Editorial

Soluble ST2 for the diagnosis of acute aortic syndromes: a new hope or just another clone war?

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Acute aortic syndromes (AAS) are cardiovascular emergencies affecting 3.5 to 6 per 100,000 patient-years in the general population, and ~35 per 100,000 patient-years in people aged >75 years (1,2). AAS subtypes are acute aortic dissection (AAD), aortic intramural hematoma (IMH), spontaneous aortic rupture and penetrating aortic ulcer (PAU), with AAD representing 60% to 90% of all cases. Stanford type A AAD, which affects the ascending aorta, benefits from immediate surgical treatment. Instead, Stanford type B AAD, which spares the ascending aorta and typically involves within the chest only the descending thoracic aorta, is treated medically and with endovascular aortic repair in selected cases (3). AAS are associated with major morbidity and mortality. Indeed, mortality associated with type A AAD not subjected to surgery reaches 20% after 24 hours, and 50% in the first week. In the last decades, increased capacity to diagnose and treat AAS has significantly improved outcomes as compared to historic series. Nonetheless, in 1,815 patients included in the International Registry of Aortic Dissection (IRAD) from 1996 to 2007, in-hospital mortality from type A AAD was still as high as 29.5%, and mortality from type B AAD was 11.8% (4). Major improvements are therefore needed in cardiovascular medicine and surgery to reduce the burden of AAS.

A diagnostic conundrum

Early diagnosis of AAS in the Emergency Department (ED) is the key to success. Indeed, early diagnosis of AAS allows timely pain relief, controlled hypotension, rapid transfer to experienced aortic units, and avoids iatrogenic harms. For instance, confusion of AAS with ischemic diseases such as myocardial infarction or ischemic stroke will lead to inappropriate administration of thrombolytics or combinations of anticoagulant and antiplatelet agents. However, the diagnosis of AAS is extremely challenging, because presenting symptoms are highly unspecific and because most diseases in differential diagnosis are more prevalent than AAS. Accordingly, the misdiagnosis rate for AAS is as high as 14–39%.

Advanced aortic imaging, typically computed tomography angiography (CTA) of the chest and abdomen, can rapidly and efficiently diagnose AAS (5,6). However, CTA exposes patients to ionizing radiations, to risks of contrast-induced nephropathy and anaphylaxis, and represents a stress-limited imaging modality. Hence, the diagnostic bottleneck is represented by criteria used to identify patients requiring CTA. So far, decision to perform CTA for suspected AAS has been largely guided by clinical judgment, first-line imaging examinations (chest X-ray, bedside ultrasonography) and routine laboratory tests (7-10). However, their diagnostic accuracy is modest. Consequently, the use of advanced imaging for AAS remains largely inefficient and has major variations amongst different physicians and practice, thus leading to a perilous mixture of misdiagnosis and over-testing (11).

Aortic troponin: a long-standing chimera

Biomarkers are heavily needed to improve the diagnostic approach to AAS. Ideally, biomarkers could be used for

initial screening and help to uncover cases of AAS with atypical presentation, thus impacting on misdiagnosis rate. They could also aid in the scrutiny of patients at non-high clinical probability of AAS, to identify cases where CTA is truly needed (i.e., for diagnostic rule-in) or trivial (i.e., for diagnostic rule-out), thus contributing to safe and efficient use of advanced aortic imaging exams in the ED. Indeed, in the last decades there have been several attempts to identify circulating biomarkers of AAS (12,13). Studies have evaluated different molecules composing aortic tissues, such as matrix metalloproteinases, transforming growth factor β, soluble elastin fragments, smooth muscle myosin heavy chain, calponin and creatine kinase (14,15). Other studies have focused on inflammatory markers, such as white blood cells, platelets, C-reactive protein (10). None of these biomarkers, however, has shown sufficient diagnostic accuracy for routine clinical use, either in rule-in or rule-out diagnostic algorithms of AAS.

