Cardiomyocyte injury induced by hemodynamic cardiac stress: differential release of cardiac biomarkers

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Abstract (250 words)

Objective: We explored whether hemodynamic cardiac stress leads to a differential release of cardiomyocyte injury biomarkers, used in the diagnosis of acute myocardial infarction (AMI).

Methods: In an observational international multicenter study, we enrolled 831 unselected patients presenting with symptoms suggestive of AMI to the emergency department. The final diagnosis was adjudicated by two independent cardiologists. Hemodynamic cardiac stress was quantified by levels of B-type natriuretic peptide (BNP). Spearman's rho correlation was used to analyze the correlations between BNP and high-sensitivity cardiac troponin T (hs-cTnT), Siemens cTnI-Ultra (cTnI-ultra), CK-MB and Myoglobin. Patients were categorized according to the extent of hemodynamic cardiac stress as quantified by BNP tertiles.

Results: Among all patients, the positive pair-wise correlation with BNP was strongest with hs-cTnT and cTnI-ultra ($r=0.58$ and 0.50 , respectively), moderate for Myoglobin ($r=0.43$), and weakest with CK-MB ($r=0.25$; $p<0.001$ for each). Similar pattern of correlations was also observed among AMI patients. Among patients diagnosed with non-cardiac cause of chest pain ($n=385$, 46%) and cardiac but non-coronary ($n=109$, 13%), BNP had significant positive correlations with hs-cTnT, cTnI-ultra and Myoglobin ($p<0.05$), but not with CK-MB ($p=NS$). A similar pattern of stronger correlation between BNP and hs-cTnT, cTnI-ultra and Myoglobin as compared to that with CK-MB was also observed within the higher BNP tertile range. There was no correlation between BNP and other biomarkers within the 1st BNP tertile group.

Conclusion: Hemodynamic cardiac stress, as quantified by BNP, as a likely cause of cardiomyocyte injury, is more closely reflected by concentrations of hs-cTnT, cTnI-ultra and Myoglobin than CK-MB.

Introduction

Biomarkers of cardiomyocyte injury, cardiac troponin T and I (cTnT and cTnI), are integral to the diagnosis of acute myocardial infarction (AMI) ^{1,2}. Although these markers have been used clinically for decades, the detailed triggers and mechanisms of their release are still incompletely understood. A better understanding of their triggers could potentially help make better use of these markers of cardiomyocyte injury in the evaluation of acute chest pain. Therefore we explored the association of hemodynamic cardiac stress, as quantified by B-type natriuretic peptide (BNP) and N-terminal proBNP levels (NT-proBNP) ³⁻⁶, with levels of high-sensitivity cTnT, cTnI, myoglobin, and CK-MB among chest pain patients presenting to the Emergency Department (ED).

Methods

The Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study is an ongoing prospective, international, multicenter study designed and coordinated by the University Hospital Basel, Switzerland. (ClinicalTrials.gov Identifier: NCT00470587). From April 2006 to June 2009, consecutive patients who presented to the ED with symptoms suggestive of AMI, within the last 12 hours were recruited. Patients with terminal kidney failure requiring dialysis were excluded. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee at each participating institution. Written informed consent was obtained from all patients. To determine the final diagnosis for each chest pain patient, two independent cardiologists reviewed all available medical records to 90-day follow-up. In situations of diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist. The details of the predefined criteria for diagnosis are given in Appendix A.

