Impaired Muscle Oxygenation and Elevated Exercise Blood Pressure in Hypertensive Patients

Links With Vascular Stiffness

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Abstract—This study examined in vivo (1) skeletal muscle oxygenation and microvascular function, at rest and during handgrip exercise, and (2) their association with macrovascular function and exercise blood pressure (BP), in newly diagnosed, never-treated patients with hypertension and normotensive individuals. Ninety-one individuals (51 hypertensives and 40 normotensives) underwent office and 24-hour ambulatory BP, arterial stiffness, and central aortic BP assessment, followed by a 5-minute arterial occlusion and a 3-minute submaximal handgrip exercise. Changes in muscle oxygenated and deoxygenated hemoglobin and tissue oxygen saturation were continuously monitored by near-infrared spectroscopy and beat-by-beat BP by Finapres. Hypertensives had higher (P<0.001) central aortic BP and pulse wave velocity versus normotensives and exhibited (1) a blunted tissue oxygen saturation response during occlusion, with slower (P=0.006) deoxygenation rate, suggesting reduced muscle oxidative capacity, and (2) a slower reoxygenation rate and blunted hyperemic response (P<0.05), showing reduced microvascular reactivity. Muscle oxygenation responses were correlated with aortic systolic and pulse pressure and augmentation index (P<0.05; age and body mass index (BMI) adjusted). When exercising at the same submaximal intensity, hypertensives required a significantly greater (P<0.001) increase in BP for achieving similar muscle oxygenation levels as normotensives. This response was correlated with the magnitude of microvascular hyperemia and aortic BP. In conclusion, nontreated patients with hypertension exhibit prominent reductions in in vivo indices of skeletal muscle oxidative capacity, suggestive of mitochondrial dysfunction, and blunted muscle microvascular reactivity. These dysfunctions were associated with higher aortic systolic BP and arterial stiffness. Dysregulations in muscle oxygen delivery/utilization and microvascular stiffness, in hypertensive patients, partially contribute to their exaggerated BP during exercise. **(*Hypertension*. 2017;70:444-451. DOI: 10.1161/HYPERTENSIONAHA.117.09558.)** ● **Online Data Supplement**

Key Words: blood pressure ■ exercise ■ hypertension ■ microcirculation ■ oxygen consumption ■ skeletal muscle ■ vascular stiffness

Essential hypertension is characterized by sustained elevations of blood pressure (BP) that can lead to target organ damage and an increased risk for cardiovascular disease.[1] Potential life-threatening outcomes of hypertension, such as stroke, renal insufficiency, and cardiac hypertrophy, had been initially perceived as a result of macrovascular alterations. These macrovascular events, however, do not occur independently of microvascular derangement.[2–4] Studies have shown that alterations in microvascular structure (rarefaction), vasomotor tonus (enhanced vasoconstriction or blunted vasodilation), and endothelial dysfunction are principal processes in the pathogenesis of hypertension and are evident in several organs/tissue types.[5–8]

In the skeletal muscle, microvascularization is important for oxygen and nutrient supply and for effective metabolite clearance. Studies in hypertension have shown structural or functional impairments in the microvasculature within skeletal muscles,[8] implying a reduced capacity for oxygen delivery and exchange. Furthermore, animal studies using experimental models of hypertension suggested that mitochondrial dysfunction (ie, decreased expression of mitochondrial components and defects in respiratory complexes) and increased oxidative stress result in impaired oxidative capacity and reduced mitochondrial ATP production.[9,10] Importantly, in these animals, the mitochondrial dysfunction and the reduced oxidative capacity were present before the development of hypertension, suggesting a possible role of these processes to the pathogenesis of hypertension.[11] However, information on skeletal muscle microvascular alterations and oxidative

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capacity in hypertension has been obtained mainly from animal models or ex vivo from human biopsies.[8,12–14] Although the above results imply that oxygen delivery, exchange, and utilization within the skeletal muscles may be impaired in hypertensive individuals versus normotensives, information under in vivo conditions is lacking. In addition, in vivo studies reporting reduced vascular reactivity in hypertensive patients examined mainly whole limbs (eg, forearm plethysmography), conduit arteries (by flow-mediated dilation), and cutaneous microvessels.[15–17] Certainly, these studies have provided a valuable insight on endothelial function; however, as endothelial cells across the vascular tree exhibit a marked phenotypic heterogeneity in structure and function, results from conduit arteries should not be extrapolated to microvessels and observations from one tissue type to apply to other tissue types.[6,17,18]

Furthermore, effective skeletal muscle oxygenation is crucial during exercise when oxygen demand of contracting muscles increases markedly, and an increase in BP is required for adequate oxygen delivery to the exercising tissues. In hypertensives, however, an exaggerated BP response to exercise has been linked to alterations in autonomic nervous system regulatory mechanisms (exercise pressor reflex) and conduit arteries' endothelial dysfunction, as assessed by flow-mediated dilation.[19–21] Whether alterations in microvascular function within the skeletal muscle impair oxygen delivery and utilization during exercise and contribute to amplifications of exercise BP in hypertensive patients remains unknown.

