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Perez-Martinez MT, Lacunza-Ruiz J, Garcia de Lara J, Noguera-Velasco JA, Lax A, Hernandez-Vicente A, Asensio-Lopez MC, Januzzi JL, Jr., Ibanez B, Pascual-Figal DA. Noncardiac Production of Soluble ST2 in ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol*, 2018. 72(12): p. 1429-1430.

which has been published in final form at: https://doi.org/10.1016/j.jacc.2018.06.062

Non-cardiac Production of Soluble ST2 in ST-Elevation Myocardial Infarction

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Short title: Trans-cardiac gradient of sST2 in STEMI

Funding: This work has been supported by two grants (PI14/01637, PI17/01742) from "Instituto de Salud Carlos III", Madrid, Spain, and a grant (19334/PI/14) from "Fundación Séneca de Ciencia y Tecnología de la Región de Murcia", Murcia, Spain.

Conflicts of interest: Dr. J-J declares consulting income from Critical Diagnostics. All other authors report no conflicts of interest.

Tweet: sST2 is acutely elevated in the circulation of patients suffering STEMI, but may not be of cardiac origin

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The soluble isoform of ST2 (sST2) represents a powerful prognostic biomarker in patients with heart failure and acute coronary syndromes. In patients with ST-elevation myocardial infarction (STEMI), concentrations of sST2 are elevated early and identify a higher risk of death, adverse myocardial remodeling and heart failure in the follow-up (1-3). However, the source of circulating sST2 remains debated (3).

Twelve STEMI patients (11 males, 62 ± 10 years) who underwent a primary angioplasty according to clinical practice were recruited in this prospective study. The culprit artery was the right coronary artery in eight, the circumflex in three and the left anterior descending in one. Blood samples were collected immediately after reperfusion and simultaneously from the aortic root and coronary sinus to allow calculation of the transcardiac gradient. Peripheral samples from the radial artery and brachial vein were also obtained. Commercial assays were used for measuring sST2 (Presage ST2, Critical Diagnostics, San Diego, California) and other cardiac markers. Median time from symptom onset to sampling was 167 min (25^{th}-75^{th} percentile, IQR: 114-233; range 75-265). Most patients were Killip class I (11 of 12); median LVEF at discharge was 60% (IQR: 56-65%; range 40-74%).

The concentrations of biomarkers are detailed in Figure 1. Friedman's test and pairwise Wilcoxon signed-ranked test with Bonferroni-Holm correction were used to study differences. Both biomarkers of necrosis troponin T and CK-MB showed a significant transcardiac gradient ($p < 0.001$); NT-proBNP (median 64 pg/mL; IQR 54-126) also had a small but significant gradient ($p = 0.012$). Median sST2 concentration was 34.7 pg/mL (IQR 27.7-43.3; range 21.0-76.4), but did not exhibit any significant transcardiac gradient and, considering all sites, no significant differences were observed ($p > 0.50$). No differences were found when considering the culprit artery or patients >35 pg/mL. We explored all clinical

correlates of sST2, and the only significant was higher sST2 concentration at reperfusion was associated with lower LVEF at discharge for all sites ($r > 0.70$; $p < 0.001$).

sST2 concentrations in the peripheral circulation are increased within the first few hours after symptoms onset in STEMI (1-2). In our study, sST2 was measured within the first 5 hours and half of patients were above the prognostic cut-off of 35 pg/ml, but sST2 concentrations were similar in all sites. Therefore, sST2 concentrations rise early in the setting of myocardial ischemia and necrosis, but the source may be from organs other than the myocardium. Bartunek et al. showed that venous and arterial endothelial cells had the ability to secrete ST2 protein and hypothesized that diastolic load is the main determinant (4). The absence of augmented levels of natriuretic peptides is against diastolic load as main determinant of ST2 production. ST2 secretion is also stimulated by inflammatory cytokines in endothelial cells, which might explain the early and systemic elevation of sST2 in STEMI (4). Among the limitations of our study, the unknown half-life of sST2 and the catheter position might influence the results; although we found no sign of a transcardiac gradient, it is possible subtle differences exist which might be obscured due to the nature of our study design. Though tissue-based autocrine and paracrine ST2 is important in the reparative processes after MI (5), our current results suggest the majority of circulating sST2 is secreted in organ beds other than the heart. sST2 levels measured early predict heart failure and medium-term LV functional recovery and remodeling (1-2). The correlation we found between sST2 levels at reperfusion and LVEF at discharge also supports the previously identified tissue based role of ST2 in post-MI recovery (5).