While the strive to uncover an aortic "troponin" has been frustrated so far, several studies have instead established D-dimer as a highly sensitive biomarker of AAS. D-dimer is a degradation product of crosslinked fibrin detectable in the plasma in the context of thrombosis and fibrinolysis and can be measured by immunoassays available to EDs almost universally 24 hours/7 days. D-dimer typically increases in patients affected by thromboembolic venous disease or disseminated intravascular coagulopathy, but D-dimer is also commonly engaged in sepsis, trauma and cancer, thus leading to low diagnostic specificity. In AAS (especially AAD), the coagulation cascade is activated on non-endothelial surfaces, and incipient false lumen thrombosis is apparent already in the early phases of AD. In metanalyses, D-dimer has shown an average sensitivity of 95–98%, a negative likelihood ratio of 0.05–0.08 and a specificity of 42–60% for AAS (16,17). Considering the severity of AAS, D-dimer is inadequate as a standalone diagnostic rule-out test for AAS, in unselected patients. Instead, retrospective data and a recent prospective multicenter study by our group has shown that application of D-dimer to patients at non-high pretest clinical probability of AAS, as defined by use of the aortic dissection detection risk score, is feasible, safe and efficient for rule-out, potentially sparing up to 1 in 2 CTA exams (18,19).

Soluble ST2: a new hope

A recent publication on the journal *Circulation* by Wang *et al.* has fostered new hopes in this critical area of cardiovascular medicine (20). In their work, Wang *et al.* have evaluated the levels of sST2 on citrate plasma samples of patients with AAD. Surprisingly, they report a striking diagnostic performance of this biomarker for diagnosis of AAD, in a range compatible with clinical use if confirmed in further studies.

ST2 (also known as T1, Fit-1 or DER-4), is an interleukin-1 receptor family member originally described in fibroblasts after serum stimulation. The ST2 gene encodes 3 main isoforms of ST2 proteins, by alternative splicing: (I) ST2L, a transmembrane isoform; (II) secreted soluble ST2 (sST2), which lacks the transmembrane and intracellular domains; and (III) ST2V, a variant form mainly expressed in the human gut. IL-33 *per se* appears to be a cytokine also functioning as an intracellular nuclear factor capable of transcriptional regulation. sST2 is believed to function mainly as a decoy receptor, preventing IL-33 binding to and signaling through ST2L (21).

The diagnostic study by Wang *et al.* is composed of three retrospective discovery sets and one prospective validation cohort, all performed in a single clinical center. In a retrospective case-control study, the authors evaluated the levels of sST2 in 245 patients with AAD and in 234 patients with acute myocardial infarction (AMI). Both groups were sampled within 24 hours from symptom onset. Second, they compared sST2 in 443 patients with AAD and in 49 patients with pulmonary embolism, within 14 days from symptom onset. Finally, they evaluated 234 patients with chronic aortic dissection (i.e., >14 days from symptom onset) and 67 healthy controls. Median sST2 levels were ~115 ng/mL in patients with AAD within 24 hours, ~90 in patients with AAD within 14 days, ~15 ng/mL in patients with AMI, ~10 ng/mL in patients with pulmonary embolism and ~5 in healthy controls.

Prospective validation was performed in a cohort of 333 patients evaluated in the ED for a clinical suspicion of AAS within 24 hours from symptom onset. In this cohort, 114 patients had a final diagnosis of AAD and 219 patients had an alternative diagnosis. Acute coronary syndromes (72 AMI and 54 angina) accounted for 57.5% of all alternative diagnoses. Using a cutoff of 34.6 ng/mL (i.e., experimental value maximizing the sum of sensitivity and specificity), sST2 had a sensitivity of 99.1% and a specificity of 84.9% for diagnosis of AAD. In the same cohort, D-dimer measured with HemosIL D-dimer HS (Instrumentation Laboratory, Bedford, MA, USA) unexpectedly showed a sensitivity of 87.7% and a specificity of 82.2%, applying the standard cutoff of 500 ng/mL. Both estimates are

substantially different from those of previously published studies and metanalyses (16,17).

sST2 source and kinetics

The expression of the components of the IL-33/ST2 system has been reported in many tissues, including myocardium, coronary vessels and adipose tissue. Several studies have shown that sST2 represents a prognostic biomarker in patients with cardiovascular diseases, in particular myocardial infarction and heart failure (21). To our knowledge, however, information about the expression and function of sST2 in the aorta is largely unknown, especially in humans. The IL-33/ST2 system has been found expressed in the aorta and in cultured vascular smooth muscle cells (VSMCs) of Wistar rats (22). In this work, a high fat diet increased aortic sST2 and decreased ST2L levels, resulting in decreased protective pathway activity. VSMCs stimulated with sST2 also showed an increase in collagen type I, fibronectin and profibrotic factors, indicating a potentially deleterious effect of sST2 on aortic remodeling.

