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Intercostal muscle blood flow is elevated in old rats during submaximal exercise

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ABSTRACT

Background: Respiratory muscle blood flows (BF) increase substantially during exercise in younger adult rats. As aging is associated with altered pulmonary function, we hypothesized that old rats will have greater intercostal muscle BF and vascular conductances (VC) than young rats during submaximal exercise.
Methods: Mean arterial pressure and respiratory muscle BFs (via carotid artery catheter and radiolabeled microspheres, respectively) were measured at rest and during submaximal exercise in young (n = 9) and old (n = 7) Fischer 344 X Brown Norway rats.
Results: At rest, diaphragm, intercostal, and transversus abdominis BFs and VCs were not different between groups (all, $p > 0.10$). During submaximal exercise, old compared to young rats had greater intercostal BF (40 ± 6 vs 25 ± 2 mL/min/100 g) and VC (0.30 ± 0.05 vs 0.18 ± 0.02 mL/min/mmHg/100 g) (both, $p \leq 0.01$). Diaphragm and transversus abdominis BFs and VCs were not different between groups during exercise (all, $p > 0.24$).
Conclusions: These data demonstrate that intercostal muscle BF and VC are increased in old compared to young rats during submaximal exercise.

1. Introduction

The respiratory muscles are structurally (high mitochondrial volume density, rich vascular network) and functionally (great oxidative potential and vascular flow capacity) designed to resist fatigue and failure (Delp and Duan, 1996; Manohar, 1986, 1988, 1990; Poole et al., 2000; Reid and Johnson, 1983). Increased respiratory muscle work has important implications during exercise, as high respiratory muscle work results in redistribution of blood flow (BF) from the exercising locomotor to respiratory muscles (Harms et al., 1997; Musch, 1993; Olson et al., 2010; Smith et al., 2017c). Although currently not possible in humans, diaphragm and accessory respiratory muscle BFs have been directly measured in rats (Musch and Terrell, 1992; Poole et al., 2000; Smith et al., 2017c,d; Smith et al., 2018b), dogs (Musch et al., 1987), swine (Armstrong et al., 1987), and ponies (Manohar, 1986, 1988, 1990). Moreover, from rest to exercise, respiratory muscle BFs increase heterogeneously such that diaphragm BF increases to a greater extent than accessory respiratory muscle (e.g., intercostal or transversus abdominis) BFs (Manohar, 1990; Musch, 1993; Poole et al., 2000; Smith et al., 2017c,d; Smith et al., 2018b). Whereas diaphragm paralysis decreases peak oxygen uptake ~20% in rats (Gosselin et al., 1997), the large increases in diaphragmatic BF during exercise suggest that the diaphragm is an important inspiratory muscle in rats as for humans.

Aging leads to significant structural and functional changes within the pulmonary system. For example, aging is associated with the loss of elastic recoil, stiffening of chest wall, and decreased expiratory flow rates (Johnson et al., 1994, 1991; Knudson et al., 1977). As a result of these changes, older adults breathe at higher lung volumes (i.e. higher percentage of total lung capacity), while also exhibiting greater ventilatory constraints, work of breathing, and ventilatory responses during exercise (DeLorey and Babb, 1999; Johnson et al., 1994; Molgat-Seon et al., 2018a; ,Smith et al., 2017e; Smith et al., 2018a). These aging-induced alterations to the pulmonary system have important implications for respiratory muscle BF during exercise. Specifically, the greater work of breathing and ventilatory response in older adults likely conflate to significantly increase respiratory muscle BF during exercise compared to younger adults. Furthermore, the loss of elastic recoil, stiffening of the chest wall and consequently elevated operating lung volumes associated with aging will likely alter the heterogeneity in respiratory muscle BF previously reported in young animals (Manohar,

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1990; Musch, 1993; Poole et al., 2000; Smith et al., 2017c,d; Smith et al., 2018b). For example, in stark contrast to the diaphragm, the optimal length of the length-tension relationship for the intercostals is near total lung capacity (Decramer, 1997; Decramer and De Troyer, 1984; Farkas et al., 1985). Furthermore, a recent study found that older compared to younger adults have greater accessory respiratory muscle activation for a given ventilation during exercise (Molgat-Seon et al., 2018b). Taken together, these data suggest that the pulmonary alterations associated with aging will command a greater respiratory muscle BF response likely comprised of elevated accessory respiratory muscle BF.