In this respect, near-infrared spectroscopy (NIRS) allows to noninvasively assess microvascular reactivity and skeletal muscle oxygenation at rest and during exercise, via continuous monitoring of functional changes in oxygenated hemoglobin dissociation. Using the arterial occlusion/reoxygenation maneuver, the NIRS technology provides information on skeletal muscle's oxidative capacity, microvascular function, and muscle oxygenation at rest and during exercise.[22–25] Our aims were to examine in vivo skeletal muscle oxygenation and microvascular function (as assessed by muscle microvascular reactivity), at rest and during submaximal handgrip exercise, and their associations with (1) arterial stiffness and other macrovascular function indices and (2) BP responses during handgrip exercise, in newly diagnosed, never-treated patients with hypertension (HYP) and age-, sex-, and BMI-matched normotensive individuals (NORMO). We hypothesized that (1) untreated individuals with hypertension will present compromised muscle oxygenation and impaired microvascular function versus normotensives and (2) these alterations could limit oxygen delivery to exercising muscles in hypertensive patients versus normotensives and contribute to further amplifications in BP responses during exercise in the former group. Continuous beat-by-beat BP and muscle oxygenation (using NIRS) were assessed throughout the protocol.

Methods

Participants

Ninety-one individuals (51 untreated hypertensive patients, and 40 healthy NORMO without known cardiovascular or pulmonary disease of similar age and BMI) participated in this study. Essential hypertension was defined as systolic BP (SBP) ≥140 mm Hg and/or diastolic BP (DBP) ≥90 mm Hg (European Society of Hypertension guidelines).[26] Inclusion criteria for HYP were visit BP ≥140/90 mm Hg and daytime ambulatory BP ≥135/85 mm Hg, without previous treatment with antihypertensive agents or other cardiovascular medication. Patients with secondary hypertension and other comorbidities (including diabetes mellitus and other cardiovascular disease) were excluded. This study was approved by the institutional review board committee; procedures were conducted in accordance with the principles of Declaration of Helsinki Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, revised/effective 2001 and institutional guidelines. All participants signed the informed consent form.

Testing Procedures and Instrumentation

Extended methods are given in the online-only Data Supplement. Each participant visited the hypertension unit (Papageorgiou Hospital) twice. During the first visit (after an overnight fast), medical history was obtained. Office BP (Microlife) and 24-hour ambulatory BP (24-hour BP; Spacelabs 90207) were assessed.[26] Physical activity status was evaluated by the International Physical Activity Questionnaire.

The next day, the participant returned to the laboratory for evaluation of arterial stiffness, microvascular reactivity, continuous beat-by-beat BP, and muscle oxygenation monitoring at rest and during exercise. Arterial stiffness was assessed by pulse wave velocity and augmentation index (AI; Sphygmocor, Australia).[27] AI% was corrected for mean heart rate of 75 bpm (AI%75).

Next, the participant was connected to the experimental apparatus for assessment of muscle oxygenation and microvascular reactivity via NIRS (Artinis, The Netherlands) and for beat-by-beat BP monitoring via photoplethysmography (Finapres Medical Systems, The Netherlands), as previously described.[24,28] The NIRS device, placed at the forearm, noninvasively, monitored changes in muscle oxygenation, by measuring micromolar (μmol/L) relative changes from baseline for oxygenated, deoxygenated, and total hemoglobin.[29,30] NIRS also assessed the tissue saturation index (TSI), as an absolute parameter for muscle oxygenation. Muscle microvascular function was assessed during reactive hyperemia, as previously described.[24] In brief, after calibration, with the participant in the seated position, baseline values were obtained, and a 5-minute arterial occlusion was performed. The cuff was rapidly inflated to suprasystolic levels (ie, 250 mm Hg), to obstruct blood flow to forearm muscles and measure the maximal capacity for oxygen extraction by skeletal muscles.[31] Stable blood flow/volume was verified by total hemoglobin. The cuff was then rapidly deflated, and reoxygenation responses were recorded.

After a subsequent 10-minute rest, the participant's maximal voluntary contraction (MVC) was assessed,[24] using a digital dynamometer (Biopac), followed by a 3-minute submaximal handgrip exercise test (at 30% MVC). The participant had visual feedback to maintain the force output to the predetermined MVC percentage.[24] Adipose tissue thickness at the NIRS site was measured using a skinfold caliper (Harpenden, United Kingdom).

The TSI occlusion slope and magnitude of decline were used as indices of muscle oxidative capacity; muscle oxygen consumption (mVO_2, μmol L^{-1} min^{-1} per 100 g) was calculated from upsloping deoxygenated hemoglobin with stable total hemoglobin.[25,32] The TSI reperfusion slope and magnitude were used as indices of the vessels' ability to accommodate the blood flow increase (microvascular reactivity).[22,23] The peak hyperemic response was calculated as the difference between peak TSI during reperfusion and baseline TSI.[24,31] During exercise, peak and average TSI responses were used as indices of muscle oxygen extraction.[33] The BP response during the first minute of exercise ($\Delta BP=BP_{exercise}-BP_{baseline}$) was divided by the average TSI response during exercise and was used as an index of exercise BP rise per unit of muscle oxygenation (ie, $\Delta BP/\Delta TSI$). NIRS measurements have been shown to be valid and highly reproducible.[22,23,25]

Statistical Analyses

Data are reported as mean±SD. Differences between groups were assessed by independent *t* tests. NIRS- and Finapres-derived variables

were averaged per testing period (ie, baseline, occlusion, exercise, and recovery) and analyzed using 2-way ANOVA with repeated measures, followed by Tukey post hoc (Statistica 7.0; StatSoft). A regression line ($y=a+bx$; b=slope and a=intercept) was applied to the occlusion/reperfusion data. Pearson correlation (r) examined the relationship between NIRS variables with arterial stiffness and BP. Partial correlations were used for identifying significant correlations after controlling for confounding variables.

