender, renal function and cardiovascular risk factors. In patients without a definite MI, cTnT levels were significantly associated with PCT and NT-proBNP values. In patients without elevated cTnT levels, there was no associated NT-proBNP rise.

Conclusions: In ICU patients admitted for non-cardiac reasons, serial cTnT levels were independently associated with markers of systemic inflammation and NT-proBNP.

Keywords: troponin, critical illness, inflammation, sepsis, ventricular dilatation, inflammatory markers

INTRODUCTION

Troponin release is common during critical illness and associated with increased morbidity, mortality and length of stay (1-15). We previously showed that 84% of patients admitted to the Intensive Care Unit (ICU) for non-cardiac reasons had at least one elevated cardiac troponin T (cTnT) result (10). Only 14% of patients fulfilled criteria for a definite myocardial infarction (MI), and 27% had changes on electrocardiogram (ECG) suggestive of a possible MI.

Troponin T is a cardiac-specific molecule that is released into the systemic circulation following myocardial cell injury. Sepsis and inflammation are the leading non-cardiac causes of elevated troponin levels during critical illness (2, 14, 16-19). In sepsis, the heart undergoes physiologic and metabolic changes, including altered coronary blood flow, reduced oxygen extraction, regional and global wall hypokinesia and ventricular dilatation (20-23). Coronary blood flow is often increased. In this situation, a potential explanation for troponin release is cellular ischaemia due to microcirculatory changes within the myocardium (23-25). Circulating inflammatory cytokines appear to contribute through direct myocytotoxic effects, perturbations in microvascular flow and effects on cell permeability (20, 26). Regional and global wall hypokinesia resulting in increased cardiac filling pressures and ventricular dilatation may also play a role.

We hypothesized that there was a relationship between cTnT levels and biomarkers of systemic inflammation and ventricular dilatation during critical illness.

MATERIALS AND METHODS

Objectives

Our objectives were:

i) to investigate the association between cTnT and C-reactive protein (CRP), Interleukin-6 (IL-6), and procalcitonin (PCT) as markers of systemic inflammation;

ii) to investigate the association between cTnT and N-Terminal pro brain natriuretic peptide (NT-proBNP) as a biomarker of ventricular dilatation.

Study protocol

The study protocol and methods have been described in detail elsewhere (10). We included a second centre (St George's University Hospital, London, UK) where the study was conducted during the same time period (June 2010 – April 2012) using the same protocol.

As previously described (10), we enrolled consecutive adult patients (≥18 years) admitted to the ICU for non-cardiac reasons. Patients with a high probability of cardiac injury or a primary cardiac diagnosis were excluded. In the first week, we measured cTnT, NT-proBNP, CRP, IL-6 and PCT and performed an ECG on a daily basis. During the second week, the blood tests and ECGs were taken on alternate days until discharge from ICU, death or day 14 after admission, whichever occurred first. Blood samples taken for research purposes were stored at -70^{0}C and ECGs were kept in secure lockers until batch analysis at the end of the study. Clinicians were allowed to order ECGs, cTnT and inflammatory markers separately as clinically indicated.

Laboratory analyses

All laboratory analyses were performed in the Department of Biochemistry at St George's University Hospital by 2 biochemists (ET and PC) who were blinded to the study and not involved in patient selection, data collection and data analysis.

Cardiac Troponin T (cTnT) was measured using the Roche electrochemiluminescent high sensitivity sandwich immunoassay on the Elecsys 2010 [quoted analytical range: 3-10,000ng/L; total coefficients of variation (CVs): 1.5-3.4% (measured between 24-2665ng/L) and reference range: <15ng/L (99th percentile)]. NT-proBNP was measured using the Diagnostic Products Corporation (DPC) Immulite 2500 chemiluminescent sandwich immunoassay [analytical range: 20–35,000pg/ml; quoted total CVs: 3.4–5.6% (measured between 40.9–32,096pg/ml) and reference range: <125pg/ml in patients <75 years and <450pg/ml in those over 75]. PCT was measured using a three-site sandwich immunoassay on the Advia Centaur (analytical range: 0.02–75ng/ml and reference range: <0.1ng/ml). CRP was measured using a latex enhanced immunoturbidimetric method on the Siemens Advia 2400 [analytical range: 4–336mg/L; total CVs: 1.1–1.4% (measured between 32–222mg/L) and reference range: <10mg/L]. IL-6 was