Biochemical Analysis

Blood samples were collected at the time of patient's presentation to ED. After centrifugation, samples were frozen at -80°C until they were assayed in a blinded fashion in a dedicated core laboratory. The high-sensitivity cardiac troponin T (hs-cTnT) assay was performed with the use of the Elecsys 2010 system (Roche Diagnostics). Limit of Detection has been determined to be $0.005\text{ }\mu\text{g/l}$, an imprecision corresponding to 10% coefficient of variation (CV) was reported at $0.013\text{ }\mu\text{g/l}$ and the 99th-percentile of a healthy reference population at $0.014\text{ }\mu\text{g/l}$ ⁷. The Siemens Ultra cardiac troponin I (cTnI-ultra) assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens). LoD has been determined to be $0.006\text{ }\mu\text{g/l}$, a 10% CV was reported at $0.030\text{ }\mu\text{g/l}$ and the 99th-percentile cutoff point of $0.04\text{ }\mu\text{g/l}$ ⁸. BNP was measured using the AxSYM BNP assay (Abbott Laboratories, Abbott Park, Ill). The analytical range as reported by the manufacturer extends from 15 to 20,000 pg/mL for the AxSYM assay⁹. NT-proBNP was measured using the Elecsys 2010 system (Roche Diagnostics). The CK-MB mass was measured using the Elecsys CK-MB immunoassay (Roche Diagnostics, Rotkreuz, Switzerland) with a measuring range of 0.1 - 500 ng/mL and a coefficient of variation of 2.1-3.5% at 5.6 ng/mL. Myoglobin mass was measured using the Elecsys Myoglobin immunoassay (Roche Diagnostics, Rotkreuz, Switzerland) with a measuring range of 21-3'000 ng/mL and a coefficient of variation (intermediate precision) of 1.8-2.3% at 36 ng/mL.

Results and Discussion

A total of 831 patients had BNP, cTnT, myoglobin, and CK-MB levels measured at presentation; and cTnI-ultra was available in 807 (97%) patients. Median time for onset of chest pain to ED presentation was 6 hours. Table 1 shows the baseline characteristics of patients.

The major novel finding of our study is that the positive pair-wise correlation with BNP was strongest for hs-cTnT and cTnI-ultra ($r=0.58$ and 0.50 , respectively), followed by that with Myoglobin ($r=0.43$), and was weakest for CK-MB ($r=0.25$; $p<0.001$ for each) (Figure 1). Our study extends the new guidelines Class III recommendation (and not measuring CK-MB and myoglobin for the diagnosis of MI)² including when detecting myocardial ischemia during hemodynamic stress. These significant pair-wise correlation persisted even when the cohort was subdivided into those who presented early (≤ 6 hours) and late (>6 hours). (Appendix B).

When stratified according to the BNP tertiles (Table 2 A), no biomarker significant correlated with BNP ($p>0.05$) among patients within the first BNP tertile group. When stratified according to the BNP tertiles and time since onset of chest pain (Appendix B), similar results were seen in first and third tertile, but interestingly in the 2nd tertile, the hs-cTnT and cTnI-ultra significantly correlated with BNP only in those who presented early (≤ 6 hours) but not in late presenters (>6 hours).

We also confirmed the finding of increased hemodynamic stress among AMI patients as highlighted by increased BNP¹⁰. In AMI, impaired blood flow results in ischemia, infarction and increased hemodynamic stress. Figure 2 shows the box plot levels of four investigational markers according to the final diagnosis. Another major finding of our study is that when stratified according the five groups of final adjudicated diagnosis (Table 2 B), CK-MB was the only marker that did not significantly correlate with BNP among cardiac but non-coronary and non-cardiac

cause of chest pain patients. The strong correlation with BNP for hs-cTnT and cTnI-ultra persisted even in patients adjudicated to have non-cardiac causes of chest pain.

The 3 biomarkers for cardiomyocyte injury (cTnT, cTnI, myoglobin, and CK-MB) significantly correlated with each other in all patients and within each subgroup by BNP tertiles, final diagnoses and onset of chest pain.

Overall, these findings were confirmed in the subgroup of patients (n=502) in which also levels of NT-proBNP were available and used for the quantification of hemodynamic cardiac stress. (Supplementary Table S1 and S2 and Figure S2).