In summary, sST2 concentrations are elevated early in the circulation of patients suffering STEMI, but the lack of a trans-cardiac gradient supports the hypothesis that the majority of circulating sST2 may not be of cardiac origin. More data are needed to better understand the ST2 system.

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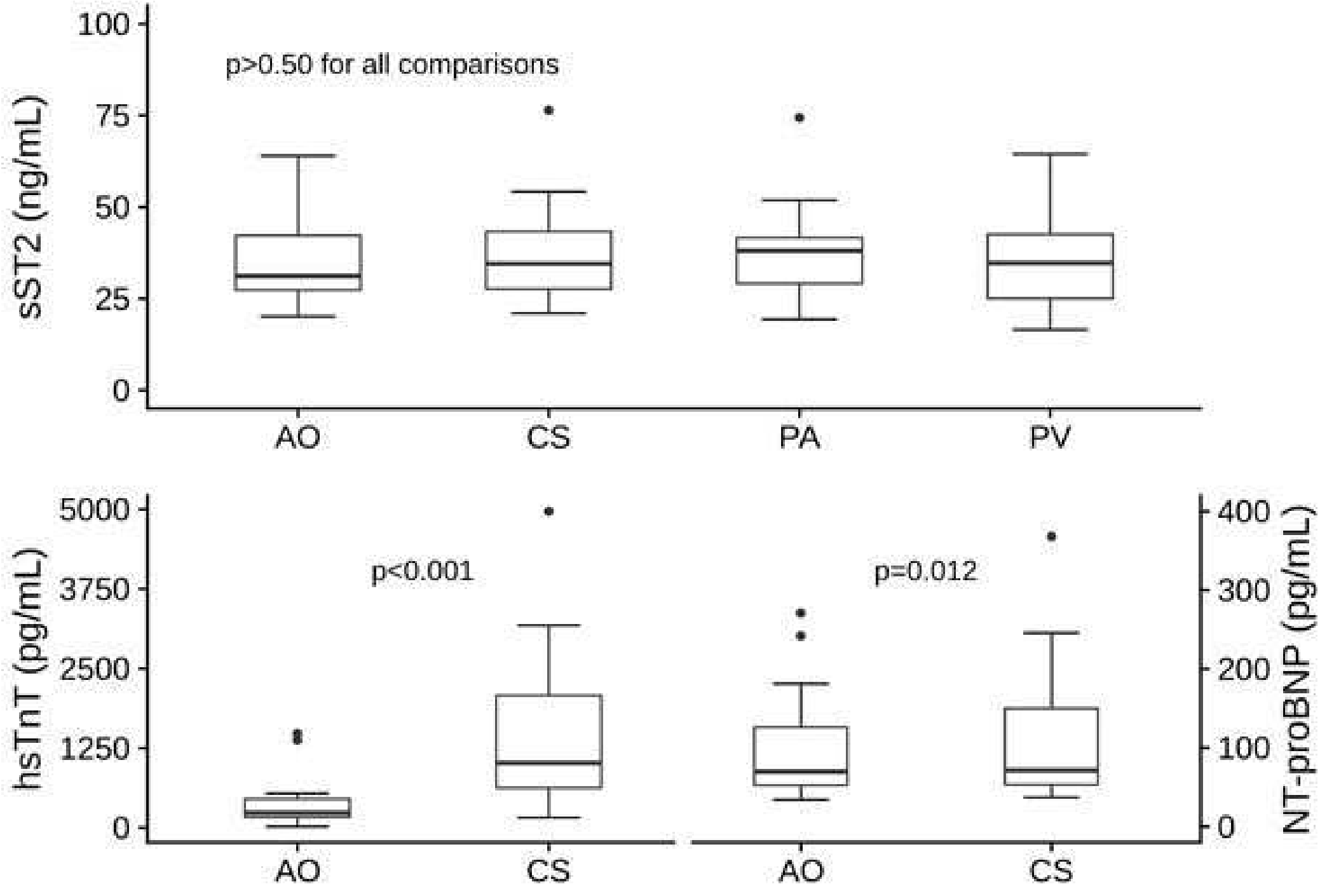
FIGURE LEGEND

Figure 1. Concentrations of biomarkers across sites: aortic root (AO), coronary sinus (CS), peripheral artery (PA), peripheral vein (PV). Box, whiskers and outliers indicate Tukey boxplots.


p>0.50 for all comparisons
sST2 (ng/mL)
100
75
50
25
0
AO
CS
PA
PV
p<0.001
p=0.012
hsTnT (pg/mL)
5000
3750
2500
1250
0
NT-proBNP (pg/mL)
400
300
200
100
0
AO
CS
AO
CS