

CORRESPONDENCE

Research Correspondence

Troponin Release Overestimates Infarct Size in Presence of Left Ventricular Hypertrophy

To the Editor: After an acute myocardial infarction (AMI), infarct size quantification is of clinical importance because it correlates with postinfarction mortality and morbidity (1). The gold standard in vivo techniques for infarct size quantification are magnetic resonance imaging and single-photon emission computed tomography; however, these methods are not universally available.

Systemic determination of both peak and area under the curve of circulating concentrations of creatine kinase (CK) and troponins positively correlate with infarct size as measured by using the gold standard techniques (2). It has also been demonstrated that single time-point troponin concentration displays a strong correlation with infarct size (2,3). Circulating levels of necrosis biomarkers not only correlate with infarct size and ejection fraction but also predict clinical outcomes after a ST-segment elevation myocardial infarction (STEMI) (2). As a result, infarct size is frequently assessed by using systemic biomarkers release, both in daily practice and in clinical trials.

Because the heart is a postmitotic organ, left ventricular hypertrophy (LVH) is attained by hypertrophy of pre-existing myocytes. Such hypertrophy is encompassed by an increase of contractile units and their proteins (including troponin). In fact, it has been shown that, compared with normal cardiomyocytes, hypertrophied cardiomyocytes display an increased troponin concentration (4) but unchanged total CK concentration (5). Therefore, we hypothesized that upon an AMI, the systemic release of troponins will be disproportionately higher than that of CK in patients with LVH. As a consequence, the prediction of infarct size based on the circulating levels of troponin might be confounded by the presence of LVH.

To test this hypothesis, data from 937 consecutive STEMI patients admitted to our coronary care unit between 2004 and 2009 were analyzed. For every patient, total CK (assessed by using a standard enzymatic method on an Olympus AU2700 analyzer [Beckman Coulter Clinical Diagnostics, Nyon, Switzerland]) and troponin I (chemoluminescence immunoassay on a Dimension Xpand system [Siemens Healthcare Diagnostics, Deerfield, Illinois]) levels were measured on admission and then every 4 h to identify peak enzyme release. A standard echocardiogram was performed 3 to 5 days post-STEMI, and patients were classified into 4 categories according to left ventricle thickness following standard echocardiography recommendations: normal left ventricle thickness and mild, moderate, and severe LVH.

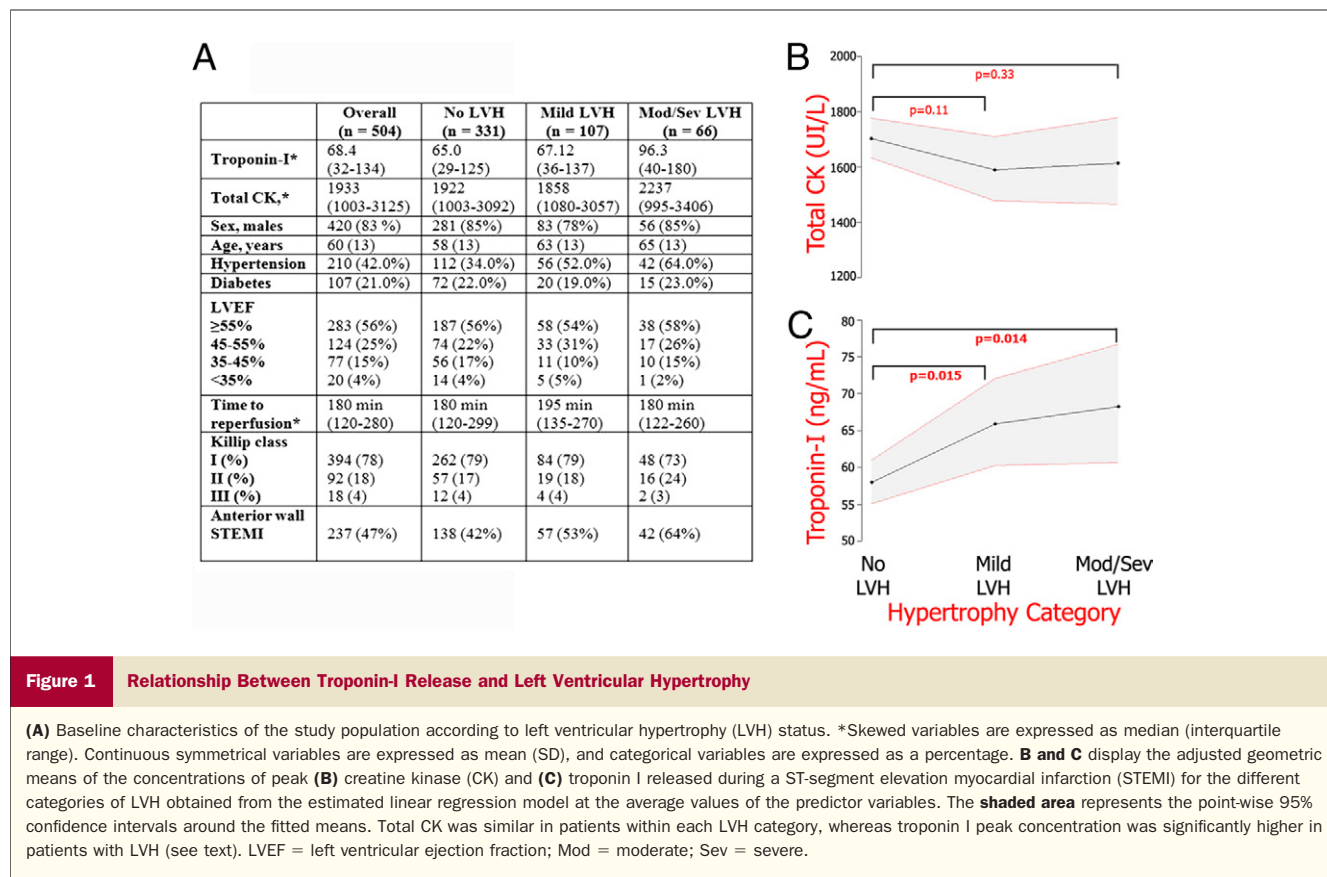
We used multivariable linear regression analysis to estimate the differences of troponin I release between LVH categories adjusted by total CK release and other potential confounders. To avoid potential bias, 56 patients with 1 of the following conditions were excluded from the analysis: mechanical complications, cardiogenic shock, asymmetric hypertrophy, skeletal muscle disease, history of STEMI, and those not revascularized by any means. These patients were excluded because the increase in circulating CK could be affected by noncardiac CK release. A total of 377 patients with missing values in any of the independent variables considered in the multivariable