Results

Participants' Characteristics

(please see Table S1 in the online-only Data Supplement). By study design, participants in the HYP and NORMO groups were different (P<0.001) in terms of office, day, and 24-hour BP and similar in age, BMI, and physical activity status (overall, participants in both groups were minimally active, except for 4 individuals in each group that were recreationally active; P=0.88). Groups did not differ in terms of smoking status, sex (male:female), blood lipids and glucose, hemoglobin, hematocrit, estimated glomerular filtration rate, and forearm skinfold thickness. HYP had higher (P<0.001) aortic BP (systolic/diastolic, 134.4±14.7/92.2±9.1 versus 109.2±8.7/77.4±5.9 mm Hg), aortic pulse pressure (PP, 42.2±10.6 versus 31.9±6.6 mm Hg), AI%75 (24.4±12.7 versus 14.5±5.8), and pulse wave velocity (8.2±1.5 versus 6.9±1.0 m s^{-1}) compared with NORMO.

Brachial Artery Occlusion and Reperfusion

The average TSI response (constructed by averaging each individual's graph data) during arterial occlusion, reperfusion, and hyperemia in HYP and NORMO groups is depicted in Figure 1. TSI did not differ between groups at baseline and declined (P<0.001) in both groups during occlusion (Figures 1 and 2A). However, during this ischemic period, a blunted and slower TSI response was evident in HYP versus NORMO (occlusion magnitude, −25.0±10.9 versus −33.0±9.9, respectively, P=0.001; occlusion slope, −0.09±0.04 versus −0.11±0.03, respectively, P=0.006; Figure 2C). mVO_2 was lower in HYP than NORMO (Figure 2B).

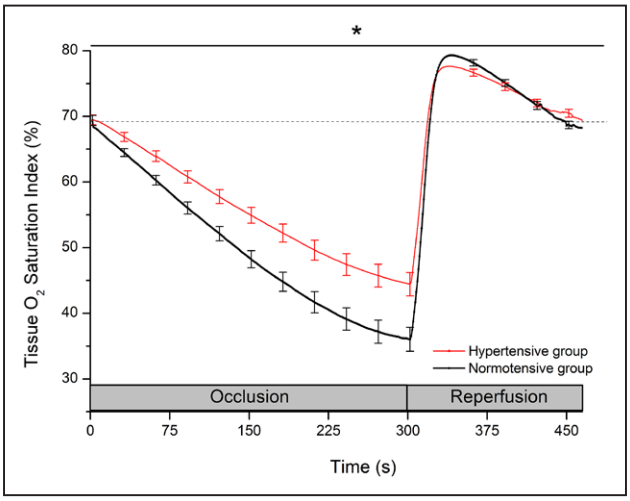

Figure 1. Average tissue saturation index (TSI, %) curves in hypertensive (HYP) and normotensive individuals (constructed by averaging each participant's graph data per group), during occlusion, reperfusion, and hyperemia. SEs per 30 s are presented. HYP exhibited slower TSI decline during occlusion and slower and blunted TSI rise during reperfusion. *Significant group×time, P<0.001.

During reperfusion, TSI rapidly increased and exceeded baseline in both groups (P<0.001), with the HYP group exhibiting a smaller reoxygenation magnitude than NORMO (35.0±13.9 versus 44.5±12.1 Δ%, P=0.001) and a slower reoxygenation rate (1.22±0.61 versus 1.51±0.62, P<0.037; Figure 2D). HYP also exhibited a blunted hyperemic response than NORMO (9.9±4.2 versus 11.7±3.2 Δ%, P=0.04).

Correlations of Muscle Oxygenation Parameters With Aortic Stiffness and Hemodynamic Indices

Significant correlations (P<0.05) were observed in TSI occlusion/reperfusion parameters with macrovascular function indices and ambulatory BP. Stronger correlations were observed between (1) the TSI occlusion range and slope with aortic PP (−0.39 and 0.36, P<0.001; Figure 3A), aortic systolic BP (−0.33 and 0.30, P<0.01), AI%75 (−0.38 and 0.35, P<0.001), and night mean BP (−0.27, P<0.01), (2) the TSI postocclusion range with aortic systolic and PP (−0.33 to −0.36, P<0.001), AI%75 (−0.37, P<0.001), and (3) the hyperemic response with aortic systolic and PP (−0.26 and −0.23, P<0.05) and night systolic BP (−0.23, P<0.05). After BMI, age, and visit mean BP adjustments, significant correlations remained between the TSI occlusion/reperfusion indices (ie, magnitude, slope) with AI%75 (0.24–0.42, P<0.001), aortic systolic BP (0.24–0.35, P<0.01), and MVC (0.24–0.34, P<0.01).

