

EDITORIAL COMMENT

Cartilage Oligomeric Matrix Protein, a Potential Biomarker for Thoracic Aortic Dissection



Levon M. Khachigian, PhD, DSc,^a Jonathan Golledge, MChir^{b,c}

Thoracic aortic dissection (TAD) is a rare, life-threatening vascular emergency, typically presenting with severe chest or upper back pain. Differentiating TAD from more common causes of chest pain (such as, acute myocardial infarction) can be challenging.¹ Prompt diagnosis and treatment are critical for survival. TAD begins with an initial tear in the intima and media of the aorta and the formation of an alternate channel, or false lumen, and potential rupture. Stanford type A dissections (DeBakey types I and II) involve the ascending aorta, whereas type B dissections (DeBakey type III) involve the descending aorta. Most are the former, which has an in-hospital mortality rate of approximately 30%, and for individuals without surgical intervention, approximately 20% at 24 hours or approximately 50% at 2 weeks after symptom onset. A substantial proportion of aortic dissection patients have recognized connective tissue disease such as Marfan syndrome (MFS), Loeys-Dietz syndrome, and other transforming growth factor β (TGF β)-related syndromes.¹ Vascular smooth muscle cell (SMC) phenotypic switching, matrix metalloproteinase (MMP) expression, and extracellular matrix (ECM) degradation underpin loss of tensile strength and vessel elasticity.

A reliable disease-specific plasma biomarker for TAD is currently lacking. This would help improve diagnosis, risk stratification, and management of this disease. In this regard, D-dimer is used, but this has low specificity for TAD because it indicates a thromboembolic event, as does C-reactive protein (CRP), which signals a systemic inflammatory response. Circulating smooth muscle myosin heavy chain sensitivity rapidly decreases after symptom onset. Circulating integrin $\alpha 2$, $\alpha 1$ chain of type II collagen, and macrophage migration inhibitory factor are elevated in TAD patients, and insulin-like growth factor binding protein 2 and MMP3 are associated with disease severity, but it is unclear whether or how these levels temporally relate to symptom onset.

In this issue of *JACC: Basic to Translational Science*, Li et al² propose that cartilage oligomeric matrix protein (COMP), a 524 kDa pentameric glycoprotein also known as thrombospondin 5, may serve as a novel biomarker for early detection and prognostic monitoring of TAD. COMP is an extracellular matrix protein largely derived from SMCs. The authors measured plasma COMP levels in 362 TAD patients (169 type A TAD patients and 193 type B TAD patients) and 136 control patients, and found that COMP levels were significantly lower in both TAD subtypes compared with control patients, with no significant difference between subtypes. COMP levels fell within 6 hours of TAD symptom onset and persisted for at least 48 hours (although it is unclear for how long thereafter), independent of risk factors such as hypertension and hyperglycemia. In contrast, plasma D-dimer levels peaked within 24 hours of symptom onset and decreased by 48 hours. Plasma CRP levels showed delayed induction, peaking 48 hours after symptom onset. Regression analysis performed by the authors revealed that every 10-ng/mL decrease in plasma COMP was associated with a

From the ^aVascular Biology and Translational Research, Department of Pathology, School of Biomedical Science, Faculty of Medicine and Health, University of New South Wales, Sydney, New South Wales, Australia; ^bQueensland Research Centre for Peripheral Vascular Disease, James Cook University, Townsville, Queensland, Australia; and the ^cDepartment of Vascular and Endovascular Surgery, Townsville University Hospital, Townsville, Queensland, Australia.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

4.99% increase in TAD incidence. COMP, like D-dimer, has a considerably shorter half-life than CRP (6 vs 19 hours), suggesting potential use as a real-time monitor of disease state.

