



Original Article

Effect of Combined Ventricular-Arterial Stiffening on Exercise Hemodynamics in Adults With Repaired Coarctation of Aorta

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ABSTRACT

Background: Patients with coarctation of aorta (COA) have arterial stiffening, and this is associated with impaired cardiac reserve and hypertensive systolic blood pressure (SBP) response during exercise. However, whether patients with COA have concomitant left ventricular (LV) stiffening and the potential impact of combined ventricular-arterial stiffening on exercise hemodynamics are unknown.

Methods: We studied 174 patients with repaired COA (aged 39 ± 11 years and male 103 [59%]) and 174 matched controls. Our study hypotheses are: (1) patients with COA have higher ventricular-arterial

RÉSUMÉ

Contexte : La coarctation de l'aorte (CA) s'accompagne d'une rigidification des artères, qui est à son tour associée à une altération de la réserve de force du cœur et à une augmentation de la pression artérielle systolique (PAS) à l'effort. On ne sait toutefois pas si la CA entraîne aussi une rigidification du ventricule gauche, et on ne connaît pas les répercussions possibles d'une rigidification ventriculaire et artérielle sur les paramètres hémodynamiques à l'effort.

Méthodologie : Nous avons étudié 174 patients présentant une CA corrigée (âge : 39 ± 11 ans; hommes : 103 [59 %]) et 174 témoins

Coarctation of aorta (COA) is characterized by left ventricular (LV) pressure overload due a combination of aortic isthmus stenosis, arch hypoplasia, aortic stiffness, and other associated LV outflow tract obstructive lesions.^{1,2} It is a leading cause of LV dysfunction and cardiovascular death in adults with congenital heart disease.³⁻⁶ Patients with COA have increased arterial stiffness due to endothelial dysfunction, and arterial stiffening is associated with systemic hypertension, LV remodelling, and exercise intolerance.³⁻⁶ A recent study showed that even in the absence of hemodynamically significant residual coarctation, adults with COA had elevated arterial elastance (Ea), which is a measure of arterial stiffness, and Ea was associated with hypertensive systolic blood pressure (SBP) response and impaired cardiac reserve during exercise because small changes in LV stroke volume resulted in a disproportionate increase in SBP.⁴

Chronic cardiac ejection into a stiff arterial system results in LV remodelling and a compensatory increase in LV end-systolic elastance (Ees) to maintain an optimal ventricular-arterial interaction and, in turn, efficient mechanical and metabolic function.^{7,8} Although an increase in Ees maintains optimal ventricular-arterial coupling, it also results in a combined ventricular-arterial stiffening, which has been linked to hypertensive SBP response and impaired cardiac reserve during exercise in elderly hypertensive patients.⁹ In addition, drugs such as verapamil that reduce both ventricular and arterial stiffening have been shown to improve exercise capacity and cardiac reserve in the acquired heart disease population.¹⁰

Although the existence of arterial stiffening and its negative impact on exercise capacity has been described in patients with COA,^{4,11-13} the concept of combined ventricular-arterial stiffening and its potential impact on exercise hemodynamic response is unknown. If there is a mechanistic link between combined ventricular-arterial stiffening and abnormal exercise hemodynamic response in patients with COA, this will provide justification to test whether medical therapies that reduce both ventricular and arterial stiffening (Ees and Ea) can provide synergistic improvement in exercise hemodynamics in this population. The purpose of this study was to determine whether patients with COA had combined ventricular-arterial stiffening and

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Ethics Statement: Our research adhered to ethical standard stipulated by the Mayo Clinic IRB.

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stiffness (end-systolic elastance [Ees] and arterial elastance [Ea]) as compared with controls; (2) ventricular-arterial stiffness was associated with LV stroke volume augmentation (Δ LVSV) and SBP augmentation (Δ SBP) during exercise among patients with COA.