adjustment were further excluded for statistical purposes. Therefore, the final study population comprised 504 patients. Given the low number of patients with severe LVH ($n = 5$), these were merged within the moderate LVH groups for analytical purposes.

Statistical analyses were performed by using the open-source statistical scripting language R (version 2.3.0., R Foundation for Statistical Computing, Vienna, Austria). The distribution of peak troponin I and CK levels were positively skewed, and a logarithmic transformation was performed. As a consequence, data of biomarkers are expressed in terms of geometric means. The ratio of geometric means of biomarkers release comparing patients with mild LVH and moderate/severe LVH versus patients with no LVH were estimated by using a multivariable linear regression model adjusted for the concentration of CK (or troponin I), sex, age, hypertension, diabetes, ejection fraction, time to reperfusion, ventricular fibrillation, AMI localization, Killip-Kimball class, and beta-blocker treatment. Standard diagnostic checks on the residuals from the fitted models showed no evidence of any failure of the assumption of normality and homogeneity of the residual variance.

Clinical variables from patients according to LVH categories are shown in Figure 1A. Distribution of excluded patients across LVH categories was similar to that of the actual study population. Peak CK values did not differ among the LVH categories. Conversely, significant differences in troponin I levels were found across LVH categories: troponin I concentrations were significantly higher in patients with mild and moderate/severe LVH compared with patients with no hypertrophy: troponin I was 13.7% greater in patients with mild LVH versus patients with no hypertrophy (95% confidence interval: 2.5 to 26.1; $p < 0.02$) and 17.8% in patients showing moderate/severe LVH versus patients with no hypertrophy (95% confidence interval: 3.3 to 34; $p < 0.02$) (Fig. 1). Time-to-peak of biomarkers release was similar in the 3 different LVH categories.

The value of biomarkers release to estimate infarct size is supported by several lines of evidence. Chia et al. (2) showed that, in STEMI patients, single time-point, peak, and area under the curve of CK (total and fractions) and troponins release significantly correlate with infarct size and ejection fraction, measured by using single-photon emission computed tomography. Intriguingly, although many reports have documented that troponin release correlates better with infarct size assessed by using gold standards, some authors have observed that, despite being a noncardioselective biomarker, total CK peak values better correlate with infarct size measured by using magnetic resonance imaging than troponin values (6). After our findings, it may be speculated that LVH can act as a confounding factor when troponins are used as infarct size estimators. Here we show that STEMI patients with LVH had significant greater troponin I release than patients with normal left ventricle thickness at a given CK value. According to the incidence of LVH in our nonselected STEMI population and others,



myocardial infarction size calculated according to peak troponin release can be overestimated in 30% of patients, something that should be taken into consideration in studies evaluating the effect of therapies in infarct size. In the presence of moderate/severe LVH, the discrepancy between total CK and troponin I can be as much as 34%. Such a variation in infarct size is of great biological impact in clinical trials testing the effect of cardioprotective interventions, and therefore the current results have a significant impact. Given that LVH has been shown to be associated with an increase in cardiomyocyte B-chain protein (5), the current data should not be used to infer that CK-myocardial band will be equally dissociated from troponin values.

Although future prospective examinations using gold standard techniques should be performed to confirm our retrospective analysis, the current results may have significant implications because troponin I release seems to overestimate infarct size in patients with LVH.

To the best of our knowledge, this is the first time that a different pattern of CK and troponin I enzyme increase has been shown in STEMI patients with LVH.

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