measured using the DPC Immulite 2500 chemiluminescent sandwich immunoassay [analytical range: 2–1000pg/ml; total CVs: 4.6–7.2% (measured between 89–724pg/ml) and reference range: <5.9pg/ml].

Data collection

We collected demographics, admission diagnosis, cardiovascular risk factors [ischaemic heart disease (IHD), diabetes, hypertension, any type of vascular disease], Acute Physiology and Chronic Health Evaluation (APACHE) II score, serum creatinine, vasopressor use, treatment with renal replacement therapy (RRT), presence of sepsis [as per previous consensus criteria (27)] and ICU and hospital outcome.

Interpretation of troponin levels

As described previously (10), the ECGs were analysed independently by two senior cardiologists who were blinded to the cTnT results and clinical details. In case of discrepancy, adjudication was undertaken by a third senior cardiologist. The diagnosis of acute MI was based on the most recent consensus criteria (28). Accordingly, patients were classified into four groups depending on their peak cTnT level and ECG taken on the same day or the day before: (i) "definite MI", with cTnT ≥15ng/L and ECG changes consistent with MI, (ii) "possible MI", with cTnT ≥15ng/L and ischaemic changes on ECG but not fulfilling criteria for definite MI, (iii) "cTnT rise alone", and (iv) "no cTnT rise" with peak cTnT <15ng/L.

Statistics

We used means for continuous variables and proportions for categorical variables to describe baseline characteristics. The 4 groups were compared using the Kruskal-Wallis method for continuous variables where the distribution was not normal and Chi squared test for categorical variables. The associations between cTnT and CRP, IL-6, PCT and NT-proBNP were investigated using two-level mixed effect models to take into account the serial measurements over the duration of stay in ICU. The patient identifiers were modelled as a random effect and the repeated blood values were effectively averaged within patients.

The models were initially fitted separately for each predictor to evaluate the unifactorial relationship with the outcome cTnT. Multivariable mixed effects models were used to adjust for potential confounders including age, gender and history of IHD, hypertension and diabetes or any form of vascular disease. We adjusted for renal function by adding a binary covariate indicating 'treatment with RRT or serum creatinine ≥140μmol/L', versus 'no RRT and serum creatinine <140μmol/L'. All variables included in the models were chosen *a priori* on clinical grounds and all chosen variables were included in the multivariable models.

Since cTnT was log-transformed to correct for positive skewness, the model results were back-transformed and presented as percentage change associated with a 'one unit' change in the variable of interest. In order to make it easier to compare the results for different biomarkers, we presented a standardised measure of effect by calculating the percentage change in cTnT that would occur if the biomarker changed by one standard deviation (SD) of its distribution (29). It was necessary to log-transform IL-6. As a result, its results could not be expressed in a meaningful way in terms of a percentage associated with a unit change. Instead we calculated the change in cTnT for a SD change in IL-6 using the SD of the log-transformed data. All results are presented as estimates with 95% confidence intervals (CI) wherever possible. To illustrate the variations of each biomarker over time in each of the 4 groups, the daily median values of CRP, IL-6, PCT, NT-proBNP and cTnT in their original units were graphically displayed.

The 4 groups were analysed as independent cohorts as we aimed to examine the differences between the characteristics of these, and the associations between the outcome cTnT and the different markers for each of the 4 groups. The model residuals were examined for normality using Quantile Quantile (QQ) Plots. Stata version 14 was used for the analyses.

