

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

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8 **Twitter:** @CRIBasel @JDFDLz

9 **Tweet:** No muscular release of cardiac troponin T in acutely damaged muscle, what is the
10 culprit in chronic inflammation?

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32 **Abbreviations**

33 AMI : Acute myocardial infarction

34 CAD : Coronary artery disease

35 CK : Creatine Kinase

36 cTn : Cardiac troponin

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

51 In a prospective observational study, approved by the ethical committee, we measured CK, hs-
52 cTnT, and hs-cTnI in 98 consecutive patients presenting with acute rhabdomyolysis (defined
53 as $CK>7500U/L$) resulting in 268 parallel measurements. Mean age was 62 years, 22% were
54 female, history of coronary artery disease (CAD) was present in 14%, hypertension in 38%,
55 ECG abnormalities in 20% (ECG available in 68/98) and echocardiographic abnormalities in
56 12% (Echocardiography available in 38/98). Acute medical illnesses was the cause in 93/98,
57 thoracic trauma or cardiopulmonary reanimation in 5/98.

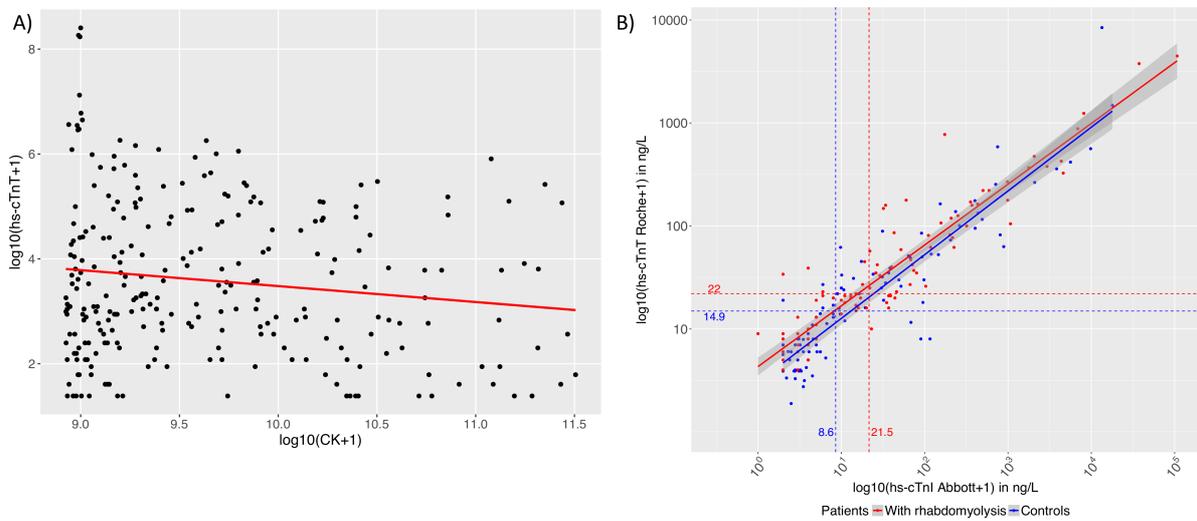
58 Log-transformed hs-cTnT ($r=-0.14$, $p=0.025$) and hs-cTnI ($r=-0.16$, $p=0.008$) showed a weak
59 and negative correlation with CK concentrations (Figure 1A), indicating no meaningful
60 association between the extent of skeletal muscle injury and hs-cTnT and hs-cTnI
61 concentrations.

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

70 Hs-cTnT and hs-cTnI concentrations measured in the same blood sample (Figure 1B) showed
71 a strong positive correlation in both cohorts (Pearson coefficient 0.91 in control and of 0.93 in
72 rhabdomyolysis, both $p < 0.001$) and behaved comparably in the control and the rhabdomyolysis
73 cohort, as confirmed by similar slopes of fitted regression lines ($\log(\text{hs-cTnT}) = 0.62 * \log(\text{hs-}$
74 $\text{cTnI})$) in the controls and $\log(\text{hs-cTnT}) = 0.59 * \log(\text{hs-cTnI})$ in the rhabdomyolysis patients). A
75 linear model including the interaction of the presence of rhabdomyolysis showed no significant
76 interaction due to the presence of rhabdomyolysis ($p\text{-for-interaction} = 0.14$). Hs-cTnT and hs-
77 cTnI concentrations were both higher in the rhabdomyolysis patients as compared to controls
78 (median hs-cTnT 22.0ng/L versus 14.9ng/L; median hs-cTnI 21.5ng/L versus 8.6ng/L,
79 $p < 0.001$, respectively).

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

87 **Third**, massive acute release of skeletal muscle epitopes in the circulation as in acute
 88 rhabdomyolysis does not lead to disproportionately increased hs-cTnT concentrations, but
 89 modest release as in chronic hereditary and acquired skeletal myopathies seems to.(3, 4) Time-
 90 dependent re-expression of cTnT in chronically diseased skeletal muscle may be considered the
 91 most likely explanation for the latter phenomenon.
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 95 **Figure 1** – Logged High-sensitivity cardiac troponin T (hs-cTnT) concentrations show A) a
 96 weak negative correlation with creatine kinase (CK), but B) a strong and positive correlation
 97 with logged hs-cTnI concentrations in rhabdomyolysis (red), with linear regression slopes
 98 comparable to those in matched controls (blue). Dashed lines : Medians for both cohorts.

99 **References**

- 100 1. Roffi, M., Patrono C., Collet J., et al. ESC Guidelines for the management of acute
101 coronary syndromes in patients presenting without persistent ST-segment elevation. *Ehj*
102 2015;32:2999–3054.
- 103 2. Gimenez MR, Twerenbold R, Reichlin T, et al. Direct comparison of high-sensitivity-
104 cardiac troponin i vs. T for the early diagnosis of acutemyocardial infarction. *Eur. Heart J.*
105 2014;35:2303–2311.
- 106 3. Jaffe AS, Vasile VC, Milone M, Saenger AK, Olson KN, Apple FS. Diseased skeletal
107 muscle: A noncardiac source of increased circulating concentrations of cardiac troponin T. *J.*
108 *Am. Coll. Cardiol.* 2011;58:1819–1824.
- 109 4. Schmid J, Liesinger L, Birner-Gruenberger R, et al. Elevated Cardiac Troponin T in
110 Patients With Skeletal Myopathies. *J. Am. Coll. Cardiol.* 2018;71:1540–1549.

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