

1**Title:** Invited commentary for asymmetric dimethylarginine (ADMA): Is it a risk factor in the
2repair of aortic coarctation?

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4**Short Title:** Invited commentary for asymmetric dimethylarginine (ADMA)

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54 Bas et al. report clinical findings of asymmetric dimethylarginine (ADMA) measurement
55 in 22 neonates and early infants undergoing surgery for aortic coarctation repair.¹ The authors
56 noted that data from previous studies indicated a secure and effective aortic cross clamp time of
57 20 minutes.¹ The study consisted of two groups of patients defined by the authors' cross clamp
58 time. Their results suggested that serum ADMA was significantly elevated postoperatively in the
59 prolonged (>20 minutes) group, as compared to the shorter group (<20 minutes). Further,
60 elevated ADMA correlated with higher postoperative inotropic support. The change in ADMA
61 levels was also significantly higher in patients with post-repair morbidity. However, there is a
62 lack of matching of preoperative conditions and a small sample size. Results may differ if all
63 cases were reanalyzed together, and the measurement values were assessed individually to
64 identify the specific cross clamp time duration that contributes significantly to elevate serum
65 ADMA levels postoperatively. The authors' statement that "treatments to reduce serum ADMA
66 levels can be valuable for preventing morbidity and mortality which develop after surgeries in a
67 transient ischemia setting by clamping the aorta" highlights an ongoing knowledge gap in our
68 field and raises awareness of the compelling clinical need for new transformative solutions.

69 Infection is the most frequent cause of postoperative morbidity in all surgical patients,
70 resulting in complications and longer hospital length of stay.² Drover et al. studied the
71 perioperative use of arginine-supplemented nutritional formulas in elective surgical patients.² In
72 conjunction with supplementation, there is a substantial reduction in infectious complications
73 and shorter hospital length of stay, with a greater reduction in non-GI surgery patients. Why is
74 arginine supplementation a promising treatment modality for postoperative patients? During
75 inflammatory processes, endotoxin and cytokines stimulate nitric oxide (NO) production by
76 endothelial cells.³ The NO production induces vasodilation, contributing to the characteristic

77hemodynamic changes seen in sepsis. However, NO production differs in cases of physical insult
78(surgery or trauma).² After surgery, immature myeloid cells express arginase 1 within 12 hours,
79which increases arginine metabolism as seen by Bas et al., depletes arginine, and suppresses T-
80lymphocyte function.^{1,2,4} In instances of limited arginine availability, arginase decreases NO
81production and impairs normal vasoactivity.² Therefore, plasma NO metabolites (NO₂/NO₃⁻) are
82decreased within 6 hours of surgery. With the induced immune dysfunction, patients are
83predisposed to a higher risk of infection. T-cell function may be improved using pharmacologic
84inhibition of arginase 1 activity or supplementation of arginine.³

85 Arginine contained in protein is methylated after protein translation to form ADMA and
86is freed into the circulation in the process of protein turnover and recycling. ADMA is then
87eliminated in the urine. ADMA can accumulate because of increased protein turnover (as is
88observed during illness) and/or in patients with renal impairment.^{5,6} It is thus possible that the
89report from Bas et al. demonstrating increased levels of ADMA as a predictor of poor clinical
90outcome reflects that this cohort of patient was “sicker” to start with. Interestingly, the provision
91of supplemental arginine in the diet improves arginine:ADMA ratios providing an interesting
92possibility of an effective nutritional intervention in this patient population.⁷

93 The variability in end-to-side and extended end-to-end repair techniques used by Bas et
94al. may amplify ADMA level differences.¹ Extended end-to-end or end-to-side anastomosis
95maintains small arch dimensions, resulting in a more gothic aortic arch shape. A new technique
96described by Kozyrev et al. provides good geometry of the arch and a tension-free
97reconstruction.⁸ Kozyrev et al. suggest arch shape may be associated with postoperative
98hypertension, an increase in systolic backward flow and volume, and a greater loss of systolic

99wave amplitude.⁸ Is a Romanesque arch preferred?⁹ Unfavorable arch geometry and dimensions
100may lead to adverse vascular remodeling and hypertension.

101 The field of congenital heart disease has benefited from diagnostic modalities of fetal
102echocardiography and cardiac echocardiography, as well as the perioperative use of prostacyclin.
103Bas et al. introduced an innovative concept of ADMA measurement. More research is required,
104and a detailed investigation of the perioperative benefit of ADMA will aid clinical teams as they
105collaboratively devise next generation treatment strategies for infants and children with complex
106congenital heart disease.

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