Too Much Is Not Enough
Hypertension and Sympathetic Vasoconstriction in Contracting Muscles

Michael J. Joyner

When young healthy humans, and especially trained endurance athletes, perform activities like running, swimming, or cycling, mean arterial pressure (MAP) does not rise much.\(^1,2\) At first glance, this seems counterintuitive, because in normal subjects, cardiac output can increase 4- to 5-fold during heavy exercise, and in elite male athletes, cardiac output values in excess of 40 L/min have been reported.\(^3\) The “failure” of MAP to rise is even more puzzling in light of the large exercise-mediated increases in vasoconstricting sympathetic outflow directed at most vascular beds.\(^2\) In the athletes, stroke volume can reach 200 mL/beat, making the maintenance of MAP even more impressive. By contrast, in middle-aged subjects with hypertension, mean arterial blood pressure frequently rises markedly during exercise in spite of more modest increases in cardiac output and small stroke volumes.\(^1\) How does this happen, and what insight does the article by Zhao et al\(^4\) from the Thomas laboratory at University of Texas Southwestern provide on this observation and related phenomenon?

First, young subjects are “protected” from a rise in MAP during exercise by marked peripheral vasodilation in the face of the increased sympathetic outflow. Because a high fraction of cardiac output during exercise is directed toward the active skeletal muscles, vasodilation in the exercising muscle is a key.\(^1,2\) This is caused by marked metabolic vasodilation along with a local metabolite-mediated blunting of \(\alpha\)-adrenergic vasoconstriction (functional sympatholysis) in the active muscles.\(^5-7\)

Thus, diastolic pressure either remains relatively constant or can even fall dramatically in the athletes mentioned above. This means that whereas systolic pressure and pulse pressure both increase, the net effect on MAP is either modest or minimal.\(^1,2\)

Second, this hemodynamic pattern, along with the storage of energy in compliant great vessels, also provides plenty of energy for coronary artery perfusion during diastole and ensures that oxygen delivery to the heart is adequate to meet the increased demands of exercise. Third, all of these changes occur in a finely regulated way that balances the “demands” of the active muscles for blood flow and oxygen with the need to regulate MAP.\(^2,6,8\) In fact, it might be argued that the “goal” of multiple redundant “collaborating” but sometimes “competing” physiological responses is maintenance of a fine balance among cardiac output, skeletal muscle blood flow, and a “reasonable” and tightly regulated MAP.

As noted above, a key to all of this is a high skeletal muscle blood flow, which occurs in part because \(\alpha\)-adrenergic vasoconstriction in the active muscles is blunted enough for blood flow to increase but not so much that MAP gets dangerously low.\(^2\) In the article by Zhao et al,\(^4\) evidence is presented showing that the blunting of sympathetic vasoconstriction in active muscles is impaired in several well-established models of hypertension. Furthermore, the normal pattern of functional sympatholysis is restored by acute administration of antioxidants, suggesting that the metabolic factors produced in or around the active muscles that blunt sympathetic vasoconstriction are destroyed or inactivated in a local environment marked by “oxidative stress.” This microenvironment in muscle is seen in a number of cardiovascular diseases, risk factors, and even normal aging and tends to blunt vasodilation and promote vasoconstriction.\(^9-11\)

In each of these conditions, oxidative stress limits the ability of endogenous NO to evoke vasodilation even when NO production seems relatively normal. In addition, it is likely, except in the most extreme forms of congestive heart failure, that skeletal muscle has a very high capacity to dilate if the dilating substances are there and able to act, and if the ability of the sympathetic nerves to restrain the dilation is blunted.\(^12\)

Based on these observations, it may be that MAP rises during exercise in hypertension at least in part because metabolic vasodilation in the active muscles is restrained excessively by the concurrent increase in sympathetic outflow. Under these circumstances, blood flow to the active muscles would be limited, diastolic pressure would rise, and together these adjustments might cause a downward spiral of acute and chronic hemodynamic events. In addition to limiting exercise capacity and the inherent risk to health associated with poor exercise tolerance, one can easily envision the challenges that inadequate peripheral vasodilation pose to a noncompliant thickened left ventricle straining against stiff great vessels and a high diastolic pressure.\(^11,13,14\)

If significant coronary artery disease were also present, a bad situation could become even worse.

There are at least 3 other attractive elements to this study. First, it represents another chapter from the Thomas laboratory on issues related to the balance between metabolic vasodilation and sympathetic vasoconstriction in contracting skeletal muscle. This group has contributed a large number of outstanding animal and human studies on this topic and helped frame the issues for a number of “collaboratively competing” groups. Second, this article is an outstanding example of translational research in animal models and how there can be an intellectual serve-and-volley between experiments conducted in different models with different levels of integration. Ideas ranging from very basic cellular signaling concepts to hemodynamic observations in

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From the Department of Anesthesiology, Mayo Clinic, Rochester, Minn.

Correspondence to Michael J. Joyner, Department of Anesthesiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail joyner.michael@mayo.edu

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whole humans “meet” in this study. So while the world is talking about translational research, the Thomas laboratory does it over and over again.  

Third, one can also see that progressive and supervised exercise training, perhaps starting with a walking program, might be a way out of the hemodynamic mess in hypertensive patients that is described above. Training can restore the normal oxidative state in muscle so that vasodilation is favored, it can make the vessels less stiff, and it can cause the microcirculation to grow in the trained muscles. Training can also improve baroreflex function and autonomic control of the heart, and it is protective/therapeutic against a number of metabolic risk factors, especially type 2 diabetes.  

So, as personalized medicine emerges, perhaps many patients with hypertension could benefit most from a personalized walking program that would restore the ability of the blood vessels in their active muscle to fend off sympathetic vasoconstriction during exercise and at the same time improve their overall autonomic and metabolic control.

Disclosures

None.

References

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