Therefore, we sought to determine respiratory muscle (diaphragm, intercostal, and transversus abdominis) BFs and vascular conductances (VCs) in old compared to young rats at rest and during submaximal exercise at the same absolute workload. This paradigm was specifically selected because older and younger individuals perform daily tasks that are equivalent in absolute terms. We hypothesized that in old, compared to young, rats intercostal muscle BF and VC would be augmented during submaximal exercise.

2. Methods

2.1. Ethical approval

Nine young (6–8 mo old) and seven old (27–29 mo old) Fischer 344 X Brown Norway (F344/BN) male rats were used in this investigation. These rats were specifically selected for this study because they represent old (senescent) rats according to the lifespan for the F344/BN strain (Larkin et al., 1996). Furthermore, the F344/BN rat does not develop many of the age-related pathologies that are common in their highly-inbred Fischer 344 cousins (Bronson, 1990; Larkin et al., 1996). Rest and submaximal exercise HR and MAP in the young and old rats were previously reported (Musch et al., 2004). One old rat was not used in the analysis because non-physiologic diaphragm BFs (more than 3 standard deviations greater than average) were measured at rest and during exercise (i.e. 1144 and 2200 mL/min/100 g, respectively). Rats were maintained at accredited animal facilities at Kansas State University on a 12:12 h light-dark cycle with food and water provided ad libitum. All procedures were approved by the Institutional Animal Care and Use Committee of Kansas State University.

For 2–3 wks, all rats were familiarized with running on a custom-built, motor-driven treadmill. During this familiarization period, rats exercised for 5–10 min/day at a speed of 20 m/min and 5% grade as to not incur exercise training adaptations (Armstrong and Laughlin, 1984; Musch et al., 1992).

2.2. Instrumentation and final experiment protocol

On the day of the experiment, all rats were anesthetized with a 5% isoflurane-oxygen mixture and maintained subsequently on a 2% isoflurane-oxygen mixture. One catheter (PE-10 connected to PE-50, IntraMedic polyethylene tubing, Clay Adams, Becton, Dickinson, Sparks, MD) was placed in the ascending aorta via the right carotid artery for the measurement of mean arterial pressure (MAP) and heart rate (HR) (model 200, DigiMed BPA, Louisville, KY) and the infusion of radiolabeled microspheres. A second catheter was placed in the caudal (tail) artery for arterial blood sampling (Musch et al., 2004; Musch and Terrell, 1992). Both catheters were tunneled subcutaneously through the dorsal aspect of the cervical region and exteriorized through a puncture in the skin. The incisions were then closed, anesthesia was terminated, and the rats were given > 90 min to recover (Flaim et al., 1984).

2.3. Measurement of respiratory muscle BFs

Following recovery, each rat was placed on the motor-driven treadmill and the carotid artery catheter was connected to the pressure transducer (model P23ID, Gould Statham, Valley View, OH). Tissue BFs were determined using the radionuclide-tagged microsphere technique that has previously been used in the exercising rat (Musch and Terrell, 1992). After the stabilization period, the caudal artery was connected to a 1-mL syringe chambered in an infusion/withdrawal pump (model 907, Harvard Instruments). Exercise was initiated, and the speed of the treadmill was increased progressively during the next 30 s to a speed of 20 m/min (5% grade). The rat was then required to exercise at the speed and grade for another 3 min. During this time, radiolabeled microspheres (^{46}Sc, ^{85}Sr, ^{141}Ce, or ^{113}Sn in random order; New England Nuclear, Boston, MA) were mixed by a vortex agitator (Fishers Scientific, Waltham, MA). At the 3 min exercise mark, the carotid artery catheter was disconnected from the pressure transducer and 0.5–0.6 × 10^6 microspheres with a 15 µm diameter were injected into the aortic arch in a 0.15-0.20 mL volume to determine respiratory muscle BFs. Simultaneously, the pump connected to the caudal artery catheter was activated and blood withdrawal was initiated at a rate of 0.25 mL/min. Blood withdrawal was terminated 30 s following the microsphere infusion and then exercise was terminated.

A second microsphere infusion was performed after > 60 min of recovery (radiolabeled different from the first microsphere infusion), while the rat sat quietly on the treadmill for determination of resting respiratory muscle BFs, MAP and HR. This experimental protocol minimizes the potential influences of the pre-exercise anticipatory response on resting muscle BFs, MAP and HR measurements (Armstrong et al., 1989).