Exercise Responses

No differences were observed in MVC between groups (Table S1). During handgrip exercise, both groups were able to maintain similar force (9.7±3.7 versus 9.7±4.0 kg, HYP and NORMO, respectively, P=0.82), without significant differences between groups in TSI responses (average decline, −5.6±8.4 versus −6.4±6.7 Δ%, P=0.62; peak decline, −8.9±11.6 versus −11.4±10.4 Δ%, P=0.32). Systolic/diastolic BP was higher in HYP versus NORMO throughout the protocol (P<0.001; Figure S1A and S1B), with no differences in heart rate between groups. During exercise, HYP exerted a greater ratio of ΔBP/ΔTSI than NORMO (increase in systolic BP/ΔTSI, +11.6±11.8 versus +5.7±5.2, respectively, P=0.006; diastolic BP/ΔTSI, +8.1±7.8 versus +4.4±3.8, P=0.01; Figure 2E and 2F), showing that HYP required a greater increase in BP to achieve the same oxygenation level in their skeletal muscles during exercise. The average oxygenation during exercise was correlated with the hyperemic response (0.39, P<0.001; Figure 3B). The ΔBP/ΔTSI responses (adjusted for age, BMI, and visit BP) were correlated with TSI occlusion/reperfusion range and slope (−0.39 to −0.43, P<0.001; Figure 3C and 3D), with the hyperemic response (−0.39 to −0.42, P<0.001), and with aortic systolic/diastolic BP (0.25, P<0.05).

Discussion

This is the first study to show that newly diagnosed, never-treated patients with hypertension exhibit slower TSI decline during occlusion and lower mVO_2, showing reduced skeletal muscle oxidative capacity under in vivo conditions versus normotensive individuals. Our novel findings also show that (1) the blunted muscle microvascular reactivity and muscle

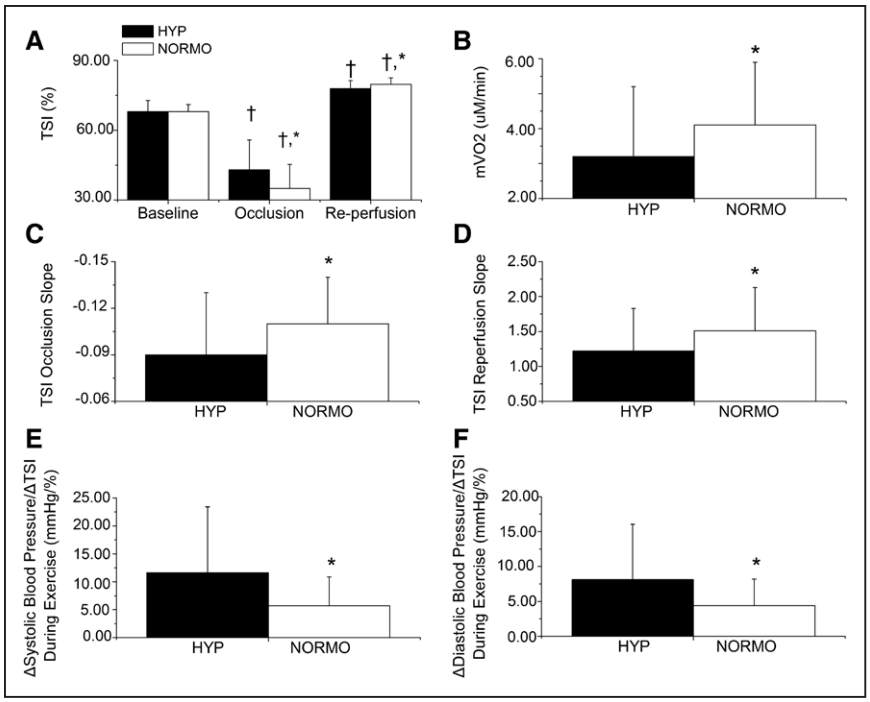

Figure 2. A, Tissue oxygen saturation index (TSI, %) during baseline, peak occlusion, and peak reperfusion in individuals with hypertension (HYP) and normotensives (NORMO). **B**, Muscle oxygen consumption (mVO_2, μmol L^{-1} $minute^{-1}$), (**C**) TSI occlusion slope, and (**D**) TSI reperfusion slope, in HYP and NORMO. Ratio of change in systolic (**E**) and diastolic (**F**) blood pressure during exercise, per unit of decline in TSI. **P*<0.01 vs hypertensives; †*P*<0.001 vs baseline within group.

oxygenation indices were associated with higher aortic systolic and PP, higher AI%75, and night systolic BP, and lower handgrip strength, independently of age, BMI, and visit BP, and (2) when exercising at the same submaximal intensity, HYP required a greater increase in BP for achieving similar muscle oxygenation levels to normotensives, as indicated by the significantly higher ΔBP/ΔTSI ratio in HYP. The significant correlation of the TSI hyperemic response with muscle oxygenation during exercise and with the ΔBP/ΔTSI ratio suggests a role of muscle microvascular derangements to alterations in the matching of oxygen supply to utilization in exercising muscles and to the exaggerated BP during exercise in hypertension.

