Letter to the editor: “Deconstructing the dogma of sympathetic restraint and its role in the cardiovascular response to exercise”

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TO THE EDITOR: I read with great interest and excitement the recently published work of Heinonen et al. (2) in which PET scan technology, pharmacological infusion, and a single leg knee extension exercise model were combined to interrogate the role of sympathetic adrenergic regulation of human cardiovascular function in exercise. Specifically, they assessed the independent responses to femoral artery norepinephrine (α1- and α2-receptor agonist) and phentolamine (α1- and α2-receptor antagonist) infusion at rest and during moderate intensity knee extension exercise in both the active (quadriceps) and inactive (hamstrings) muscle groups within the exercising limb. I believe this is a very important study and congratulate the authors on their innovative, technically demanding study. However, I would like to address two issues that I hope can add to the understanding of findings of this study and, perhaps more importantly, to the general understanding of the role and importance of sympathetic restraint in blood pressure regulation and blood flow distribution during exercise.

The first issue concerns the currently popular hypothesis that sympathetic restraint is important in exercising muscle blood flow distribution (in combination with functional sympatholysis, it is proposed to minimize blood flow to areas of low demand and optimize it in areas of high demand) (1). The authors focus on their finding that α-receptor blockade resulted in an increase in the resting hamstring vascular conductance (and blood flow) of the exercising limb, but not in the exercising quadriceps muscle group. The authors describe this as “…pharmacological inhibition of α-adrenergic tone markedly disturbed the distribution of blood flow and oxygen extraction in the exercising human limb by increasing blood flow especially in inactive muscles, adipose tissue and bone.” The authors interpreted this finding as consistent with the notion that “an important role of vascular α-adrenoceptors is to limit its spread from active to inactive muscles [my emphasis], and thereby optimize blood flow and oxygen extraction to the most metabolically active tissues of the limb.” They also indicated it to be consistent with the Moore et al. (4) observation of sympathetic activation restricting the conduction of vasodilation along arterioles from active to inactive muscle fiber regions within the local microvasculature in mouse gluteus maximus muscle.

With regard to this, I would point out the importance of recognizing that the inactive fibers in Heinonen et al. (2) were in a completely different muscle group (hamstrings). Exercise-evoked vasodilation cannot spread from the active quadriceps group to the inactive hamstring muscle group, given the vascular anatomy and distance. Therefore, interpreting the findings to support the hypothesized (1) influence of sympathetic restraint on the microvascular bed within a contracting muscle represents a conflation of active and inactive muscle groups within an exercising limb with active and inactive muscle fibers within an exercising muscle and should be reconsidered. In this regard, it was quite puzzling to me that the authors virtually ignored their assessment of α-receptor agonist and antagonist action on blood flow distribution within the exercising quadriceps muscles. What did they find? No change in blood flow distribution, i.e. no effect of removing or adding exercising muscle α-receptor activation on less versus more active muscle fibers in the exercising muscle. This latter finding and what it supports would seem to be of critical importance in challenging the popular notion of sympathetic restraint’s role in optimizing blood flow distribution within exercising muscle.

The second issue concerns the accepted notion that sympathetic restraint is unconditionally occurring in exercising muscles (1). The authors focus on their finding that α-receptor activation evoked vasoconstriction in the exercising quadriceps muscles. The authors conclude that “during exercise, even if marked functional sympatholysis prevailed, local norepinephrine infusions, mimicking exaggerated sympathetic nerve activity, were capable of limiting blood flow in the exercising muscles” and note that this has implications for hyperadrenergic conditions and potential effects on exercise tolerance.

I would point out that it has been well established that sympathetic adrenergic vasoconstriction can occur in exercising muscle, as the phenomenon of functional sympatholysis is understood to be a blunting of sympathetic vasoconstriction, not an abolishment (5). What was quite puzzling to me in this regard was that the authors ignored the lack of effect of α-receptor blockade on exercising quadriceps vascular conductance and muscle blood flow. This challenges the dogma that sympathetic restraint is necessarily active in (or upstream of) exercising skeletal muscle and is highly relevant for the issue of the role of sympathetic restraint in blood pressure regulation during submaximal exercise, where autonomic failure patient hypotension with even mild exercise onset (3) is constantly cited as evidence for this restraint existing and being essential for blood pressure regulation (1).

In summary, the work of Heinonen et al. (2) has some extremely important findings regarding in vivo human exercising muscle vascular responsiveness to α-receptor activity, but more so in terms of challenging current thinking rather than falling in line with it. For this, I commend the authors on their excellent study.

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AUTHOR CONTRIBUTIONS

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REFERENCES