Complementing these clinical observations, the authors interrogated the role of COMP in a murine model of β -aminopropionitrile (BAPN)-induced aortic dissection. In C57BL/6 mice given BAPN, plasma COMP levels fell within 1 week before the development of aortic dissection. COMP expression was also reduced in the thoracic aorta at this time. *COMP*^{-/-} mice given BAPN, compared with wild-type (WT) counterparts, had increased TAD formation and aortic dilation after 28 days. There was also evidence of increased leukocyte infiltration and elastin degradation together with elevated levels of MMP2 and MMP9 expression in the aorta. These data indicate that COMP deficiency potentiates BAPN-induced dilation and establishes a causal link between COMP deficiency and TAD pathogenesis. This raises the question of whether individuals with COMP mutations³ are at greater risk of developing TAD.

The authors also investigated the role of COMP in a murine model of MFS after finding that plasma COMP levels were significantly lower in MFS patients than age- and sex-matched control patients. MFS arises from mutations in *Fbn1* which compromises vascular wall integrity and puts patients at considerable risk of aortic root dilatation. COMP expression in the aorta was significantly lower in heterogenous *Fbn1*^{C1041G/+} mice compared with WT mice. Furthermore, noting that COMP controls vascular SMC phenotype and plasticity,⁴ and given that extracellular signal-regulated kinase signaling drives aortic aneurysm pathogenesis through SMC phenotype switching, the authors investigated TAD in *Fbn1*^{C1041G/+} mice in which COMP was overexpressed in aortic SMCs. *Fbn1*^{C1041G/+}*COMP*^{SM-Tg} mice showed less extracellular signal-regulated kinase phosphorylation, elastic lamina breakage and aortic dilation than *Fbn1*^{C1041G/+} mice. These findings suggest that COMP perturbs TAD pathogenesis in the context of MFS and highlight the protective role of SMC-derived COMP in this process.

The idea that COMP protects against aortic dilation is not new. The authors had earlier observed that plasma COMP levels also inversely correlated with abdominal aortic aneurysm (AAA).⁵ Lower COMP levels were detected in patients with AAA and in suprarenal aortas of angiotensin II (Ang II)-infused *ApoE*^{-/-} mice, a model of AAA but also reported to have TAD. In *COMP*^{-/-} mice infused with Ang II, aortic diameter, elastin degradation, and inflammatory cell infiltration at 28 days were greater compared with WT mice, indicating that COMP protects against Ang

II-induced AAA. Conversely, inflammation, MMP activity, and oxidative stress in the suprarenal aortas were reduced in Ang II-infused *ApoE*^{-/-} mice in which COMP was overexpressed. Moreover, COMP prevented AAA formation in *ApoE*^{-/-}*COMP*^{SM-Tg} mice compared with *ApoE*^{-/-} mice. At a mechanistic level, COMP binds the extracellular N-terminus of the AT1 receptor through its epidermal growth factor domain and inhibits AT1- β -arrestin-2 signaling. AAA incidence, aortic dilatation, and elastin degradation were reduced in *AT1a*^{-/-}*COMP*^{-/-} mice and *β -arrestin-2*^{-/-}*COMP*^{-/-} mice compared with *COMP*^{-/-} mice, indicating that COMP deficiency induces AAA formation in an AT1a receptor- and β -arrestin-2-dependent manner. The precise mechanism(s) underlying the ability of COMP to alleviate aortic injury remains unknown, and it is unclear whether G protein-coupled receptors or β -arrestin-2 play a role.

Qin et al⁶ had earlier shown that COMP levels were lower in aortic aneurysm specimens compared with ascending aorta control tissue from dilated cardiomyopathy patients who underwent heart transplantation. That study also showed that a disintegrin and metalloproteinase with thrombospondin motifs-7 (ADAMTS-7) levels were elevated in the aortic aneurysm group. Mice lacking ADAMTS-7 have attenuated vascular inflammation and thoracic aortic aneurysm and dissection.⁷ Because ADAMTS-7 is able to bind and degrade COMP,⁸ and ADAMTS-7 silencing reduces COMP degradation in SMCs,⁹ future studies might explore a mechanistic relationship between ADAMTS-7 and COMP in TAD.