Results: Despite similar systolic SBP, patients with COA had higher Ea (1.8 ± 0.4 vs 1.4 ± 0.4 mm Hg/mL, $P < 0.001$), higher Ees (2.41 ± 0.65 vs 2.17 ± 0.40 mm Hg/mL, $P < 0.001$), but similar Ea/Ees (0.87 ± 0.29 vs 0.83 ± 0.33 , $P = 0.2$). Δ LVSV was 6.1 ± 1.4 mL/beat. Combined ventricular-arterial stiffness had a stronger correlation with Δ LVSV as compared with Ea alone ($r = -0.53$ vs $r = -0.41$, $P = 0.006$) and as compared with Ees alone ($r = -0.53$ vs $r = -0.46$, $P = 0.02$). Δ SBP was 48 ± 21 mm Hg. Combined ventricular-arterial stiffness had a stronger correlation with Δ SBP as compared with Ea alone ($r = 0.57$ vs $r = 0.43$, $P < 0.001$) and as compared with Ees alone ($r = 0.57$ vs $r = -0.39$, $P < 0.001$).

Conclusion: Patients with COA had combined ventricular-arterial stiffening, and this was associated with impaired cardiac reserve and hypertensive SBP response during exercise. These findings provide foundation for further studies to determine whether drugs that reduce both ventricular and arterial stiffness will improve exercise capacity and hemodynamics in this unique population.

the relationship between ventricular-arterial stiffening and exercise hemodynamics. Our study hypotheses are: (1) patients with COA have higher ventricular-arterial stiffness (Ees and Ea) as compared with controls; (2) ventricular-arterial stiffness was associated with LV stroke volume augmentation (Δ LVSV) and SBP augmentation (Δ SBP) during exercise among patients with COA.

Methods

Study population

Adults (aged ≥ 18 years) with repaired COA who underwent transthoracic echocardiogram and cardiopulmonary exercise test between January 1, 2000, and December 31, 2018, were identified from the Mayo Adult Congenital Heart Disease registry. The Mayo Clinic Institutional Review Board approved the study. The inclusion criteria were: (1) absence of hemodynamically significant residual coarctation defined as the aortic isthmus continuous wave Doppler peak velocity of < 2.5 m/s in the absence of collaterals; (2) brachial SBP measured in the right arm in the absence of the aberrant origin of the right subclavian artery; and (3) sinus rhythm at the time of echocardiogram. The exclusion criteria were: (1) significant mitral valve disease defined as a native mitral valve mean gradient > 3 mm Hg or $>$ mild mitral regurgitation, severe mitral annular calcification based on qualitative assessment, or mitral valve prosthesis; (2) significant aortic valve disease defined as a native aortic valve peak velocity > 2 m/s or $>$ mild aortic regurgitation or prosthetic aortic valve.

To determine whether patients with COA had combined ventricular-arterial stiffening as compared with patients without

appariés. Nos hypothèses étaient les suivantes : 1) la rigidité ventriculaire et artérielle (élastance télé-systolique [ETS] et élastance artérielle [EA]) est plus importante chez les sujets présentant une CA que chez les sujets témoins; 2) la rigidité ventriculaire et artérielle est associée à une augmentation du volume d'éjection ventriculaire gauche (Δ VEVG) et à une augmentation de la pression artérielle systolique (Δ PAS) à l'effort chez les patients présentant une CA.

Résultats : Malgré une PAS comparable, les patients présentant une CA avaient une EA plus élevée que les sujets témoins ($1,8 \pm 0,4$ vs $1,4 \pm 0,4$ mmHg/ml, $p < 0,001$) et une ETS également plus élevée ($2,41 \pm 0,65$ vs $2,17 \pm 0,40$ mmHg/ml, $p < 0,001$), mais un rapport EA/ETS similaire ($0,87 \pm 0,29$ vs $0,83 \pm 0,33$, $p = 0,2$). La Δ VEVG était de $6,1 \pm 1,4$ ml/battement. La rigidité ventriculaire et artérielle mixte était plus fortement corrélée avec une Δ VEVG, comparativement à l'EA seule ($r = -0,53$ vs $r = -0,41$, $p = 0,006$) et à l'ETS seule ($r = -0,53$ vs $r = -0,46$, $p = 0,02$). La Δ PAS était de 48 ± 21 mmHg. La rigidité ventriculaire et artérielle mixte était plus fortement corrélée avec la Δ PAS, comparativement à l'EA seule ($r = 0,57$ vs $r = 0,43$, $p < 0,001$) et à l'ETS seule ($r = 0,57$ vs $r = -0,39$, $p < 0,001$).

