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Editorial

Hypertensive Response With Exercise to Reveal Increased Cardiovascular Risk in Adults With Aortic Coarctation Repair: Value and Caution

Philip J. Millar, PhD,[a,b] and Erwin N. Oechslin, MD[c]

[a] Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada

[b] Toronto General Research Institute, Toronto General Hospital, Toronto, Ontario, Canada

[c] Division of Cardiology, Peter Munk Cardiac Center, Toronto Congenital Cardiac Center for Adults, and University of Toronto, Toronto, Ontario, Canada

See article by Yogeswaran et al., pages 676–682 of this issue.

Exercise represents a common stress used to perturb the cardiovascular system and uncover physiological differences of clinical relevance not observed at rest.[1] On the basis of data from cardiopulmonary exercise testing, it is now widely appreciated that an abnormal heart rate response to exercise (ie, chronotropic incompetence) is predictive of increased all-cause mortality as well as incidence of coronary artery disease.[2-4] Less clear has been the clinical value of measuring blood pressure during exercise testing.[4] A decrease in systolic blood pressure below resting levels (ie, exercise-induced hypotension) is associated with increased risk of cardiac events, particularly in patients with aortic valvular stenosis,[5,6] and in those with accompanying myocardial ischemia or previous myocardial infarction.[4,7] Conversely, a hypertensive response to exercise (HRE), defined commonly as systolic blood pressure $\geq$ 210 mm Hg for men and $\geq$ 190 mm Hg for women,[1,4,7] has been linked with a higher risk of major cardiovascular events and future hypertension in healthy individuals with normal resting blood pressure.[4,7-9] The capacity for exercise to unmask a group of individuals at heightened cardiovascular risk, particularly those in high-risk populations which require long-term monitoring, would be of significant clinical value.

One such group are adults with repaired coarctation of the aorta (CoA) who, despite "successful" (and even early) surgical or percutaneous intervention, maintain an increased risk of systemic hypertension and early cardiovascular mortality.[10,11] The high lifetime morbidity and mortality has shifted the understanding of CoA from a "simple" congenital anatomical malformation that could be "cured" to a more complex pathophysiology,[12] which includes vascular and autonomic dysfunction.[13-17] Because the risk of cardiovascular outcomes are considered secondary to the hypertensive burden, screening for re-coarctation and aggressive monitoring and treatment of hypertension are recommended.[18-20] Further, a high number of patients with repaired CoA might show masked hypertension,[21] making the monitoring of blood pressure during ambulatory or exercise conditions essential. Blood pressure responses to exercise are already recommended as a surrogate for assessing the CoA gradient[18] and the existence of HRE in patients with repaired CoA is well documented and can occur independent of re-stenosis.[22-28] Unfortunately, few studies have determined the clinical significance of HRE in those with repaired CoA. In 2 studies of adults with repaired CoA, HRE was predictive of future ambulatory systolic blood pressure and the need for antihypertensive treatment,[22,23] however, the significance of isolated HRE is still debated in current guidelines.[19]

In this issue of the *Canadian Journal of Cardiology*, Yogeswaran and colleagues[29] present a single-centre, retrospective analysis of 138 adults with repaired CoA, examining the prognostic value of HRE on a composite end point of cardiovascular adverse events. Patients (59% men) were screened from data collected between 1994 and 2014 and excluded if they had significant residual or recurrent CoA. From this sample, they identified 26 (19%) patients with HRE, defined as a systolic blood pressure $\geq$ 200 mm Hg on the first collected cardiopulmonary exercise test. A comparison of baseline characteristics between patients with normal blood pressure responses or HRE showed that both groups had similar age, age at first CoA repair, resting blood pressure, peak oxygen consumption (VO_2), peak heart rate, mean aortic valve gradient, and CoA peak velocity, although those with HRE had higher left ventricular filling pressure, relative wall thickness, and less usage of antihypertensive therapy. In response to HRE findings, 21 of the 26 patients underwent changes in antihypertensive therapy. Nonetheless, during follow-up of 85 $\pm$ 13 months, the presence of HRE in

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Corresponding author: Dr Philip J. Millar, ANNU 348A, 50 Stone Rd East, Guelph, Ontario N1G 2W1, Canada. Tel.: +1-519-824-4120; fax: +1-519-763-5902.