The sequence of events resulting in cardiomyocyte injury is unclear, however hemodynamic cardiac stress itself might likely be the cause of cardiomyocyte injury, indicating it is more common than previously thought and not restricted to acute cardiac conditions. The phenomenon of hemodynamic cardiac stress induced cardiomyocyte injury has first been described in patients with acute heart failure^{11,12}. We can only hypothesize why increased hemodynamic cardiac stress leads to a predominate release of cTnT and I, as assessed by sensitive assays, and myoglobin rather than CK-MB. Potential reasons include the different mechanism of release, release kinetics including the half lives of the markers (13), different levels of injury necessary to result in the loss of these structural cardiomyocyte proteins and different reflection of reversible and irreversible injury (1, 14, 15). Another possible explanation is the relative difference in the tissue concentrations between the different biomarkers. Our data highlight that this seems to be a graded and possible continuous phenomenon.

Several limitations of the study merit consideration. First, the vast majority of patients were Caucasians and terminal renal failure patients were excluded. Therefore, the impact of race and terminal renal failure on biomarker association could not be determined. Second, as an observational study, we are unable to test

the clinical benefit nor establish a causal link between BNP or NT-proBNP with cardiomyocyte injury biomarkers (ie whether hemodynamic stress occurred before or after index event). Third, the onset of chest pain time is the only kinetic measure that was explored in this study. Fourth, heart failure is known to lead to both cTn and BNP elevations, and its potential as a confounding factor was not studied. History of heart failure was not recorded in the case report form. However, the results of the study were unchanged even when patients on diuretics, n=214 (26%), were removed from the analyses. Fifth, there were several other factors (mainly those found significantly different among the three tertile groups as in table 1, such as age, CAD etc) that are potential confounders and were not assessed.

Conclusion

Hemodynamic cardiac stress, as quantified by BNP (or NT-proBNP) levels, is more closely reflected by concentrations of hs-cTnT, cTnI-ultra and Myoglobin than CK-MB. Our study findings support the use of cTnI and T for the detection of myocardial injury during increased hemodynamic stress. Furthermore, increased hemodynamic stress and myocardial injury is commonly seen among acute chest pain patients, even among those diagnosed with a non-cardiac cause of chest pain. Further research is needed to explore the kinetic differences in BNP and cTn.

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Conflict of interest

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Table 1 shows the baseline characteristics of all patients and also according to the BNP tertiles. The medications are those which the patients were taking at the time of admission.

Baseline characteristics (n = 831)					
Factor	All patients	BNP tertiles			p value
		1st (≤ 38 pg/ml)	2nd (38.01 – 132 pg/ml)	3rd (≥ 132.01 pg/ml)	
Age (in years)*	64 [51 - 75]	51 [43 - 61]	65 [54 - 74]	75 [65 - 82]	<0.01
Male gender	565 (68)	203 (73)	188 (68)	174 (63)	0.04
BMI*	26 [24 - 29]	26 [24 - 30]	27 [24 - 30]	26 [24 - 29]	0.14
Glomerular Filtration Rate (ml/min/m ²)*	90 [73 - 107]	101 [88 - 114]	90 [75 - 105]	76 [58 - 95]	<0.01
Coronary Artery Disease	324 (39)	56 (20)	105 (38)	163 (59)	<0.01
Previous Myocardial infarction	218 (26)	35 (13)	70 (25)	113 (41)	<0.01
Hypertension	524 (63)	125 (45)	179 (65)	220 (79)	<0.01
Hypercholesterolemia	343 (41)	92 (31)	122 (44)	129 (47)	<0.01
Diabetes mellitus	141 (17)	30 (11)	48 (18)	63 (23)	0.01
Stroke	55 (7)	4 (1)	15 (5)	36 (13)	<0.01
Lung disease	93 (11)	32 (12)	26 (9)	35 (13)	0.48
Peripheral Artery Disease	62 (8)	5 (2)	19 (7)	38 (14)	<0.01
Chronic Renal insufficiency	88 (11)	5 (2)	15 (5)	68 (25)	<0.01
Aspirin	338 (41)	74 (27)	123 (45)	141 (51)	<0.01
^Δ ACE or ARB	325 (39)	66 (24)	98 (36)	161 (58)	<0.01
Beta-Blocker	329 (40)	57 (21)	99 (36)	173 (63)	<0.01
Ca antagonist	139 (17)	29 (10)	47 (17)	63 (23)	<0.01
Statin	400 (48)	81 (29)	146 (53)	173 (63)	<0.01
Diuretic	214 (26)	33 (12)	59 (21)	122 (44)	<0.01

*Median[InterQuartile Range] ^ΔACE or ARB: Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker

Supplementary Appendix Table S1 shows the baseline characteristics of all patients and also according to the N-terminal pro B-type Natriuretic peptide (NT-proBNP) tertiles. The medications are those, which the patients were taking at the time of admission.