Ethics

The study was approved by a formal Research Ethics Committee (REC) and the Research & Development Department in our hospital. Written informed consent was obtained from the patients prior

to enrolment. As previously described, if a patient did not have capacity to consent, the opinion of a personal consultee was sought in accordance with section 32 of the Mental Capacity Act 2005 (UK). In this case, the patients were asked to give informed consent after they had regained capacity. If consent was declined, all collected samples and ECGs were discarded. In case retrospective consent could not be obtained due to death or lack of capacity, the REC approved that these patients could be included in the analysis.

RESULTS

Patient population

We enrolled 179 patients of whom 7 were excluded (5 patients had an acute coronary syndrome on admission to ICU which was not recognised by the research team at enrolment and 2 patients were transferred to another hospital within 48 hours of ICU admission). The baseline characteristics of the remaining 172 patients are shown in Table 1. The main reasons for admission to ICU were sepsis (37%), post-emergency surgery (21%), respiratory failure (11%), neurological emergency, including drug overdose (10%), gastrointestinal bleed (7%), acute kidney injury (4%) and other non-cardiac causes (10%).

Prevalence of troponin rise

145 patients (84%) had at least one cTnT value ≥15ng/L during their stay in ICU. Among them, 21 (12%) had contemporaneous ECG changes consistent with a definite MI of whom 14 were recognised by the clinical team and 4 underwent coronary angiography. Fifty-one patients (35%) had ECG changes suggestive of a possible MI and 73 (42%) had a cTnT rise without any ECG changes. 27 patients (16%) had no cTnT rise ≥15ng/L. The mean, median, ranges (minimum – maximum) and interquartile ranges (IQR) of the cTnT levels are shown in Table 2. Between 1–11 daily measurements were taken per patient, and estimates were based on repeated measures over the observation period. The highest cTnT values were observed in patients with a definite MI. Patients with a "raised cTnT only" had the highest

APACHE II score on admission, the highest proportion of patients with sepsis and also the highest IL-6 results. (Table 2)

At the time of peak cTnT levels, 71% patients had sepsis and 67% were on vasopressor treatment. Noradrenaline was the most frequently used vasopressor (89%).

Association between troponin levels and inflammatory markers

The medians for CRP, IL-6, PCT, NT-proBNP and cTnT were displayed for the 4 groups separately. (Figure 1) The graph illustrates the large variations of the different biomarkers between the 4 groups and the patterns of change within each group.

Table 3 demonstrates the associations between cTnT and CRP, IL-6 and PCT and the presence of sepsis, both unadjusted and adjusted for potential confounders. Multivariable analysis showed an independent temporal association between cTnT and IL-6 in all patients with a cTnT rise. An increase in IL-6 by one SD was associated with a 16-23% rise in cTnT depending on individual cTnT group. In patients without a cTnT rise, there was no significant association between cTnT and IL-6.

Cardiac troponin T was also independently associated with PCT levels in all patients except those with a definite MI. An increase in PCT by one SD was associated with a 13-17% rise in cTnT.

There was an independent association between sepsis and cTnT results in patients with a definite MI and those with raised cTnT levels only. In cTnT positive patients without contemporaneous ECG changes, the mean cTnT levels were raised by 23% in patients with sepsis compared to those without sepsis. (Table 3). The adjusted estimates of percentage effect size and 95% CI, were displayed using a high low graph for the 4 groups. (Figure 2)

Association between troponin levels and NT-proBNP

There was a strong independent association between cTnT and NT-proBNP levels in all patient groups except those with a definite MI. (Table 3) An increase in NT-proBNP by one SD was associated with a

0.02% increase in cTnT. In patients without elevated cTnT levels, there was no associated NT-proBNP rise.

DISCUSSION

Our study confirmed an association between cTnT levels and markers of systemic inflammation and NT-proBNP in critically ill patients admitted for non-cardiac reasons. In cTnT positive patients, there was a significant association between cTnT release and IL-6 levels independent of age, gender, renal function and presence of cardiovascular risk factors. An increase in IL-6 by one SD was associated with a 16-23% rise in cTnT. In addition, there was an independent association between cTnT levels and NT-proBNP in all patients except in those with a definite MI.