Conclusion : La CA s'accompagnait d'une rigidification ventriculaire et artérielle, elle-même associée à une altération de la réserve de force du cœur et à une augmentation de la PAS à l'effort. Ces résultats pourront servir de fondements à des études complémentaires visant à déterminer si un traitement qui réduit la rigidité ventriculaire et artérielle pourrait améliorer la capacité à l'effort et les paramètres hémodynamiques dans cette population particulière.

COA, we selected a control group of patients without structural heart disease who underwent echocardiogram within the same study period. We performed 1:1 matching of patients with COA and the control group using the propensity score method based on age, sex, body mass index, history of hypertension, and SBP at the time of echocardiogram.

We assessed ventricular and arterial stiffness using Ees and Ea. Δ LVSV was assessed using Δ O₂ pulse and calculated as O₂ pulse (Δ O₂ consumption divided by heart rate) at peak exercise minus O₂ pulse at rest. Δ SBP was calculated as SBP at peak exercise minus SBP at rest.

Echocardiography

LV volumes and ejection fraction were measured using the biplane Simpson's method as previously described.¹⁴ LV Ees was assessed using the modified single-beat method based on the following indices: SBP using arm blood pressure cuff, Doppler derived LV stroke volume, pre-ejection time, and total ejection time based on continuous wave Doppler of aortic flow.^{15,16} Doppler-derived effective arterial elastance index, which is a lumped measure of the total stiffness of the arterial system, was calculated as $0.9 \times$ brachial SBP/stroke volume index.^{3,15,16}

Cardiopulmonary exercise testing

Similar to previous studies from our group,^{4,6} all patients underwent cardiopulmonary exercise test with a treadmill ergometer using an incremental protocol (Naughton protocol or the modified Bruce protocol) that allowed reaching exhaustion in approximately 10 minutes of exercise. Peak O₂ consumption (VO₂ max) and ventilatory equivalent for carbon dioxide were measured as previously described.^{4,6} We

Table 1. Baseline characteristics

	COA (n = 174)	Control (n = 174)	P
Age (y)	39 ± 11	39 ± 11	0.9
Age (min-max)	19-56	21-57	—
Time from COA repair (y)	37 ± 8	—	—
Male	103 (59%)	103 (59%)	0.9
Body mass index (kg/m ²)	28 ± 5	28 ± 5	0.9
Body surface area (m ²)	1.9 ± 0.2	1.9 ± 0.3	0.7
Systolic BP (mm Hg)	129 ± 16	129 ± 18	0.9
Diastolic BP (mm Hg)	67 ± 13	78 ± 8	0.003
Pulse pressure (mm Hg)	62 ± 14	51 ± 10	< 0.001
Heart rate (bpm)	74 ± 8	66 ± 7	0.002
Comorbidities/medications			
Hypertension	62 (36%)	62 (36%)	0.9
Hyperlipidemia	29 (17%)	16 (9%)	0.06
Diabetes	9 (5%)	6 (3%)	0.7
Beta blockers	29 (17%)	12 (7%)	0.004
Calcium channel blockers	21 (12%)	14 (8%)	0.2
RAAS antagonist	46 (26%)	19 (11%)	< 0.001
Laboratory data			
Haemoglobin (g/dL)	14.2 ± 1.2	13.9 ± 1.0	0.3
Estimated GFR (mL/min/1.73 m ²)	88 ± 21	109 ± 33	< 0.001

BP, blood pressure; COA, coarctation of aorta; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.

used the Jones equation for determining the predicted VO₂: predicted VO₂ for male subjects = [60.0 - (0.55 × age)] × 1.11; predicted VO₂ for female subjects = [48.0 - (0.37 × age)] × 1.11.¹⁷

Because we did not measure LVSV during exercise, we used O₂ pulse as surrogate for LVSV, and O₂ pulse was calculated as O₂ consumption divided by heart rate at rest and at peak exercise, respectively. Only exercise test with maximal effort was included in this study, and the maximum effect was defined as symptom-limited exercise test with a respiratory exchange ratio greater than 1.1.^{4,6}

