Commentary: Medical management after surgical treatment of acute Stanford type A aortic dissection: Causation or “shear” coincidence?

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Surgical patients may pose challenges in any or all of the 3 phases of care: preoperative, intraoperative, and postoperative. Acute Stanford type A aortic dissection (ATAAD) continues to have room for improvement in *each* of the phases of care. This is borne out both by the continued high mortality and morbidity of ATAAD in the perioperative period¹ and by the poor long-term outcomes in patients who have survived initially successful operative treatment.² With respect to the latter, both aorta-related and unrelated causes of mortality and morbidity exist, all of which have been foci for investigation to improve outcomes.

The roles of aortic loading conditions in ATAAD and aortic aneurysmal disease have been investigated in theoretical, experimental, and clinical studies over several decades. Most of these studies, however, have been plagued by gross oversimplifications of *what* the loads themselves *actually are*, and *how* the loads and aortic mechanical properties are measured experimentally or modeled theoretically. Systemic arterial “blood pressure” is taken to be the principal load on the aorta that initiates and propagates dissection, with the additional recognition that cyclic temporal fluctuations in intraluminal aortic pressure contribute to at least dissection propagation (the latter being work initiated by Wheat and coworkers³). The aorta is modeled either as rigid (this being absurd) or as linearly elastic, and isotropic and time independent. These, however, are clearly substantial oversimplifications. Forces and stresses are vectors, whereas pressure is a scalar. The aorta is exposed to both normal and shear stresses, as expressed in the Cauchy stress tensor; the former act perpendicular to surfaces (the mean of the magnitudes of the 3 normal stresses is the pressure), whereas the latter act parallel or along surfaces. Finally, the aorta is nonlinearly viscoelastic and anisotropic. Although some work⁴ has advanced state-of-the-art fluid and solid mechanics modeling concepts and applied them

Stress and strain maps of the human aorta.

Central Message

Therapy with β -blockers after acute type A dissection appears to have long-term benefits, but whether this is a direct effect or only an association remains unclear.

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to ATAAD, little of this has been translated to the clinical setting.

In this issue of the *Journal*, Chen and colleagues² report the results of a retrospective population-based study in Taiwan of survivors of operatively treated ATAAD, specifically focusing on the impact of β -adrenergic receptor antagonists (β -blockers) on outcomes. Chen and colleagues² divided patients into groups according to β -blocker use versus nonuse, and by means of propensity matching were able to place 396 patients in each group, so that they could conduct comparative analyses. Briefly summarized, they found that β -blocker use was associated with improved survival and fewer major adverse cardiovascular events. A cumulative dosage effect was observed; durable adherence to β -blocker therapy was associated with improved survival outcomes.

But are these findings evidence of *causation*? Conventional thinking regarding pharmacologic management of aortic loading conditions is that the negative inotropic (and chronotropic) effects of β -blockade act not simply to reduce intraluminal pressure but to reduce pulse pressure (ie, pressure wave amplitude and “dP/dt”—the latter of which is improperly or inexactly defined in most studies⁴) as “anti-impulse” therapy. This hypothesis was supported by the initial studies by Pyeritz’s group in the 1990s on the effects of β -blockade in proximal thoracic aortic aneurysm progression in patients with Marfan syndrome.⁵

The current findings of Chen and colleagues² may be explained by either correlation or causation. It could be that

β -blockade was causally related to mortality reduction, or it could be that a correlation was identified related to the ability to tolerate β -blockers. Indeed, the ability to tolerate β -blockers is observed in more hemodynamically robust and stable patients. Next, even if a causal link between β -blocker intake and improved outcomes were present, this might be hemodynamic or nonhemodynamic in origin. That is, the mechanisms through which β -blockade may exert beneficial effects may or may not relate to reductions in pathological aortic loading or, even less likely, directly salutary effects on the aorta. There was no difference in late aortic reinterventions or hospitalizations for hypertensive crises between the groups, arguing against a hemodynamic benefit specific to β -blockade. A possible explanation for this particular finding is that good hemodynamic management is important after ATAAD surgery but that the choice of agents to achieve satisfactory hemodynamic end points is relatively unimportant; this explanation is a subset of an overall paradigm in which the molecular mechanisms underlying the hemodynamic effects are less important than the hemodynamic effects themselves. Indeed, as a follow-up study to the initial work of Pyeritz's group,⁵ a recent multicenter randomized, controlled trial of the β -adrenergic receptor antagonist atenolol versus the angiotensin II type 1 receptor losartan in children and young adults with Marfan syndrome did not identify any difference in rates of aortic root dilatation.⁶ This still does not provide a causative mechanism for the *differentially superior survival* outcomes associated with β -blocker use in the current study of Chen and colleagues.² Broadly, through several different molecular mechanisms,⁷ β -blockers may exert cardioprotective effects, which in turn may translate to improved survival and reduced morbidity; however, none

of the findings in this study identified *mechanistic links* between β -blocker use and improved outcomes. This is an all-too-common problem, namely that of phenomena without mechanisms, which when scaled to the level of the studies as whole entities, becomes a problem of empiricism without science.

So where does this study leave us? It is probably true that β -blockade does have broad benefit in the population of ATAAD survivors, as it does in the bulk of patients with a wide array of different cardiovascular diseases. But it could be that, as is unfortunately all too often the case, as evidenced by investigators using the word *effect* instead of the more accurate *association*, that what is being observed is simply a correlation.

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