A major strength of this study is the in vivo assessment of skeletal muscle oxygenation (using NIRS) with simultaneous beat-by-beat BP evaluation, at rest and during exercise, in hypertensive patients that, to our knowledge, have not been investigated. Another strength is that HYP were newly diagnosed, not under any antihypertensive medication that could have affected their micro-, macro-endothelial function, and oxidative capacity.[34,35] Groups with similar age, BMI, and physical activity levels were compared; participants with hyperglycemia or under treatment for hypercholesterolemia or other cardiovascular medication were excluded. Using these strict inclusion criteria, we tried to evaluate the effect of hypertension per se on muscle microcirculation and

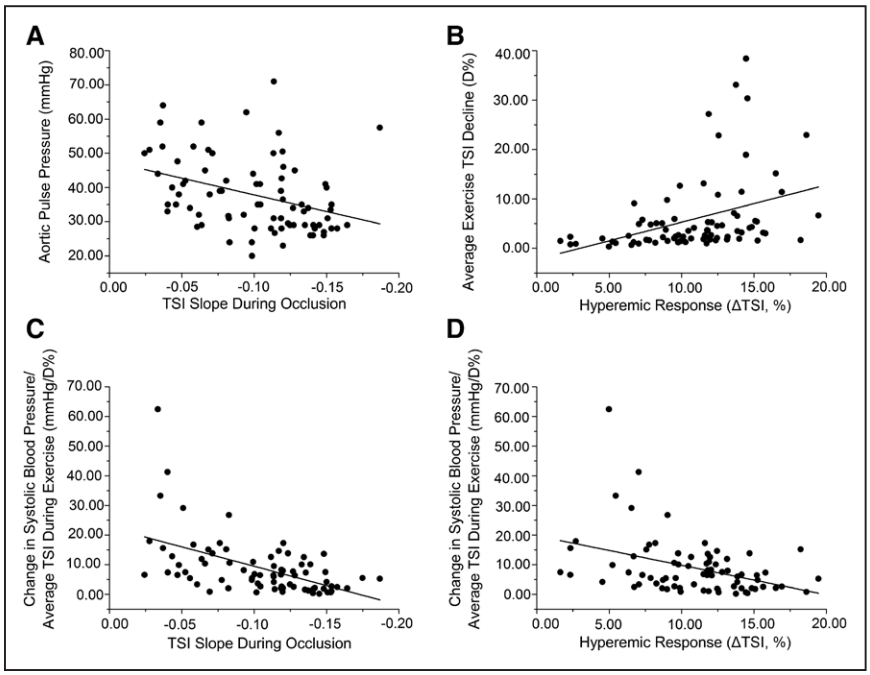

Figure 3. Correlations of (**A**) tissue oxygen saturation index (TSI, %) occlusion slope with central aortic pulse pressure (*R*=0.34, *P*=0.003; SC, 0.28, *P*<0.05), (**B**) hyperemic response with the average TSI decline during exercise (*R*=0.40, *P*=0.001; SC, 0.43, *P*<0.001), (**C**) occlusion slope with the change in systolic blood pressure (BP) during exercise per unit of muscle oxygenation (ΔBP/ΔTSI; *R*=0.53, *P*<0.001; SC, 0.42, *P*<0.001), (**D**) hyperemic response with the change in systolic BP during exercise per unit of muscle oxygenation (ΔBP/ΔTSI; *R*=0.40, *P*=0.001; SC, 0.42, *P*<0.001). SC indicates significant correlations after adjustment for age, body mass index, and visit mean BP.

minimize the effect of other confounding factors/disease processes (ie, diabetes mellitus and peripheral vascular disease) that could have contributed to further microvascular alterations. As high BMI, hypercholesterolemia, hypertriglyceridemia, and diabetes mellitus are characteristics of the hypertensive population,[36] in a larger cohort of patients, when individuals in prodiabetic stages or with greater BMI were included in the HYP group (data not shown here), differences in muscle oxygenation and microvascular reactivity between hypertensive and normotensive individuals were further amplified.

In this study, NIRS was used to noninvasively assess skeletal muscle oxygenation and microvascular reactivity at rest and during exercise. The NIRS technique exploits the principle that the near-infrared light beam penetrates the tissue. Within the skeletal muscle, light is absorbed by hemoglobin in small arterioles, capillaries, and venules of the microcirculation, causing changes in oxygenated, deoxygenated, and total hemoglobin NIRS signals, and provides information on the balance of oxygen delivery and utilization.[29,31,37] The NIRS signals arise predominantly from capillaries as these microvessels compose the largest portion of vascular volume in skeletal muscle (>90%), and the NIRS light can only pass through vessels <1 mm.[25,31,37,38] Thus, NIRS signals mainly reflect changes in capillary (hemoglobin related) oxygen levels and provide information on the microcirculation.[25,31,37,38]

Muscle Oxidative Capacity and Microvascular Reactivity

The occlusion/reperfusion technique used here has been used in NIRS studies examining healthy individuals and individuals with disease.[39,40] During arterial occlusion, with inflow and outflow restricted, a closed circuit system is created, and the rate of deoxygenated hemoglobin increase represents the oxygen consumed by the muscle (ie, mVO_2).[41] Thus, the lower mVO_2 and slower TSI decline observed in HYP points to reduced skeletal muscle oxidative capacity, compared with NORMO. This is in direct agreement with ex vivo data showing a reduction in skeletal muscle mitochondrial coenzyme-Q10 and cytochrome-C oxidase content that coincided with rarefaction, in hypertensive humans.[14,42] Recent discoveries in spontaneously hypertensive rats have also suggested that mitochondrial dysfunction (ie, decreased expression of mitochondrial components and transcriptional factors involved in mitochondrial biogenesis, and defects in assembly of respiratory complexes) can result in increased oxidative stress, uncoupling of oxidative pathways from mitochondrial ATP synthesis, and subsequently, cause failure of cellular energetic processes, and contribute to the pathogenesis of hypertension.[10,11,43]