These results support the current theories for troponin release in the absence of myocardial necrosis. A popular theory is that troponin release may be caused by cellular ischaemia without irreversible cell necrosis due to altered microcirculation (30, 31). Using isolated cultured myocardial cells, Schwartz et al showed that during limited periods of ischaemia, cultured cardiac myocytes remained viable but developed blebs containing cytoplasmic material (31). If ischaemia was corrected relatively quickly, the blebs were either reabsorbed or shed into the circulation without myocyte damage. In patients with septic shock, post-mortem examinations have also shown more pronounced histological abnormalities in troponin-positive patients compared to patients without a troponin rise (32).

Ventricular dilatation and wall stress are other possible explanations for troponin release during sepsis. Studies in humans and animals suggest that cytokines, in particular IL-1β, IL-6 and tumour necrosis factor alpha (TNF-α) may play a role (33). TNF-α is known to increase the permeability of endothelial cells. Its effect on myocardial cells appears to be similar, thus leading to leakage of cTn (34). However, in healthy volunteers who underwent intravenous injection of endotoxin and subsequently developed significant elevations in serum TNF-α, IL-6, and IL-8 levels, there was no significant increase in systemic cTn levels which suggests that TNF-α alone may not be sufficient to induce significant changes (35).

In vitro studies have shown that serum obtained from patients with septic shock was able to depress rat cardiomyocytes' contractility and induce ventricular dilatation (36, 37). Fernandes et al. described a correlation between raised troponin levels and left ventricular systolic dysfunction in critically ill patients with sepsis (38). Similarly, ver Elst et al showed that in patients with septic shock, elevated cTn levels were strongly associated with left ventricular dysfunction, as assessed by transoesophageal echocardiography (30). In a separate study of 37 patients with septic shock, those with raised troponin levels had a higher incidence of regional wall motion abnormalities on echocardiography (56% versus 6%, p=0.002), lower ejection fraction (46% versus 62%, p=0.04) and higher mortality (56% versus 24%, p=0.04) compared to patients with normal troponin levels (39). Finally, Landesberg et al investigated general ICU patients with severe sepsis / septic shock and demonstrated that left ventricular diastolic dysfunction and right ventricular dilatation were the echocardiographic signs which correlated best with troponin elevation (40).

Atrial and ventricular filling pressures in the left and right chambers are the main determinants of release of natriuretic peptides. NT-proBNP is a marker of ventricular dilatation and strain. In a sub-analysis of the Albumin Italian Outcome Sepsis trial including 995 patients with severe sepsis or septic shock, Masson et al showed that 97% of patients had NT-proBNP levels above the upper limit of normal and 85% of patients had cTnT levels greater than normal (41). However, cardiac function was not directly assessed.

Our findings support the hypothesis that troponin release during critical illness may be representative of both - systemic inflammation and ventricular strain. With serial troponin levels of 172 patients from 2 different centers for up to 14 days, our study is one of the largest in the literature. The findings are strengthened by the fact that we a) only included ICU patients admitted for non-cardiac reasons, b) analysed patients in 4 different groups depending on whether they had a definite, possible or no MI during their stay in ICU, c) corrected for important confounding factors, d) had all ECGs interpreted independently by senior cardiologists who were blinded to the troponin results, and e) tested hypotheses which had been formed *a priori*.

It is still important to acknowledge some limitations. The observational nature of the study prevents us from defining causality between inflammatory markers and cTnT elevations. Second, we analysed patients with and without sepsis which may have impacted the strength of the associations. Third, we did not measure IL-1β or TNF-α, two key inflammatory cytokines. Similarly, we did not perform routine echocardiography in all patients to correlate the NT-proBNP results with ventricular dilatation and acknowledge that other mechanisms beyond ventricular stretch stimulate BNP release (42). Finally, we defined sepsis according to the previous consensus criteria as our study was conducted before the new sepsis criteria were published (27).