Unfortunately, the study by Wang *et al.* does not provide any additional data in terms of sST2 origin and release in AAS and in the diseased human aorta in general. One possibility is that pools of sST2 are already present in the aortic tissues before AAD occurs, with consequent spill-over into the plasma via the false lumen. Another possibility is that sST2 is produced and released during AAD development as a consequence of aortic tearing and of the related inflammatory and coagulative reactions. In both cases, it is unknown whether plasma sST2 is released from resident aortic cells or from inflammatory cells homing to the dissected aorta. These pathophysiological issues may be highly relevant both in terms of release kinetics and in terms of diagnostic accuracy for AAS. For instance, it is unclear whether sST2 levels may increase similarly in AAS subtypes different from AAD, particularly in IMH and PAU, which present well-established pathological, pathophysiological and clinical specificities.

Study cohort

The study cohorts used in the study by Wang *et al.* need scrutiny. First, the average age of AAD patients in the study by Wang *et al.* was 50 years. In the IRAD registry, which is composed of patients from Europe, United States and Japan, the average age is 62 years. This major difference in participant age suggests caution in the generalization of results. Second, for unspecified reasons, Wang *et al.* excluded from the prospective cohort patients with comorbidities (pseudoaneurysm, heart failure, renal dysfunction, severe pulmonary diseases or active cancer). We are not informed about the exact definition of these clinical entities and we are left unaware about the actual incidence of these criteria on enrolment. Finally, the study by Wang *et al.* did not include patients with AAS different from AAD (i.e., IMH and PAU) in the retrospective sets. Surprisingly, none of these subtypes were diagnosed also in the prospective cohort. Considering that IMH and PAU constitute from 10% to 30% of all AAS types in other centers, this data likely suggests selection bias in patient enrolment. Of note, IMH and PAU provide within AAS additional diagnostic challenges, due to lack of clinical malperfusion signs and higher incidence of negative D-dimer tests. Finally, in line with selection bias occurring in the prospective cohort, control patients were found affected by coronary artery disease (AMI or angina) in 50% of cases, which is way higher than expected from prospective enrolment in the ED setting.

Taken together, we must conclude that Wang *et al.* essentially describe a cohort of earlier presenting, younger and healthier patients than all-comers with suspected and confirmed AAS seen in other countries. As sST2 increases with age and cardiovascular morbidity, since IMH and PAU were overlooked and because the kinetics of plasma sST2 in AAD is unknown, caution is needed in generalizing the study results and current estimates of the diagnostic accuracy of sST2 may be optimistic.

Technical issues

Relevant technical issues must also be considered. Wang *et al.* have used for sST2 detection the DuoSet ELISA assay (R&D Systems, Minneapolis, MN, USA), with sodium citrate plasma as a substrate. Other two assays are available on the market for sST2 measurement: one from MBL (Medical & Biological Laboratories, Woburn, MA, USA), and the Presage® ST2 Assay (Critical Diagnostics, CA, USA). Only the latter is FDA cleared and CE marked, while the other two methods are research assays. Technical differences between these detection assays may be relevant and previous studies have shown that the results obtained with the different methods may not be directly comparable (23). For instance, the actual epitopes recognized by the kits are not known. Of note, Wang *et al.* have assayed sST2 with both the R&D and Presage kits

on a subset of 67 individuals. The authors report that the Pearson's correlation coefficient of log-transformed sST2 levels with the two assays was 0.9, and 35 ng/mL obtained with the R&D assay was equivalent to 71 ng/mL obtained with the Presage assay. Nonetheless, further studies will be needed to validate these findings with other sample types (e.g., EDTA plasma) and other assays, particularly with the Presage assay, which is validated and cleared for clinical use.

Conclusions

The optimal sensitivity and specificity of plasma sST2 for diagnosis of AAD reported by Wang *et al.* foster hopes of a dramatic step forward in the diagnostic approach to suspected AAS. However, a series of pathophysiological, clinical and technical issues indicate that caution is needed when interpreting these experimental results. At this point, questions still appear to be more than answers and external validation of these results is needed to define if sST2 truly represents a new dawn for acute cardiovascular diagnosis and care. Ideally, new studies should involve older and comorbid patients, apply meaningful pre-test patient risk stratification, extend the time window from symptom onset, use a validated diagnostic assay for sST2 and perform real-world and standard-of-care patient recruitment in the ED.

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Footnote

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