During reperfusion, the slower and smaller TSI in HYP versus NORMO was correlated with aortic systolic and PP and AI%75 (independently of age, BMI, and BP levels). In accordance, a slow TSI during reperfusion has been previously shown in patients with coronary heart disease, overt metabolic syndrome, and gestational diabetes mellitus and associated with cardiovascular risk factors.[24,38,39] A slow reperfusion TSI was revealed as an independent predictor of mortality in patients with sepsis.[39]

The stronger correlations of TSI indices with aortic rather than brachial BP are important because aortic BP has been more strongly associated with indices of preclinical organ damage than brachial BP.[44,45] In hypertension, the vascular phenotype is characterized by reduced compliance, elasticity/distensibility, and increased stiffness.[46] With increased stiffness in large vessels, the pulsatile pressure/flow of the left ventricular ejection (which is normally transformed in a continuous flow) moves downstream to the small vessels of the arterial tree.[46,47] The chronic increase in BP along with the mechanical stress on the vascular wall and inflammation are postulated to induce remodeling of the muscular vessel wall, mainly in small arterioles, but also in precapillary resistance vessels, leading to luminal restrictions and capillary rarefaction.[7,46,47] Microvascular rarefaction can reduce the vessel surface area available for oxygen delivery and increase the diffusional distance between vessels and their target cells, reducing blood-to-cell oxygen transfer, leading to tissue ischemia. In line, reduced muscle oxygen consumption was observed in our hypertensive patients. On the other hand, increased peripheral resistance and endothelial dysfunction of small resistance arteries, dysfunctional characteristics observed early in hypertension, can also contribute to an increase in BP, resulting in conduit arteries remodeling and further arterial stiffness. In turn, these can contribute to enhancements in AI and further increases in aortic BP, indicating a vicious cycle, in which the microcirculation maintains or even amplifies an initial increase in BP.[46] In accordance, our data show for the first time, an inverse correlation between the magnitude of the hyperemic response within skeletal muscle microvessels and muscle oxygenation with aortic systolic and PP and AI%, suggesting a link between arterial stiffness and microvascular dysfunction with limitations in in vivo skeletal muscle oxygenation early in hypertension.

In our newly diagnosed patients with hypertension, the more apparent reductions in muscle oxidative capacity indices than alterations in microvascular reactivity suggest an early role of skeletal muscle mitochondrial dysfunction in the pathogenesis of hypertension. In agreement, a study in spontaneously hypertensive rats showed that alterations in mitochondrial enzymes in cardiac muscle preceded the clinical manifestation of hypertension.[9] Future studies should explore whether oxidative capacity dysfunctions in hypertensives could be reversed with appropriate pharmacotherapy as animals studies suggested that treatment with renin–angiotensin system inhibitors (angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors) can upregulate mitochondrial biogenesis and stimulate mitochondrial protein production.[34,35] Our findings also emphasize the importance of exercise training in hypertension because enhancement of mitochondrial function through improvements in fitness can cause BP reductions and improve patient outcomes.[46]

Muscle Oxygenation and BP Responses During Exercise

During exercise, sympathetic activity is increased causing vasoconstriction in inactive muscles, whereas, in exercising muscles, the vasoconstrictor activity is diminished by release of local vasodilators (functional sympatholysis).[48,49] In

hypertensive individuals, an impaired functional sympatholysis during exercise along with an exaggerated sympathetic and BP response has been consistently observed.[21] Therefore, we hypothesized that muscle oxygenation would be blunted in HYP during exercise. In contrast to this hypothesis, the average muscle oxygenation during handgrip was not significantly different between groups. However, an excessive increase in BP was required in HYP to maintain perfusion and achieve similar oxygenation levels to the normotensive group. This finding could be explained by (1) the type and intensity of exercise used, that is, a 3-minute submaximal handgrip exercise was performed, not exercise to exhaustion; thus, max mitochondrial taxing was possibly not achieved, (2) the hypertension stage examined, and (3) the phase of microvascular rarefaction present. That is, studies in animal models of hypertension showed a biphasic rarefaction, with the initial phase consisting of microvessel constriction to the point of nonperfusion, possibly because of increased sensitivity to vasoconstrictor stimuli (functional rarefaction) and the second phase consisting of a disappearance of nonperfused vessels, where underperfusion cannot be reversed (structural rarefaction). In accordance with this idea, our newly diagnosed patients were able to achieve the necessary perfusion for performing the submaximal exercise assigned; however, a greater perfusion pressure was required. Thus, an augmentation in exercise BP was necessary for optimal oxygenation. The significant inverse correlation observed between muscle oxygenation and microvascular reactivity indices during arterial occlusion, with the force maintained during the handgrip task, agrees with results in hypertensive rodents, showing a link between skeletal muscle microvascular dysfunction and alterations in performance outcomes.[12] Whether patients with more severe hypertension would be unable to achieve perfusion and exhibit faster signs of exercise intolerance requires further investigation.