Despite these limitations, we believe that our findings advance the understanding of troponin release during critical illness. Obviously, the results do not allow any recommendations regarding optimal management of troponin-positive patients after an MI has been excluded. We note the findings of a nationwide survey of 310 intensivists in the US regarding the management of ICU patients with elevated troponin levels without typical features of acute coronary syndrome (43). 76% of respondents stated that they would start either aspirin or clopidogrel, and 47% would commence heparin, 49% recommended high dose statins, 69% would start beta-blockers and 38% would use an angiotensin-converting-enzyme inhibitor. In addition, 73% of the intensivists would request a cardiology consultation and 52% would make a referral for coronary angiography. Given the wide variety of opinions, a better understanding and more guidance regarding the management of troponin-positive patients is urgently required.
In conclusion, our results show that cTnT is associated with NT-pro-BNP and markers of systemic inflammation, especially in patients without a definite MI.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MO and DT designed the protocol and led the research project. KL, JS, BS and CM recruited patients and collected the necessary specimens and ECGs. PC and ET performed the laboratory analyses. SA, JL and JP performed the statistical analyses. MO wrote the first draft. All authors revised the manuscript and contributed to the data interpretation. All authors approved the final manuscript.

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2. Professor David Bennett made significant contributions to the study protocol. He sadly died on 21st February 2012 and is still deeply missed.

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FIGURE LEGENDS

Figure 1 Patterns of variations described by medians over time from Day 1 to Day 14 for the outcome cardiac troponin T and biomarkers of inflammation and ventricular strain in four groups

The daily median values of CRP, IL-6, PCT, NT-proBNP and cTnT in their original units were graphically displayed to illustrate the variations of each biomarker over time in each of the 4 groups. NT-proBNP was scaled down for the graph by dividing it by 100 to allow the presentation on the same scale as other parameters.

Abbreviations: CRP = C-reactive protein; cTnT = cardiac troponin T; IL-6 = Interleukin-6; MI = myocardial infarction; NT-proBNP = N-terminal pro brain natriuretic peptide; PCT = procalcitonin

Figure 2 Adjusted percentage effect size and 95% Confidence Intervals for different biomarkers in 4 groups

Abbreviations: CRP = C-reactive protein; cTnT = cardiac troponin T; IL-6 = Interleukin 6; MI = myocardial infarction; UCI = Upper confidence interval; LCI = Lower confidence interval; NT-proBNP = N-terminal pro brain natriuretic peptide; PCT = procalcitonin