Baseline characteristics (n = 502)					
Factor	All patients	NT-proBNP tertiles			p value
		1st (≤ 87 pg/ml)	2nd (87.1 – 408.2 pg/ml)	3rd (≥ 408.3 pg/ml)	
Age (in years)*	65 [52 - 76]	51 [43 - 60]	66 [56 - 77]	76 [69 - 82]	<0.01
Male gender	332 (66)	124 (74)	104 (62)	104 (63)	0.04
BMI*	26 [24 - 29]	26 [23 - 29]	27 [24 - 29]	26 [24 - 29]	0.15
Glomerular Filtration Rate (ml/min/m ²)*	93 [75 - 109]	104 [92 - 120]	92 [77 - 105]	75 [59 - 94]	<0.01
Coronary Artery Disease	186 (37)	32 (19)	73 (44)	81 (49)	<0.01
Previous Myocardial infarction	141 (28)	21 (13)	51 (31)	69 (41)	<0.01
Hypertension	310 (62)	64 (38)	111 (67)	135 (81)	<0.01
Hypercholesterolemia	218 (43)	59 (35)	76 (46)	83 (50)	0.02
Diabetes mellitus	81 (16)	13 (8)	26 (16)	42 (25)	<0.01
Stroke	36 (7)	2 (1)	9 (5)	25 (15)	<0.01
Lung disease	61 (12)	22 (13)	17 (10)	22 (13)	0.63
Peripheral Artery Disease	37 (7)	5 (3)	10 (6)	22 (13)	<0.01
Chronic Renal insufficiency	50 (10)	2 (1)	6 (4)	42 (25)	<0.01
Aspirin	202 (40)	43 (26)	77 (46)	82 (49)	<0.01
^Δ ACE or ARB	325 (39)	38 (23)	72 (43)	97 (58)	<0.01
Beta-Blocker	204 (41)	30 (18)	76 (46)	98 (59)	<0.01
Ca antagonist	87 (17)	19 (11)	34 (20)	34 (20)	0.04
Statin	183 (37)	43 (26)	66 (40)	74 (44)	<0.01
Diuretic	141 (28)	16 (10)	44 (26)	81 (49)	<0.01

*Median[InterQuartile Range] ^ΔACE or ARB: Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker

Table 2 shows the correlation between B-type Natriuretic peptide (BNP) and high-sensitive cardiac troponin-T (hs-cTnT), Siemens Ultra cardiac troponin I (cTnI-ultra), Creatine Kinase-Myocardial Band (CK-MB) and Myoglobin as bivariate analysis with spearman correlation; according to BNP tertiles (A) and final adjudicated diagnosis (B).

Table A

Correlation with BNP and:	All patients		BNP tertiles					
			1st (≤ 38 pg/ml)		2nd ($>38-132$ pg/ml)		3rd (≥ 132.01 pg/ml)	
	r	p value	r	p value	r	p value	r	p value
Hs-cTnT	0.58	<0.01	-	NS	0.16	0.01	0.41	<0.01
cTnI-ultra	0.50	<0.01	-	NS	-	NS	0.41	<0.01
CK-MB	0.28	<0.01	-	NS	-	NS	0.24	<0.01
Myoglobin	0.43	<0.01	-	NS	0.14	0.03	0.28	<0.01