Statistical analysis

Propensity score, which is the probability of having COA, was calculated using logistic regression based on age, sex, body mass index, hypertension diagnosis, and SBP at the time of echocardiogram as previously described.^{3,4} Data were presented as mean ± standard deviation and count (%), and between-group comparisons were performed using Fisher's exact test and unpaired *t*-tests as appropriate. First, we assessed the correlation between ventricular stiffness (Ees) and exercise hemodynamics, and between arterial stiffness (Ea) and exercise hemodynamics using linear regression. Next, we assessed the correlation between combined ventricular-arterial stiffness and exercise hemodynamics by imputing both Ees and Ea as predictor variables in the model. To determine whether ventricular-arterial stiffness had a more robust correlation with exercise hemodynamics as compared with ventricular stiffness or arterial stiffness alone, we compared the correlation coefficients of these models using the Meng test. A *P* value of < 0.05 was considered statistically significant. All statistical analyses were performed with JMP software (version 14.1.0; SAS Institute Inc, Cary, NC).

Results

A total of 174 patients with COA (aged 39 ± 11 years and male 103 [59%]) met the study inclusion criteria, and 76

(44%) of them had a bicuspid aortic valve. The age at the time of initial COA repair/intervention was 1.8 (0.3-8.3) years, and the procedures were resection and end-to-end anastomosis (n = 58, 33%), subclavian flap repair (n = 35, 20%), patch aortoplasty (n = 19, 11%), interposition graft repair (n = 42, 24%), balloon aortic dilation (n = 11, 6%), and stent implantation (n = 9, 5%). Among the 26 patients who had reinterventions, the age at the time of reintervention was 20 ± 9 years, and the procedures were patch aortoplasty (n = 3), interposition graft repair (n = 5), and stent implantation (n = 18).

Table 1 shows a comparison of the clinical characteristics of the COA and control groups. Although both groups were matched based on SBP, the COA group had higher Ea (1.82 ± 0.42 vs 1.44 ± 0.40 mm Hg/mL, *P* < 0.001), higher Ees (2.41 ± 0.65 vs 2.17 ± 0.40 mm Hg/mL, *P* < 0.001), but similar Ea/Ees (0.87 ± 0.29 vs 0.83 ± 0.33, *P* = 0.2) (Table 2). There were no significant differences between males vs females respectively for Ea (1.84 ± 0.36 vs 1.79 ± 0.35 mm Hg/mL, *P* = 0.4), Ees (2.39 ± 0.41 vs 2.43 ± 0.38 mm Hg/mL, *P* = 0.1), and Ea/Ees (0.89 ± 0.21 vs 0.86 ± 0.30, *P* = 0.2) in the COA group. Similarly, there were no significant differences between males vs females respectively for Ea (1.42 ± 0.39 vs 1.46 ± 0.31 mm Hg/mL, *P* = 0.1), Ees (2.19 ± 0.45 vs 2.15 ± 0.37 mm Hg/mL, *P* = 0.2), and Ea/Ees (0.84 ± 0.29 vs 0.83 ± 0.32, *P* = 0.5) in the control group.

Determinants of stroke volume and SBP augmentation during exercise

All the patients with COA underwent exercise test, and the median interval between echocardiogram and exercise test was 1 (1-2) days. The patients with COA exercised for 7.9 ± 2.8 minutes and achieved a VO₂ max of 27.4 ± 8.8 mL/kg/min corresponding to 73 ± 22% of predicted. O₂ pulse increased from 4.6 ± 1.9 mL/beat at rest to 10.7 ± 3.1 mL/beat at peak exercise, and ΔO₂ pulse (surrogate for ΔLVSV) during