E-mail: pmillar@uoguelph.ca

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patients with repaired CoA was an independent risk factor for future cardiovascular adverse events, defined as cardiovascular death, stroke, acute coronary syndrome, deterioration of left ventricular systolic function (ejection fraction $< 35\%$), or hospitalization from heart failure.[29] These data provide the first evidence that the presence of HRE in patients with repaired CoA and normal resting blood pressure confers increased risk of adverse clinical cardiovascular events.

Interestingly, the present results might actually underestimate the prognostic yield of HRE in repaired CoA. First, the authors failed to report the respiratory exchange ratio at peak exercise to ensure that participants reached true maximal effort (a value > 1.09 is considered a suitable threshold in adults[30]). Early termination of exercise could obscure peak cardiovascular responses and increase the chances of a false negative determination of HRE. A caveat to this point is that the presence of HRE in the early stages of cardiopulmonary exercise testing (ie, submaximal exercise) might be a stronger predictor of risk than maximal exercise.[9,31,32] Second, the authors based patient group allocation on the results of the first recorded cardiopulmonary exercise test, although data in healthy individuals show that the reproducibility of HRE can be poor.[33] Whether patients with a consistent HRE over time are at a greater risk of adverse cardiovascular events is not known.

An important methodological consideration of this study is that blood pressure responses to exercise were measured from the brachial artery, which could differ from measurements of central blood pressure. An examination of adults with suspected coronary artery disease showed that in individuals with HRE declines in left ventricular function were only present in those with low pulse pressure amplification (ie, a smaller gradient in pulse pressure between central and peripheral measurements).[34] Low pulse pressure amplification is associated with increased arterial stiffness and characteristics of the reflected pulse wave.[35] A recent study noted that patients with repaired CoA show increased central systolic blood pressure, ascending aortic stiffness, and magnitude (and arrival time) of the backward compression wave compared with controls despite similar resting brachial blood pressure.[17] Whether differences in these characteristics help identify patients with repaired CoA at risk for HRE or at heightened clinical risk requires future study.

A potential limitation acknowledged by the authors was the low percentage (31%) of patients who had also undergone ambulatory blood pressure recordings.[29] Although resting blood pressure was not different between patients with HRE or a normal systolic blood pressure response to exercise, in those with ambulatory measurements, the prevalence of hypertension was significantly higher in patients with HRE,[29] suggesting the presence of masked hypertension. This raises the important question of whether the existence of HRE provides prognostic value above standard ambulatory blood pressure recordings. Nevertheless, the fact that HRE can be obtained from routinely recommended cardiopulmonary exercise testing,[18] could remove the constraints of device availability and patient burden with ambulatory blood pressure recordings. Furthermore, cardiopulmonary exercise testing provides additional measures, such as cardiovascular fitness and heart rate reserve, shown to be predictive of 5-year survival in adults with congenital heart disease.[36] Determination of maximal cardiorespiratory responses are also helpful for prescribing aerobic exercise, an effective lifestyle intervention to lower blood pressure.[37]

The mechanisms responsible for HRE are hypothesized to include increased sympathetic activation, central aortic stiffness, left ventricular mass, and reduced endothelial function,[4,7,8] alterations also reported to be present in patients with repaired CoA.[13-15,17] One potentially stimulating observation from these data is the presence of higher left ventricular filling pressure and relative wall thickness in patients with HRE. Were these patients exposed to higher preoperative blood pressures? Are the limited number of ambulatory blood pressure recordings reflective of the larger cohort suggesting higher baseline blood pressure? In patients with heart failure with reduced ejection fraction, acute increases[38] as well as chronic elevations[39] in filling pressure are linked to paradoxical sympathetic activation. Patients with repaired CoA have similar elevations in resting central sympathetic outflow,[13] whereas those with HRE can have accentuated plasma norepinephrine and renin concentrations during peak exercise.[28] Further work is required to determine whether exaggerated neurohumoral activation triggers the HRE in these patients and identify the afferent mechanisms that might be involved. Interestingly, an examination of participant characteristics related to systolic blood pressure exercise responses in 260 patients with repaired CoA showed no associations with type of surgery, year of surgery, age at surgery, follow-up time, age at follow-up, or medications other than diuretics, however, they did observe a positive relationship with residual CoA gradient (an exclusion criteria in the present study) and a negative relationship with diuretic therapy.[24] The cohort of patients with HRE had a trend for a lower rate of diuretic usage than those with a normal systolic blood pressure response to exercise, although overall numbers were low.

