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RESEARCH LETTER

Exaggerated Inspiratory Muscle Metaboreflex in Arterial Hypertension

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Hypertension is highly prevalent in the United States with increased incidence with older age.[1] Hypertension is the leading risk factor for cardiovascular disease (CVD) development. Hypertension-mediated autonomic and cardiovascular pathophysiology play an important role in disease progression and symptomology of patients with CVD. Recent evidence supports that older patients with hypertension without overt CVD may exhibit pulmonary system abnormalities that are often associated with overt heart failure, exertional symptoms, and mortality.[2,3] Specifically, older patients with hypertension have higher ventilatory to carbon dioxide slopes during exercise than older adults with normotension, with >70% of these slopes being abnormal in patients with hypertension.[2] Heart failure is also associated with pulmonary system abnormalities that directly relate to exercise intolerance and exertional symptoms including inspiratory muscle weakness and reduced inspiratory muscle endurance.[3] We found that inspiratory muscle metaboreflex activation via high inspiratory muscle work results in exaggerated increases in mean arterial pressure (MAP) and leg vasoconstriction, resulting in reduced leg blood flow in patients with heart failure compared with controls.[4] However, it is unclear whether these inspiratory muscle abnormalities are present earlier in the progression of CVD. We hypothesized that older patients with hypertension have lower inspiratory muscle endurance and greater increases in MAP with inspiratory muscle metaboreflex activation (via high-intensity inspiratory resistive breathing task [IRBT]) than age-matched healthy controls.

We enrolled 9 patients with hypertension and 9 controls. All patients with hypertension were diagnosed with essential hypertension, and at-home blood pressure measurements were performed to exclude white-coat effect.[5] All participants provided informed consent. All aspects of this study were approved by the Mayo Clinic's institutional review board and conformed to the principles outlined in the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author on reasonable request.

The experimental design consisted of 2 visits. During visit 1, participants were familiarized with all experimental procedures. During visit 2, participants performed IRBTs at 2% of maximal inspiratory pressure for 10 minutes (control condition) and 60% maximal inspiratory pressure until task failure (metaboreflex condition) with >20 minutes between them. During the IRBTs, the breathing frequency was 20 breaths per minute with a 50% duty cycle. Maximal inspiratory pressure was measured. MAP and heart rate were measured continuously via finger photoplethysmography. MAP was calibrated to brachial artery blood pressure. Mouth pressure was measured continuously.

Key Words: blood pressure ■ diaphragm ■ essential hypertension ■ inspiratory muscle work ■ respiratory muscles

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Data are reported as mean±SD. Mean values and 95% CIs are shown in Figure [A] and [C]. Time-to-task failure and change in MAP were compared between groups using unpaired *t* tests. MAP and heart rate were compared within (rest, 2 minutes, and 10 minutes or task failure) and between groups for 2% and 60% IRBTs using 2-way mixed ANOVA. Tukey post hoc analysis was performed to determine where significance existed. Statistical significance was set at $P<0.05$.