Table B

Correlation with BNP and:	Final Adjudicated diagnosis									
	Acute Myocardial Infarction		Unstable Angina		Cardiac but non-coronary		Non-cardiac		Unknown	
	r	p value	r	p value	r	p value	r	p value	r	p value
Hs-cTnT	0.45	<0.01	0.37	<0.01	0.55	<0.01	0.43	<0.01	0.46	<0.01
Siemens-Ultra I	0.36	<0.01	-	NS	0.51	<0.01	0.34	<0.01	0.35	<0.01
CK-MB	0.20	0.02	-	NS	-	NS	-	NS	0.25	0.04
Myoglobin	0.25	<0.01	0.28	<0.01	0.31	<0.01	0.24	<0.01	0.41	<0.01

r denotes spearman correlation, NS - Non-significant

Supplementary Appendix

Table S2 shows the correlation between N-terminal pro B-type Natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin-T (hs-cTnT), Siemens Ultra cardiac troponin I (cTnI-ultra), Creatine Kinase-Myocardial Band (CK-MB) and Myoglobin as bivariate analysis with spearman correlation; according to Pro BNP tertiles (A) and final adjudicated diagnosis (B).

Table A

Correlation with NT-proBNP and:	All patients		NT-proBNP tertiles					
			1st (≤ 87 pg/ml)		2nd (87.1 – 408.2 pg/ml)		3rd (≥ 408.3 pg/ml)	
	r	p value	r	p value	r	p value	r	p value
Hs-cTnT	0.73	<0.01	0.26	<0.01	0.25	0.01	0.43	<0.01
cTnI-ultra	0.62	<0.01	-	NS	-	NS	0.37	<0.01
CK-MB	0.40	<0.01	-	NS	-	NS	0.19	0.01
Myoglobin	0.54	<0.01	-	NS	-	NS	0.28	<0.01

Table B

Correlation with NT-proBNP and:	Final Adjudicated diagnosis									
	Acute Myocardial Infarction		Unstable Angina		Cardiac but non-coronary		Non-cardiac		Unknown	
	r	p value	r	p value	r	p value	r	p value	r	p value
Hs-cTnT	0.44	<0.01	0.55	<0.01	0.65	<0.01	0.62	<0.01	0.41	0.01
Siemens-Ultra I	0.35	<0.01	0.42	<0.01	0.53	<0.01	0.46	<0.01	-	NS
CK-MB	0.23	0.03	-	NS	0.27	0.03	0.17	0.01	-	NS
Myoglobin	0.34	<0.01	0.30	<0.01	0.38	<0.01	0.37	<0.01	0.42	0.01

r denotes spearman correlation, NS - Non-significant

Figure 1 shows the scatter plots between log transformed B-type Natriuretic peptide (BNP) and A) Creatine Kinase-Myocardial Band (CK-MB), B) Myoglobin, C) high-sensitivity cardiac troponin-T (hs-cTnT) and D) Siemens Ultra cardiac troponin I (cTnI-ultra).

Figure 2 shows the box plot levels of B-type Natriuretic peptide (BNP) and Creatine Kinase-Myocardial Band (CK-MB), Myoglobin, high-sensitivity cardiac troponin-T (hs-cTnT) and Siemens Ultra cardiac troponin I (cTnI-ultra) according to the final diagnosis. The boxes represent interquartile ranges, the horizontal line in each box represents the median, and the whiskers show the minimum and maximum values (excluding outliers that were more than 1.5 times the values represented at each end of the box).

Supplementary Figure

Figure S1 shows the scatter plots between log transformed N-terminal pro B-type Natriuretic peptide (NT-proBNP) and A) Creatine Kinase-Myocardial Band (CK-MB), B) Myoglobin, C) high-sensitive cardiac troponin-T (hs-cTnT) and D) Siemens Ultra cardiac troponin I (cTnI-ultra).

Fig. 1

Fig. 2

Highlights

- Hemodynamic cardiac stress, as quantified by BNP levels, is more closely reflected by concentrations of hs-cTnT, cTnI-ultra and Myoglobin than CK-MB.
- The strong correlation between the amount of hemodynamic cardiac stress and the amount of cardiomyocyte injury seems to be restricted to patients in the highest tertile
- Increased hemodynamic stress and myocardial injury is commonly seen among acute chest pain patients, even among those diagnosed with a non-cardiac cause of chest pain.
- Further research is needed to explore the kinetic differences in BNP and troponin