In summary, it has been shown previously that maximal exercise systolic blood pressure is associated with daytime ambulatory systolic blood pressure in adults with repaired CoA,[22] a major focus of long-term patient monitoring.[18-20] The present data by Yogeswaran et al[29] now extend this work, providing important new information that the presence of HRE in adults with repaired CoA and normal resting blood pressure reveals a group of patients with an increased risk of adverse cardiovascular events. These findings raise stimulating questions about the valuable role of measuring blood pressure responses to routine cardiopulmonary exercise testing in this population, particularly as a means to identify at-risk repaired CoA phenotypes requiring more aggressive blood pressure monitoring and management.[29] Advancement of this work now requires confirmation in a larger prospective multicentred setting, comparison of the prognostic value between HRE and 24-hour ambulatory blood pressure recordings, as well as a focus on the physiological mechanisms responsible for the HRE in these patients and potential therapeutic interventions. Finally, because aggressive management of hypertension is the standard of care,[18-20] the results of this study also reaffirm caution for monitoring and treating patients with repaired CoA solely on the basis of the measurement of resting clinic blood pressure.

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References

1. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128:873-934.
2. Lauer MS, Francis GS, Okin PM, et al. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA 1999;281:524-9.
3. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;93:1520-6.
4. Le VV, Mitiku T, Sungar G, Myers J, Froelicher V. The blood pressure response to dynamic exercise testing: a systematic review. Prog Cardiovasc Dis 2008;51:135-60.
5. Magne J, Lancellotti P, Piérard LA. Exercise testing in asymptomatic severe aortic stenosis. JACC Cardiovasc Imaging 2014;7:188-99.
6. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, et al. Guidelines on the management of valvular heart disease. Eur Heart J 2012;33:2451-96.
7. Schultz MG, La Gerche A, Sharman JE. Blood pressure response to exercise and cardiovascular disease. Curr Hypertens Rep 2017;19:89.
8. Schultz MG, Sharman JE. Exercise hypertension. Pulse (Basel) 2014;1:161-76.
9. Schultz MG, Otahal P, Cleland VJ, et al. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis. Am J Hypertens 2013;26:357-66.
10. Canniffe C, Ou P, Walsh K, Bonnet D, Celermajer D. Hypertension after repair of aortic coarctation — a systematic review. Int J Cardiol 2013;167:2456-61.
11. Brown ML, Burkhart HM, Connolly HM, et al. Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. J Am Coll Cardiol 2013;62:1020-5.
12. Krieger EV, Krieger E, Stout K. The adult with repaired coarctation of the aorta. Heart 2010;96:1676-81.
13. Lee MG, Hemmes RA, Mynard J, et al. Elevated sympathetic activity, endothelial dysfunction, and late hypertension after repair of coarctation of the aorta. Int J Cardiol 2017;243:185-90.
14. de Divitiis M, Pilla C, Kattenhorn M, et al. Ambulatory blood pressure, left ventricular mass, and conduit artery function late after successful repair of coarctation of the aorta. J Am Coll Cardiol 2003;41:2259-65.
15. de Divitiis M, Pilla C, Kattenhorn M, et al. Vascular dysfunction after repair of coarctation of the aorta: impact of early surgery. Circulation 2001;104:I165-70.
16. Millar PJ, Proudfoot NA, Dillenburg RF, Macdonald MJ. Reduced heart rate variability and baroreflex sensitivity in normotensive children with repaired coarctation of the aorta. Int J Cardiol 2013;168:587-8.
17. Quail MA, Short R, Pandya B, et al. Abnormal wave reflections and left ventricular hypertrophy late after coarctation of the aorta repair. Hypertension 2017;69:501-9.
18. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in collaboration with the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e143-263.
19. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010;31:2915-57.
20. Silversides CK, Kiess M, Beauchesne L, et al. Canadian Cardiovascular Society 2009 consensus conference on the management of adults with congenital heart disease: outflow tract obstruction, coarctation of the aorta, tetralogy of Fallot, Ebstein anomaly and Marfan's syndrome. Can J Cardiol 2010;26:e80-97.
21. Di Salvo G, Castaldi B, Baldini L, et al. Masked hypertension in young patients after successful aortic coarctation repair: impact on left ventricular geometry and function. J Hum Hypertens 2011;25:739-45.
22. Vriend JW, van Montfrans GA, Romkes HH, et al. Relation between exercise-induced hypertension and sustained hypertension in adult patients after successful repair of aortic coarctation. J Hypertens 2004;22:501-9.
23. Luijendijk P, Bouma BJ, Vriend JWJ, et al. Usefulness of exercise-induced hypertension as predictor of chronic hypertension in adults after operative therapy for aortic isthmic coarctation in childhood. Am J Cardiol 2011;108:435-9.
24. Hager A, Kanz S, Kaemmerer H, Hess J. Exercise capacity and exercise hypertension after surgical repair of isolated aortic coarctation. Am J Cardiol 2008;101:1777-80.
25. Correia AS, Gonçalves A, Paiva M, et al. Long-term follow-up after aortic coarctation repair: the unsolved issue of exercise-induced hypertension. Rev Port Cardiol 2013;32:879-83.
26. Hauser M, Kuehn A, Wilson N. Abnormal responses for blood pressure in children and adults with surgically corrected aortic coarctation. Cardiol Young 2000;10:353-7.
27. Freed MD, Rocchini A, Rosenthal A, Nadas AS, Castaneda AR. Exercise-induced hypertension after surgical repair of coarctation of the aorta. Am J Cardiol 1979;43:253-8.
28. Ross RD, Clapp SK, Gunther S, et al. Augmented norepinephrine and renin output in response to maximal exercise in hypertensive coarctectomy patients. Am Heart J 1992;123:1293-9.
29. Yogeswaran V, Connolly HM, Al-Otaibi M, et al. Prognostic role of hypertensive response to exercise in patients with repaired coarctation of aorta. Can J Cardiol 2018;34:676-82.
30. Wasserman K. The Dickinson W. Richards lecture. New concepts in assessing cardiovascular function. Circulation 1988;78:1060-71.
31. Schultz MG, Picone DS, Nikolic SB, Williams AD, Sharman JE. Exaggerated blood pressure response to early stages of exercise stress testing and presence of hypertension. J Sci Med Sport 2016;19:1039-42.
32. Schultz MG, Otahal P, Picone DS, Sharman JE. Clinical relevance of exaggerated exercise blood pressure. J Am Coll Cardiol 2015;66:1843-5.
33. Sharabi Y, Almer Z, Hanin A, et al. Reproducibility of exaggerated blood pressure response to exercise in healthy patients. Am Heart J 2001;141:1014-7.

34. Shim CY, Hong GR, Park S, et al. Impact of central haemodynamics on left ventricular function in individuals with an exaggerated blood pressure response to exercise. J Hypertens 2015;33:612-20 [discussion: 620].

35. Avolio AP, Van Bortel LM, Boutouyrie P, et al. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension 2009;54:375-83.

36. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation 2012;125:250-9.

37. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2013;2:e004473.

38. Millar PJ, Murai H, Floras JS. Paradoxical muscle sympathetic reflex activation in human heart failure. Circulation 2015;131:459-68.

39. Ferguson DW, Berg WJ, Sanders JS. Clinical and hemodynamic correlates of sympathetic nerve activity in normal humans and patients with heart failure: evidence from direct microneurographic recordings. J Am Coll Cardiol 1990;16:1125-34.