The Li et al study² had a number of limitations. First, the control group included 139 healthy individuals matched for age and sex with the experimental group. An ideal diagnostic biomarker for TAD would be one which clearly differentiates individuals with bona fide TAD from those with TAD-like symptoms but who have a different diagnose (such as, acute myocardial infarction). Thus, whether the findings of Li et al² can be translated to a clinical diagnostic setting is unclear. Second, factors adjusted for the clinical study were limited to age, hypertension, and glucose, but not to other important confounders (such as, smoking, medications, anthropometric measures). Third, the number of patients in the MFS study was limited to 5 cases and 10 controls, making generalization difficult. Fourth, findings from 3-week-old mice models may not translate to patients with TAD. Fifth, use of male mice may limit possible extrapolation to female TAD patients. Finally, the murine BAPN model did not include Ang II in the form of co- or sequential administration, whereby Ang II triggers TAD

occurrence and reflecting of a more severe TAD phenotype.¹⁰

A specific biomarker for TAD would provide an invaluable resource for emergency triage, diagnosis, risk assessment, prognosis, and management of this potentially fatal vascular disease. Future well-designed, large, multicenter studies measuring COMP in patients with a possible diagnosis of TAD are needed to rigorously test whether this biomarker can be of clinical value.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Khachigian's research is supported by grants from the Australian National Health and Medical Research Council (NHMRC), Heart Foundation, Department of Industry Science and Resources (CRCP),

and a Cardiovascular Senior Researcher Grant from NSW Health. Dr Golledge's research is supported by grants from NHMRC, Medical Research Futures Fund, Queensland Government (SCRF), Heart Foundation, and Townsville Hospital and Health Services. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Levon M. Khachigian, Vascular Biology and Translational Research, Department of Pathology, School of Biomedical Science, Faculty of Medicine and Health, University of New South Wales, Wallace-Wurth Building, Corner of High Street & Botany Street, Sydney, New South Wales 2052, Australia. E-mail: L.Khachigian@unsw.edu.au.

REFERENCES

1. Golledge J, Eagle KA. Acute aortic dissection. *Lancet*. 2008;372:55-66.
2. Li Z, Gong Z, Li W, et al. The reduction of COMP serves as a predictor for warning of aortic dissection progression. *JACC Basic Transl Sci*. 2025;10(8):101329.
3. Briggs MD, Hoffman SM, King LM, et al. Pseudoachondroplasia and multiple epiphyseal dysplasia due to mutations in the cartilage oligomeric matrix protein gene. *Nat Genet*. 1995;10:330-336.
4. Wang L, Zheng J, Du Y, et al. Cartilage oligomeric matrix protein maintains the contractile phenotype of vascular smooth muscle cells by interacting with alpha(7)beta(1) integrin. *Circ Res*. 2010;106:514-525.
5. Fu Y, Huang Y, Yang Z, et al. Cartilage oligomeric matrix protein is an endogenous beta-arrestin-2-selective allosteric modulator of ATI receptor counteracting vascular injury. *Cell Res*. 2021;31:773-790.
6. Qin W, Cao Y, Li L, Chen W, Chen X. Upregulation of ADAMTS-7 and downregulation of COMP are associated with aortic aneurysm. *Mol Med Rep*. 2017;16:5459-5463.
7. Gong Z, Huang J, Wang D, et al. ADAMTS-7 deficiency attenuates thoracic aortic aneurysm and dissection in mice. *J Mol Med (Berl)*. 2023;101:237-248.
8. Liu CJ, Kong W, Ilalov K, et al. ADAMTS-7: a metalloproteinase that directly binds to and degrades cartilage oligomeric matrix protein. *FASEB J*. 2006;20:988-990.
9. Du Y, Gao C, Liu Z, et al. Upregulation of a disintegrin and metalloproteinase with thrombospondin motifs-7 by miR-29 repression mediates vascular smooth muscle calcification. *Arterioscler Thromb Vasc Biol*. 2012;32:2580-2588.
10. Zheng HQ, Rong JB, Ye FM, Xu YC, Lu HS, Wang JA. Induction of thoracic aortic dissection: a mini-review of beta-aminopropionitrile-related mouse models. *J Zhejiang Univ Sci B*. 2020;21:603-610.

KEY WORDS BAPN, biomarker, COMP, Marfan syndrome, thoracic aortic dissection