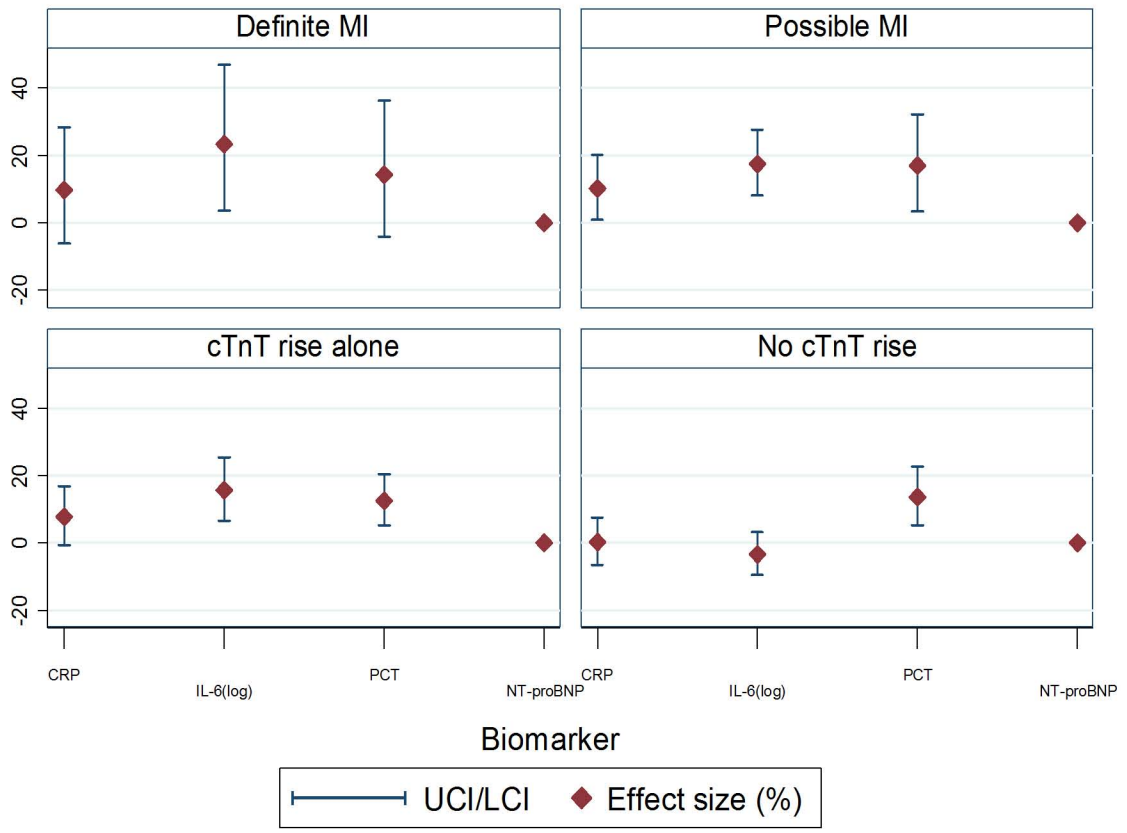

Table 1. Baseline characteristics of patients in the 4 groups

Characteristics	All groups	Definite MI	Possible MI	Raised cTnT only	No cTn rise	P value *
Group size (n)	172	21	51	73	27	
Total number of cTnT results	997	138	318	415	126	
Median number of cTnT results per patient (min - max)	6 (1-11)	7 (1-11)	6 (1-11)	6 (1-11)	3 (1-11)	
Age, mean (SD)	63.0 (16.6)	61.4 (14.4)	68.6 (14.4)	64.9 (15.2)	48.4 (17.7)	<0.01
Female gender, n (%)	72 (42%)	8 (38%)	22 (43%)	34 (47%)	8 (30%)	0.48
White ethnicity, n (%)	142 (83%)	18 (86%)	40 (80%)	63 (90%)	21 (84%)	0.33
APACHE II score on admission to ICU, mean (SD)	18.2 (6.6)	18.0 (6.22)	18.9 (6.2)	20.0 (6.5)	12.5 (4.8)	<0.01
Serum creatinine ≥140µmol/L at any time during study period, n (%)	76 (44.2%)	10 (47.6%)	26 (51%)	39 (53.4%)	1 (3.7%)	<0.001
Treatment with RRT, n (%)	54 (31.4%)	7 (33.3%)	16 (31.4%)	30 (41.1%)	1 (3.7%)	0.005
RRT or serum creatinine ≥140 µmol/L, n (%)	87 (50.6%)	10 (47.6%)	31 (60.8%)	45(61.6%)	1 (3.7%)	<0.001
Comorbidities						
Ischaemic heart disease, n (%)	33 (20%)	6 (29%)	12 (24%)	13 (18%)	2 (7%)	0.23
Hypertension, n (%)	67 (39%)	8 (38%)	30 (59%)	24 (33%)	5 (19%)	<0.01
Diabetes, n (%)	51 (30%)	8 (38%)	20 (39%)	20 (27%)	3 (11%)	0.06
Any form of vascular disease, n (%)	34 (20%)	4 (19%)	15 (29%)	14 (19%)	1 (3.7%)	0.06

Mortality						
in hospital, n (%)	42 (24%)	6 (29%)	16 (31%)	19 (26%)	1 (3.7%)	0.03
in ICU, n (%)	32 (19%)	5 (24%)	11 (22%)	15 (21%)	1 (3.7%)	0.44