Table 2. Echocardiography and exercise test

Echocardiographic data	COA	Control	<i>P</i>
LV mass and volumes			
LV end-diastolic volume index (mL/m ²)	53 ± 12	59 ± 9	0.009
LV end-diastolic volume index (mL/m ²)	19 ± 6	23 ± 6	0.03
LV ejection fraction (%)	64 ± 9	62 ± 8	0.4
LV stroke volume index (mL/m ²)	39 ± 10	46 ± 9	0.005
Heart rate (bpm)	74 ± 8	66 ± 7	0.002
Cardiac index (L/min/m ²)	2.9 ± 0.6	3.1 ± 0.5	0.1
LV mass index (g/m ²)	108 ± 22	93 ± 29	< 0.001
Vascular function			
Ea (mm Hg/mL)	1.82 ± 0.42	1.44 ± 0.40	< 0.001
EaI (mm Hg/mL m ²)	3.46 ± 0.71	2.8 ± 0.83	< 0.001
TACI (mL/mm Hg m ²)	0.82 ± 0.32	1.34 ± 0.50	< 0.001
SVRI (dyne-s/cm ⁵ m ²)	2552 ± 718	2411 ± 663	0.6
LV systolic stiffness and coupling			
Ees (mm Hg/mL)	2.41 ± 0.65	2.17 ± 0.40	< 0.001
Ea/Ees	0.87 ± 0.29	0.83 ± 0.33	0.2
LV diastolic function			
Septal <i>e'</i> (m/s)	0.08 ± 0.04	0.11 ± 0.04	0.002
Lateral <i>e'</i> (m/s)	0.10 ± 0.04	0.14 ± 0.05	< 0.001
Septal E/ <i>e'</i>	12 ± 4	9 ± 5	0.008
Lateral E/ <i>e'</i>	10 ± 5	7 ± 3	< 0.001
LA volume index (mL/m ²)	31 ± 11	26 ± 6	0.01
Tricuspid regurgitation velocity (m/s)	2.6 ± 0.3	2.5 ± 0.2	0.09
Exercise data			
VO ₂ max (mL/kg/min)	27.4 ± 8.8	—	—
VO ₂ max (min-maximum)	18.3-39.6	—	—
Percent predicted peak VO ₂ (%)	73 ± 22	—	—
VE/VCO ₂	26.3 ± 4.8	—	—
Oxygen pulse (mL/beat)	10.7 ± 3.1	—	—
Systolic BP at rest (mm Hg)	127 ± 18	—	—
Diastolic BP at rest (mm Hg)	69 ± 14	—	—
Systolic BP at peak (mm Hg)	175 ± 41	—	—
Diastolic BP at peak (mm Hg)	59 ± 19	—	—
Heart rate at rest (bpm)	75 ± 14	—	—
Heart rate at peak (bpm)	167 ± 26	—	—

BP, blood pressure; COA, coarctation of aorta; E, mitral inflow pulsed wave Doppler early velocity; *e'*, tissue Doppler early velocity; EaI, effective arterial elastance index; Ees, end-systolic elastance; LA, left atrium; LV, left ventricle; SVRI, systemic vascular resistance index; TACI, total arterial compliance index; VE/VCO₂, ventilatory equivalent for carbon dioxide; VO₂, oxygen consumption.

exercise was 6.1 ± 1.4 mL/beat. The Δ SBP was not significantly different between males and females (6.3 ± 1.5 vs 5.9 ± 1.3 mm Hg, $P = 0.08$). There was a modest inverse correlation between Ees and Δ O₂ pulse ($r = -0.46$, $\beta \pm$ standard error -0.81 ± 0.37 , $P < 0.001$) and a modest inverse correlation between Ea and Δ O₂ pulse ($r = -0.41$, $\beta \pm$ standard error -0.64 ± 0.25 , $P < 0.001$). Combining Ea and Ees in the same model (as a metric of combined ventricular-arterial stiffness) resulted in an improvement in correlation coefficient ($r = -0.53$, $P < 0.001$). Combined ventricular-arterial stiffness had a stronger inverse correlation with Δ O₂ pulse as compared with Ea alone ($r = -0.73$ vs $r = -0.61$, Meng test $P = 0.006$) and as compared with Ees alone ($r = -0.73$ vs $r = -0.66$, Meng test $P = 0.02$).

The SBP at rest was 127 ± 18 mm Hg and increased to 175 ± 41 mm Hg at peak exercise, and the Δ SBP was 48 ± 21 mm Hg. The Δ SBP was higher in males as compared with females (52 ± 19 vs 46 ± 17 mm Hg, $P = 0.03$). There was a modest direct correlation between Ees and Δ SBP ($r = 0.39$, $P < 0.001$) and a modest direct correlation between Ea and Δ SBP ($r = 0.43$, $P < 0.001$). Combining Ea and Ees in the same model also resulted in an improvement in correlation coefficient ($r = 0.57$, $P < 0.001$). Combined ventricular-arterial stiffness had a stronger direct correlation with Δ SBP

as compared with Ea alone ($r = 0.57$ vs $r = 0.43$, Meng test $P < 0.001$) and as compared with Ees alone ($r = 0.57$ vs $r = 0.39$, Meng test $P < 0.001$).