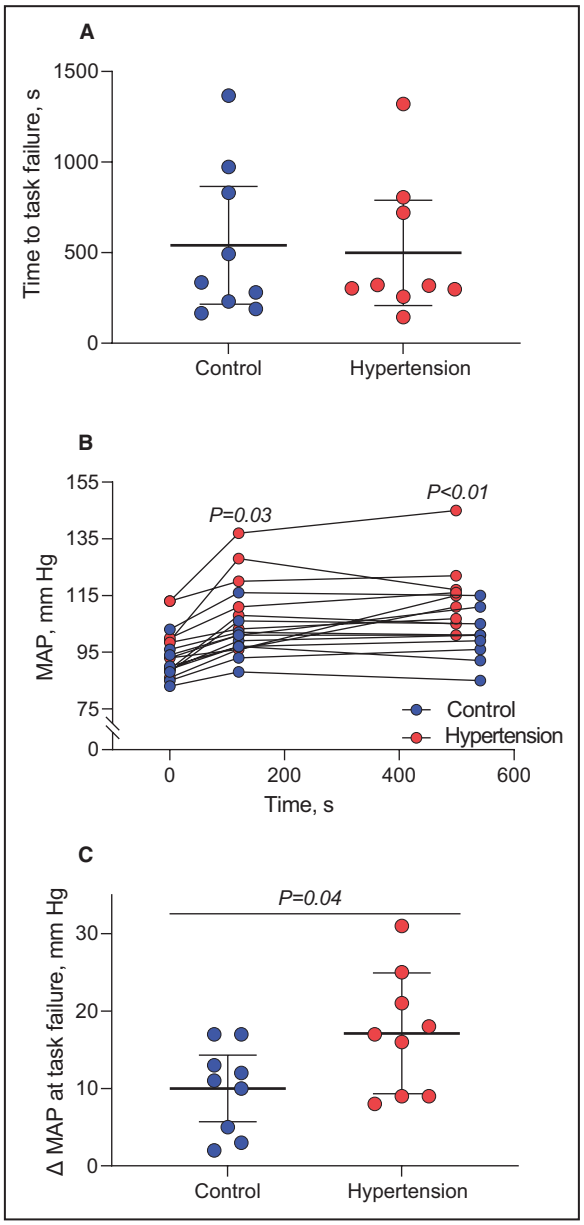

Figure. Time-to-task failure and blood pressure response during the 65% inspiratory resistive breathing task in the hypertension and control groups.
Time-to-task failure was not statistically significant between older participants with hypertension and control participants (**A**) ($P=0.93$ via unpaired *t* test). Older participants with hypertension had higher mean arterial pressure (MAP) at minute 2 and task failure compared with controls (**B**) (both, $P<0.04$ via 2-way ANOVA). Older participants with hypertension had greater increases in MAP from rest to task failure than controls (**C**) ($P=0.04$ via unpaired *t* test).

There were no statistically significant differences between hypertension and control groups, respectively, in sex distribution (4 men/5 women versus 6 men/3 women), age (67±10 versus 70±7 years), body mass index (29±4 versus 28±4 kg/m^2), maximal inspiratory pressure (109±37 versus 112±30%predicted), $\dot{V}O_2$peak (100±24 versus 113±13%predicted) as well as resting systolic blood pressure (127±15 versus 118±11 mm Hg), diastolic blood pressure (82±7 versus 77±6 mm Hg), and MAP (97±8 versus 91±7 mm Hg) (all $P>0.11$). Medication prescribed to the participants with hypertension included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n=4), diuretics (n=3), β-blockers (n=3), and calcium channel blockers (n=4). Hypertension duration was 9±8 years.

Results from the 60% IRBT time-to-task failure were not statistically significant between groups ($P=0.93$) (Figure [A]). During the 60% IRBT, the hypertension group had higher MAP at minute 2 and task failure (both, $P<0.04$) (Figure [B]). Change in MAP from rest to task failure was greater for patients with hypertension than controls ($P=0.04$) (Figure [C]). Hypertension duration was not statistically related to time-to-task failure or change in MAP during the 60% IRBT (both, $P>0.31$). During the 60% IRBT, there was no group main effect for heart rate ($P=0.26$). During the 2% IRBT, there was no time or group main effects for MAP or heart rate (both, $P>0.12$).

Our primary novel finding is that older patients with hypertension had exaggerated MAP responses to inspiratory muscle metaboreflex activation than controls. These findings have important implications for older patients with hypertension as exaggerated cardiovascular responses to inspiratory muscle metaboreflex activation are important contributors to exercise intolerance and exertional symptoms for patients with CVD.[3] Further, the present findings are directionally consistent with those recently reported in heart failure with preserved ejection fraction[4]; a population with a high prevalence of hypertension. In this context, our findings suggest that these inspiratory muscle pathophysiologic mechanisms may present earlier in the CVD progression than previously recognized. In contrast, there were no statistically significant differences in inspiratory muscle strength and endurance between controls and participants with hypertension. Taken together, our findings coupled with those from a recent study revealing an exaggerated ventilatory response during exercise in hypertension[2] warrant further

investigation into the impact of inspiratory muscle work on the integrative physiologic mechanisms to exercise and exercise tolerance in hypertension.

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Disclosures

None.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757
2. Hope K, Chant B, Hinton T, Kendrick AH, Nightingale AK, Paton JF, Hart EC. Ventilatory efficiency is reduced in people with hypertension during exercise. *J Am Heart Assoc*. 2023;12:e024335. doi: 10.1161/JAHA.121.024335
3. Smith JR, Senefeld JW, Larson KF, Joyner MJ. Consequences of group III/IV afferent feedback and respiratory muscle work on exercise tolerance in heart failure with reduced ejection fraction. *Exp Physiol*. 2023;108:1351–1365. doi: 10.1113/EP090755
4. Hammer SM, Bruhn EJ, Bissen TG, Muer JD, Villarraga N, Borlaug BA, Olson TP, Smith JR. Inspiratory and leg muscle blood flows during inspiratory muscle metaboreflex activation in heart failure with preserved ejection fraction. *J Appl Physiol (1985)*. 2022;133:1202–1211. doi: 10.1152/japplphysiol.00141.2022
5. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75:1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026