Abbreviations: APACHE = Acute Physiology and Chronic Health; cTnT = cardiac troponin T; ICU = intensive care unit; RRT = renal replacement therapy; SD = standard deviation

* p-values are for the test of heterogeneity among the four proportions or means as appropriate

Table 2. Biomarkers of inflammation and ventricular dilatation in the 4 groups

Parameter	Definite MI (n=21)	Possible MI (n=51)	Raised cTnT only (n=73)	No cTnT rise (n=27)
cTnT (ng/L)				
Mean (SD)	250.1 (477)	238.5 (486)	88.7 (143)	3.9 (4.1)
Median	80.5	61	46	1.7
IQR	171	150	82	4
Range (min - max)	9 - 3093	5 - 3335	<0.3 - 1337	<0.3 – 14
IL-6 (pg/mL)				
Mean (SD)	131.5 (323)	386.7 (1566)	1919 (20863)	142.0 (434)
Median	48.1	55.8	55.1	51.8
IQR	72	131.3	146.7	75.1
Range (min - max)	<2 - 2522	<2 - 18120	<2 to >300000	5.49 – 4037
CRP (mg/L)				
Mean (SD)	113.1 (78)	126.8 (86.5)	132.6 (97)	134.7 (84.3)
Median	101.2	108.9	107.4	126.1
IQR	125.1	113.8	144.2	125.3
Range (min - max)	<4 - 448.3	<4 - 428.2	<4 - 499.1	<4 - 326.6
PCT (ng/ml)				
Mean (SD)	4.1 (10.3)	6.3 (13.1)	8.2 (18.1)	2.3 (5.9)
Median	0.7	1.5	2	0.4
IQR	2.4	5.1	6.7	0.9
Range (min - max)	0.1 - 75	0 - 75	0 - 199.5	0 - 41.3
NT-pro-BNP (ng/ml)				
Mean (SD)	15.8 (21.3)	15.1 (19.5)	7.27 (11.5)	1.97 (3.6)
Median	6.6	7.4	3.0	0.3
IQR	22.5	19.6	7.4	1.3
Range (min - max)	0.02 - 155	0.08 - 108	0.02 – 75.5	0.02 – 16.5
Sepsis*	15 (71%)	38 (75%)	57 (78%)	13 (48%)
Any vasopressor use *	14 (67%)	37 (73%)	49 (67%)	10 (37%)
Noradrenaline use *	13 (62%)	32 (63%)	44 (60%)	9 (33%)

Abbreviations: CRP = C-reactive protein; cTnT = cardiac troponin T; IL-6 = Interleukin 6; MI = myocardial infarction; NT-pro-PNP = N-terminal pro brain natriuretic peptide; PCT = procalcitonin; SD = standard deviation; IQR = interquartile range.

Values preceded by < indicate minimum level detected.

Estimates presented in this table are based on all observations for all patients.

* on day of peak cTnT level

Table 3. Unadjusted and adjusted estimates of associations of cTnT with sepsis and CRP, IL-l, PCT and NT-proBNP in different troponin groups