Discussion

Arterial stiffening is a well-recognized sequela in adults with repaired COA, and chronic arterial pressure overload due to arterial stiffening leads to LV remodelling and dysfunction.³⁻⁶ Arterial stiffening as measured by Ea is associated with impaired cardiac reserve and hypertensive SBP response during exercise.⁴ However, it is unknown whether patients with COA have concomitant ventricular stiffening and how this may influence exercise hemodynamics in this population. In this study, we demonstrated that patients with COA had combined ventricular-arterial stiffening as compared with patients without COA with similar age, sex, and SBP, and that combined ventricular-arterial stiffening was associated with impaired cardiac reserve and hypertensive SBP response to exercise.

Impaired aerobic capacity and cardiac reserve have been described in patients with COA.^{4,6} In a previous study, we reported a negative correlation between arterial stiffness and Δ O₂ pulse (LVSV augmentation) in patients with COA as

compared with controls.⁴ Building on this foundation, the current data suggest that the blunted LVSV response in the patients with COA was not entirely due to arterial stiffening but rather due to combined ventricular-arterial stiffening. Furthermore, the strength of correlation was such that a substantial portion of the variance in LVSV augmentation remained unexplained by Ees and/or Ea, suggesting that diastolic dysfunction and a failure to augment end-diastolic volume may be a contributing factor to Δ LVSV limitation during exercise. However, we can only speculate because we do not have data about exercise end-diastolic and end-systolic volumes or peak Ees. These findings are consistent with studies conducted in patients with acquired heart disease, showing that high basal Ees in ventricular stiffening was associated with impaired cardiac reserve because of blunting of end-systolic volume decline during exercise.^{9,18} In addition, combined ventricular-arterial stiffening impacts cardiomyocyte metabolic function by increasing myocardial O₂ consumption required for each cardiac ejection.¹⁹ This will further comprise cardiac reserve and increase the risk of O₂ demand-supply mismatch during stress and, in turn, the risk of cardiomyocyte injury and fibrosis.

In addition, the current study suggests that ventricular stiffness (in addition to arterial stiffness) contributed to hypertensive SBP response. This is consistent with data from patients with heart failure with preserved ejection fraction, showing that combined ventricular-arterial stiffening was associated with enhanced SBP sensitivity to changes in loading conditions, thus exacerbating hypertensive SBP response during exercise.⁹

These findings have important clinical implications. The medical management of hypertension in patients with COA has focused on reduction of arterial load,^{20,21} and this management paradigm determines the choice of antihypertensive drug therapy. The current study showing the presence of combined ventricular-arterial stiffening (rather than arterial stiffening alone) expands potential therapeutic options. Because agents such as verapamil, which reduces both ventricular and arterial stiffness, have been shown to improve exercise capacity in hypertensive patients with stiff ventricles,¹⁰ the current data provide foundational data to explore whether such therapies will be beneficial in patients with COA. In addition, cardiopulmonary rehabilitation programs may reduce stiffness and improve coupling in this population.

Limitations

The control group did not have exercise data, and hence we were unable to determine whether less ventricular-arterial stiffening in this group was associated with a more favourable hemodynamic response during exercise in this group. In addition, the noninvasive estimation of LV hemodynamics used in this study was extrapolated from studies conducted in patients with acquired heart disease, and hence there is an implicit assumption that these estimates will hold true for patients with COA as well. Although we have speculated about the potential role of diastolic dysfunction in the blunted stroke volume response, we do not have data about exercise end-diastolic and end-systolic volumes or peak Ees.

Conclusion

Patients with COA had combined ventricular-vascular stiffening as compared with patients without COA with

similar age, sex, and SBP. Both ventricular stiffening (Ees) and arterial stiffening (Ea) contributed to impaired cardiac reserve and hypertensive SBP response during exercise. These findings provide foundation for further studies to determine whether drugs that reduce both ventricular and arterial stiffness will improve exercise capacity and hemodynamics in this unique population.

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Disclosures

The authors have no conflicts of interest to disclose.

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