The significant correlation of the hyperemic magnitude at resting conditions, with the ΔBP/ΔTSI response during exercise, suggests a partial involvement of small vessel stiffness to the exaggerated exercise BP response, along with the exaggerated sympathetic stimulation, previously described in hypertension.[21] In support, animal studies have shown that the reduced microvascular distensibility and rarefaction resulted not only in increased skeletal muscle vascular resistance at resting conditions, but also contributed to a blunted functional hyperemia of skeletal muscles at higher levels of metabolic demand, such as, during exercise.[50] Postulated mechanisms for these dysfunctions include: (1) the capillary rarefaction and increased perfusion heterogeneity in hypertensives impair flow and oxygen delivery to the working muscles; thus, a greater increase in BP is required to achieve perfusion, and (2) the structural alterations in the resistance vasculature may act as a vascular amplifier that further enhances the effects of a hypertensive stimulus, such as exercise.[12,50] In addition, the impaired oxidative capacity suggestive of mitochondrial dysfunction/uncoupling in the skeletal muscle of hypertensive patients could lead to an increase in reactive oxygen species, reducing endothelial NO synthase, and resulting in a decrease NO bioavailability.[46] The increased oxidative stress and inflammation further reduces NO, promoting endothelial dysfunction within the small vessels' wall and impairing vasodilation in exercising muscles.

In conclusion, the impaired in vivo skeletal muscle oxygenation and microvascular reactivity in newly diagnosed, never-treated patients with hypertension were associated with higher aortic systolic and PP and AI. Importantly, our data show for the first time that, during submaximal exercise, hypertensive patients required a 2-fold increase in BP compared with normotensives, to achieve similar muscle oxygenation levels. Our data point to a partial involvement of microvascular stiffness and dysregulations in skeletal muscle oxygen delivery/utilization to the exaggerated BP during exercise, in hypertensive patients.

Perspectives

Our novel findings suggest more prominent alterations in skeletal muscle oxidative capacity than in microvascular reactivity in individuals with hypertension, implying an early role of skeletal muscle oxidative capacity and mitochondrial respiratory dysfunction in the pathogenesis of hypertension. The finding that muscle oxygenation indices were correlated with central aortic systolic and PP and arterial stiffness indices rather than with visit brachial pressure is also noteworthy as central BP has been more strongly associated with preclinical organ damage.[44] Our data also suggest that microvascular stiffness contributes to limitations of muscle oxygenation and to the exaggerated BP during exercise, in hypertension. Future studies should explore whether lifestyle (ie, exercise) or pharmacological interventions could enhance skeletal muscle oxidative capacity and microvascular function and improve hypertensive patient outcomes.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Untreated hypertensive patients exhibit impairments in skeletal muscle oxygenation and blunted microvascular hyperemia that were associated with amplifications in aortic systolic blood pressure and augmentation index.
- During submaximal exercise, hypertensives required a double increase in blood pressure to achieve similar muscle oxygenation to normotensives.

What Is Relevant?

- The alterations in muscle oxygen consumption and oxidative capacity indices in newly diagnosed hypertensives suggest mitochondrial dysfunction early in disease process.
- Microvascular stiffness and reduced muscle oxygenation contributes to exaggerated blood pressure responses during exercise in hypertensives.

Summary

Dysregulations in skeletal muscle oxygen delivery/utilization and microvascular stiffness in hypertensive patients partially contribute to their exaggerated exercise blood pressure response.

Impaired Muscle Oxygenation and Elevated Exercise Blood Pressure in Hypertensive Patients: Links With Vascular Stiffness

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ONLINE SUPPLEMENT

IMPAIRED MUSCLE OXYGENATION AND ELEVATED EXERCISE BLOOD PRESSURE IN HYPERTENSIVE PATIENTS: LINKS WITH VASCULAR STIFFNESS

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S1. Expanded materials and methods

Office Blood Pressure Assessment

Blood Pressure (Microlife) was assessed by a trained physician, according to a standard protocol using an appropriate cuff size. BP calculated as the mean value of the second and third measurement of three consecutive BP readings taken at 2-minute intervals, after the participant was seated for 10 minutes.

Ambulatory 24-hour Blood Pressure Assessment

The participant was equipped with a portable device (Spacelabs 90207; Spacelabs Healthcare, Redmond, WA, USA), 24 hour-ambulatory BP monitoring (24h-BP). Monitors were programmed to record BP at 20-min intervals during a typical work day and 30-min intervals during the subsequent night.

Pulse Wave Velocity Assessment

Arterial stiffness was assessed by pulse wave velocity (PWV; Sphygmocor, Australia) using a standard protocol.[1] Waveforms at the right common carotid and right femoral site were recorded sequentially after a 15-min supine rest. Surface distance between the two recording sites was measured (sternal notch to carotid site and to femoral site). Wave transit time was calculated using a simultaneously recorded electrocardiogram as a reference. Augmentation index (AIx) was expressed as a percentage of the ratio of augmentation pressure to central pulse pressure (the difference between central systolic and diastolic pressure). Aortic augmentation pressure was calculated as the difference between the first and second systolic peaks of the ascending aortic waveform, obtained from applanation tonometry. AI% was corrected for the mean heart rate of 75 bpm (AI%75).

