Rhabdomyolysis: A non-cardiac source of increased circulating concentrations of cardiac troponin T?

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Abbreviations

AMI : Acute myocardial infarction

CAD : Coronary artery disease

CK : Creatine Kinase

cTn : Cardiac troponin

Cardiac troponin (cTn) T and I are regarded equivalent in the diagnosis of acute myocardial infarction (AMI)(1), as they correlate closely with each other and show very high and comparable diagnostic accuracies.(2) In contrast, isolated high concentrations of cTnT, but not cTnI, have been reported in patients with chronic hereditary and acquired skeletal myopathies.(3, 4) The reported strong positive correlation between creatine kinase (CK), a quantitative marker of muscle injury, and high-sensitivity (hs)-cTnT ($r=0.679$, $p<0.001$) indicated either re-expression of cTnT in diseased skeletal muscle or cross-reactivity of the cTnT assay with circulating muscle epitopes as possible explanations.(4) To advance the understanding of the involved mechanisms, we aimed to investigate high-sensitivity assays for hs-cTnT (Elecsys, Roche) and hs-cTnI (Architect, Abbott) in patients with acute rhabdomyolysis, an in-vivo model of massive acute skeletal muscle protein release into the circulation, and compare their inter-assay association with matched acute chest pain patients presenting with non-coronary chest pain to the emergency department.

In a prospective observational study, approved by the ethical committee, we measured CK, hs-cTnT, and hs-cTnI in 98 consecutive patients presenting with acute rhabdomyolysis (defined as CK>7500U/L) resulting in 268 parallel measurements. Mean age was 62 years, 22% were female, history of coronary artery disease (CAD) was present in 14%, hypertension in 38%, ECG abnormalities in 20% (ECG available in 68/98) and echocardiographic abnormalities in 12% (Echocardiography available in 38/98). Acute medical illnesses was the cause in 93/98, thoracic trauma or cardiopulmonary reanimation in 5/98.

Log-transformed hs-cTnT ($r=-0.14$, $p=0.025$) and hs-cTnI ($r=-0.16$, $p=0.008$) showed a weak and negative correlation with CK concentrations (Figure 1A), indicating no meaningful association between the extent of skeletal muscle injury and hs-cTnT and hs-cTnI concentrations.

Propensity score matching with well-characterized patients adjudicated to have non-coronary chest pain in the Advantageous Predictors of Acute Coronary Syndrome Evaluation study (NCT00470587) on age, sex, history of hypertension, CAD, AMI, stroke, and chronic skeletal muscle disease was performed to assess whether hs-cTnT and hs-cTnI concentrations behave disproportionally different in patients with rhabdomyolysis than in the matched controls. Following matching, cardiovascular comorbidities were equalized, while patients with acute rhabdomyolysis had more extensive systemic inflammation as quantified by C-reactive protein concentrations and worse renal function as compared to the matched control cohort.

Hs-cTnT and hs-cTnI concentrations measured in the same blood sample (Figure 1B) showed a strong positive correlation in both cohorts (Pearson coefficient 0.91 in control and of 0.93 in rhabdomyolysis, both $p<0.001$) and behaved comparably in the control and the rhabdomyolysis cohort, as confirmed by similar slopes of fitted regression lines ($\log(\text{hs-cTnT}) = 0.62 * \log(\text{hs-cTnI})$) in the controls and $\log(\text{hs-cTnT}) = 0.59 * \log(\text{hs-cTnI})$ in the rhabdomyolysis patients). A linear model including the interaction of the presence of rhabdomyolysis showed no significant interaction due to the presence of rhabdomyolysis (p-for-interaction=0.14). Hs-cTnT and hs-cTnI concentrations were both higher in the rhabdomyolysis patients as compared to controls (median hs-cTnT 22.0ng/L versus 14.9ng/L; median hs-cTnI 21.5ng/L versus 8.6ng/L, $p<0.001$, respectively).

Three important insights of major clinical relevance evolved from these analyses. **First**, acutely diseased skeletal muscle as in rhabdomyolysis does not seem to be a relevant source of hs-cTnT concentrations in the circulation. **Second**, cardiomyocyte injury due to the underlying acute medical disease leading to rhabdomyolysis such as severe sepsis, stroke or even asymptomatic AMI is the most likely source of cTnT and cTnI concentrations in patients with rhabdomyolysis and responsible for the higher concentrations of cTnT/cTnI than the matched controls.(1) Further research with systematic cardiac imaging in rhabdomyolysis patients is warranted.

Third, massive acute release of skeletal muscle epitopes in the circulation as in acute rhabdomyolysis does not lead to disproportionally increased hs-cTnT concentrations, but modest release as in chronic hereditary and acquired skeletal myopathies seems to.(3, 4) Time-dependent re-expression of cTnT in chronically diseased skeletal muscle may be considered the most likely explanation for the latter phenomenon.

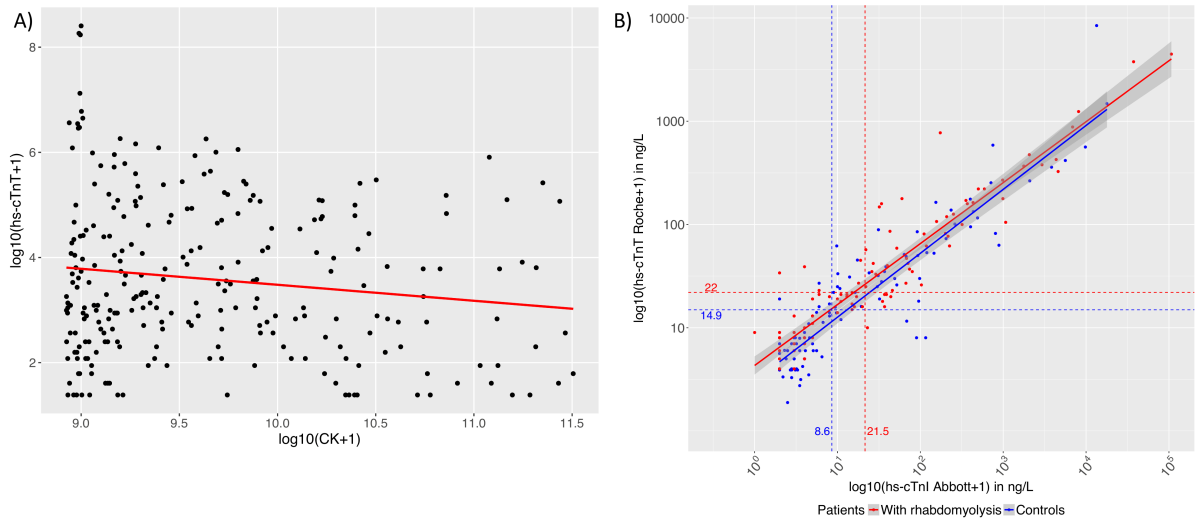

Figure 1 – Logged High-sensitivity cardiac troponin T (hs-cTnT) concentrations show A) a weak negative correlation with creatine kinase (CK), but B) a strong and positive correlation with logged hs-cTnI concentrations in rhabdomyolysis (red), with linear regression slopes comparable to those in matched controls (blue). Dashed lines : Medians for both cohorts.

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