Parameter	Unadjusted estimates: Effect of factor on cTnT as a percentage per unit cTnT, except sepsis* (95% CI)				Adjusted estimates: Effect of factor on cTnT as a percentage per unit cTnT, except sepsis* (95% CI)				Standardised effect sizes for adjusted analysis equivalent to a SD change in the relevant marker		
	Effect size (%)	LCI	UCI	p-value	Effect size (%)	LCI	UCI	p-value	Effect size (%)	LCI	UCI
Patients with definite MI (n=21)											
Sepsis	33	6.0	68	**0.01**	28.85	1.99	62.79	**0.03**			
CRP	0.13	-0.07	0.33	0.20	0.12	-0.08	0.32	0.25	9.70	-6.16	28.23
IL-6 (log)**	N/A			**0.006**	N/A			**0.02**	**23.37**	3.68	46.80
PCT	1.62	-0.06	3.33	0.06	1.30	-0.42	3.04	0.14	14.20	-4.21	36.15
NT-proBNP	0.00	-0.0003	0.001	0.23	0.0004	-0.0004	0.0012	0.31	0.01	-0.01	0.02
Patients with a possible MI (n=51)											
Sepsis	10.01	-5.48	28.03	0.22	5.98	-8.81	23.18	0.45			
CRP	0.13	0.03	0.23	**0.01**	0.11	0.01	0.21	**0.03**	**10.08**	0.85	20.16
IL-6 (log)**	N/A			**<0.001**	N/A			**<0.001**	**17.45**	8.14	27.56
PCT	1.32	0.36	2.29	**0.007**	1.20	0.25	2.15	**0.01**	**16.86**	3.31	32.17
NT-proBNP	0.00	0.0006	0.001	**<0.001**	0.0010	0.0005	0.0015	**<0.001**	**0.02**	0.01	0.03
Patients with raised cTnT only (n=73)											
Sepsis	22.12	6.56	39.95	**0.004**	23.17	4.99	37.80	**0.01**			
CRP	0.09	0.00	0.17	**0.045**	0.08	0.00	0.16	0.07	7.87	-0.47	16.92
IL-6 (log)**	N/A			**0.001**	N/A			**<0.001**	**15.68**	6.58	25.56
PCT	0.68	0.30	1.07	**<0.001**	0.70	0.28	1.03	**0.001**	**12.58**	5.23	20.45
NT-proBNP	0.00	0.0010	0.002	**<0.001**	0.0018	0.0006	0.0024	**0.001**	**0.02**	0.01	0.03
Patients without raised cTnT (n=27)											
Sepsis	-1.58	-15.80	15.03	0.84	-8.72	-21.03	5.51	0.22			
CRP	0.06	-0.03	0.15	0.16	0.00	-0.08	0.09	0.92	0.36	-6.35	7.55

IL-6 (log)**	N/A			0.31	N/A			0.31	-3.32	-9.45	3.24
PCT	2.86	1.35	4.38	**<0.001**	2.21	0.89	3.54	**0.001**	**13.74**	5.35	22.79
NT-proBNP	0.01	0.0036	0.008	**<0.001**	0.0049	0.0025	0.0073	**<0.001**	**0.02**	0.01	0.03

Continuation of Table 3:

Abbreviations: CI = Confidence interval; CRP = C-reactive protein; cTnT = cardiac troponin T; IL-6 = Interleukin 6; MI = myocardial infarction; UCI = Upper confidence interval; LCI = Lower confidence interval; NT-proBNP = N-terminal pro brain natriuretic peptide; PCT = procalcitonin; RRT = renal replacement therapy

Adjusted mixed model gives average cTnT (outcome) after allowing for gender, age, ischaemic heart disease, hypertension, RRT use or creatinine ≥140 μmol/L, diabetes and any form of vascular disease.

Use of standard effect sizes to estimate equivalent changes in cTnT:

Examples:

a) Relationship between cTnT and NT-proBNP: The standardised effect size for NT-proBNP in patients with a definite MI is 0.01. To obtain the equivalent change in cTnT for a change in NT-proBNP, calculate the following: $(value + 1)^{a}$ where *value* is the estimate as a *proportion,* and *a* is the change in NT-proBNP.
For instance, the value of NT-proBNP is 0.01% (= 0.0001); to compute a 10 unit change, the formula translates into: $(0.0001 + 1)^{10} = 1.001$. This means, for a 10 unit change in NT-proBNP, the associated change of cTnT is 0.001 (ie 0.1%).

b) Impact of sepsis: The adjusted effect size describes the difference in cTnT between those with and without sepsis; eg if the value is 28.85%, the mean cTnT is raised by 28.85% in patients with sepsis compared to those without sepsis.

* Results are presented as the percentage change in cTnT as the inflammatory marker increases by one unit.

** Since Il-6 was log transformed as well as cTnT, the 'one-unit change' estimates are not very meaningful and have been omitted