Physical Activity Status Assessment

Participants filled out the International Physical Activity Questionnaire (IPAQ) for assessment of physical activity status.[2]

Muscle Oxygenation and Beat-by-Beat Blood Pressure Assessment

The participant was connected to the experimental apparatus for the assessment of microvascular reactivity and muscle oxygenation (at rest and during exercise) via near-infrared spectroscopy (NIRS, Artinis, The Netherlands) and for beat-by-beat continuous monitoring of BP (Finapres Medical Systems, The Netherlands). The finger cuff of the Finapres apparatus was placed in the middle finger and the inflatable cuff was placed at the heart's level, on the non-dominant arm.[3] Measurements determined non-invasively with the Finapres device have been found in good correspondence with those obtained simultaneously using an intra-arterial catheter at rest and during exercise.[4]

Maximal Voluntary Contraction and Isometric Exercise Testing

After a subsequent 10-min rest, the participant performed three maximal isometric handgrip contractions with their dominant hand using a digital dynamometer (Biopac MP150, USA) with a 90-s interval in between trials. The highest of the three readings was considered as the maximal voluntary contraction (MVC). Next, the participant performed a 3-min submaximal handgrip exercise test (at 30% MVC), during which he/she had visual feedback to maintain the force output to the predetermined MVC percentage. Force output was continuously recorded. A 3-min recovery followed. Exercise was discontinued if an excessive response to exercise was observed (i.e. BP>220/120 mmHg).

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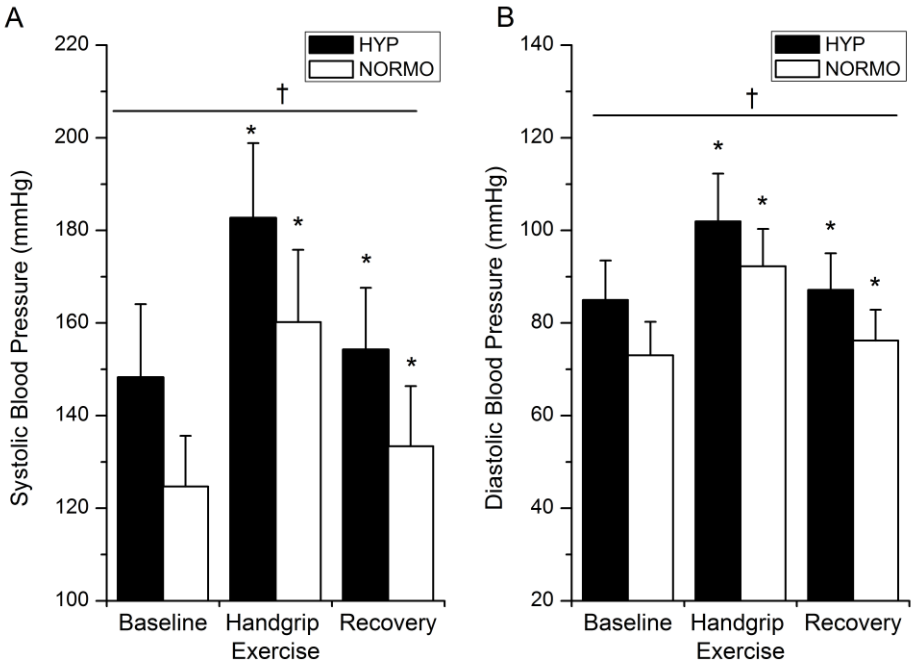
Table S1. Participants' characteristics

Variables	HYP	NORMO	p
Age (years)	45.9±9.9	43.8±12.1	0.37
Sex (male %)	60%	60%	0.85
Body mass index (kg/m^2)	27.9±4.5	27.3±5.4	0.58
Waist to hip ratio	0.92±0.09	0.91±0.07	0.65
Visit SBP/DBP (mmHg)	148.4±14.8/97.5±7.6	120.9±8.7/78.1±6.3	0.000
24h-SBP/DBP (mmHg)	141.2±13.2/90.0±7.9	115.6±7.8/72.6±5.4	0.000
Day-SBP/DBP (mmHg)	146.4±12.5/94.4±7.5	120.8±7.7/76.9±5.5	0.000
Night-SBP/DBP (mmHg)	129.0±15.6/80.5±9.4	106.6±8.4/64.4±5.9	0.000
Hemoglobin (mmol/l)	8.87±0.93	8.94±0.74	0.83
Hematocrit (fraction)	0.428±0.041	0.429±0.034	0.92
LDL-Cholesterol (mmol/l)	3.57±0.95	3.50±0.92	0.73
HDL-Cholesterol (mmol/l)	1.25±0.33	1.24±0.26	0.84
Total Cholesterol (mmol/l)	5.53±1.12	5.36±1.04	0.48
Blood Glucose (mg/dl)	4.88±0.59	4.95±0.54	0.52
eGFR (ml/min/1.73m^2)	121.4±29.6	120.4±29.9	0.88
Forearm adipose tissue thickness (mm)	3.93±1.4	3.97±1.1	0.88
Maximal Voluntary Contraction (MVC, kg)	43.7±14.4	44.9±17.6	0.73

HYP: hypertensive patients, NORMO: normotensive participants; eGFR: estimated glomerular filtration rate, based on the Cockroft-Gault equation

Figure S1. Blood pressure responses at rest, during exercise, and recovery in the hypertensive and normotensive groups



Systolic (A) and diastolic (B) blood pressure responses during rest, handgrip exercise, and recovery in hypertensive (HYP) and normotensive (NORMO) groups. †$p<0.001$ HYP vs NORMO throughout the protocol; *$p<0.001$ vs. baseline values within group.

HYP exhibited higher systolic and diastolic blood pressure responses than NOMOR throughout the protocol ($p<0.001$).