2.4. Determination of BF and VC

Following the completion of the exercise protocols and resting measurements, rats were euthanized with an overdose of sodium pentobarbital (> 50 mg/kg body wt.) via the right carotid artery catheter and placement of each catheter was verified by anatomic dissection. The lungs were excised and weighed. The diaphragm, intercostals, and transversus abdominis muscles of each rat were dissected out. The tissues were blotted, weighed, and placed immediately into counting vials. The radioactivity of each tissue was determined with a gamma scintillation counter (model 5230, Auto Gamma Spectrometer, Packard, Downers Grove, IL). The radioactivity of the tissues was then analyzed by computer, taking into account the cross-talk fraction between the different isotopes. Absolute muscle BF was then calculated by the reference sample method (Ishise et al. (1980)) and expressed in milliliters per min per 100 g of tissue. Adequate mixing of the microspheres was verified for each microsphere infusion as demonstrated by < 15% difference in BF to the right and left kidneys (Musch et al., 2004). VC was then calculated by normalizing BF to MAP measured at the time of the microsphere infusion and expressed as mL/min/mmHg/100 g.

2.5. Statistical analyses

Values are reported as mean ± standard error (SE). All statistical analyses were performed by using SigmaStat 2.0 (Jandel Scientific, San Rafael, CA). Unpaired *t*-tests were used to compare body weight. MAP, HR as well as respiratory muscle (diaphragm, intercostal, and transversus abdominis) BFs and VCs were compared within (rest vs 20 m/min, 5% grade) and between (young vs old) groups using mixed factorial analysis of variance and Tukey post-hoc tests when appropriate. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Body weight and cardiovascular responses

The old rats were heavier compared to the young rats (O: 497 ± 19; Y: 339 ± 8 g, $p < 0.01$). There were no differences

Table 1
MAP and HR at rest and during submaximal exercise.

	MAP (mmHg)	HR (beats/min)
Young (n = 9)		
Rest	123 ± 4	393 ± 12
Exercise	136 ± 3*	496 ± 13*
Old (n = 6)		
Rest	131 ± 2	417 ± 6
Exercise	134 ± 2	455 ± 7*,†

Values are mean ± SE. MAP, mean arterial pressure; HR, heart rate.
* $p < 0.05$ vs. rest.
† $p < 0.05$ vs. young.

between groups in MAP at rest ($p = 0.09$) or during submaximal exercise ($p = 0.69$) (Table 1). MAP increased from rest to submaximal exercise for the young ($p < 0.01$), but not the old rats ($p = 0.38$). HR was not different ($p = 0.27$) between groups at rest, but the old rats had a lower ($p = 0.03$) HR during submaximal exercise compared to the young rats. Both groups increased ($p < 0.01$) HR from rest to submaximal exercise.

3.2. Respiratory muscle BF and VC

At rest, diaphragm, intercostal, and transversus abdominis BFs were not different between groups ($p > 0.10$) (Fig. 1). From rest to exercise, diaphragm, intercostal, and transversus abdominis BFs increased in both age groups (all $p < 0.01$). During exercise, old rats had greater intercostal BF than young rats ($p = 0.01$), while no differences were present in diaphragm and transversus abdominis BFs between groups (both $p > 0.24$). Resting diaphragm, intercostal, and transversus abdominis VCs were not different between groups (all $p > 0.12$) (Fig. 2). Diaphragm intercostal, and transversus abdominis VCs increased from rest to exercise in both groups ($p < 0.01$). Old rats had greater intercostal VC than young rats during exercise ($p < 0.01$) with no difference between groups in diaphragm or transversus abdominis VCs (both $p > 0.28$).

4. Discussion

The present investigation is the first to determine the effects of aging on respiratory muscle BF control at rest and during submaximal exercise. The principal novel finding was that, compared to young, old rats exhibited augmented intercostal BF and VC during submaximal exercise. Furthermore, we found that diaphragm and transversus abdominis BFs and VCs were not different between old and young rats during submaximal exercise. These results indicate that accessory respiratory muscle BF control is altered with aging, which has important implications for the integrated response to exercise.

When designing an investigation where the experimental condition (e.g., aging) influences peak aerobic capacity, it is contentious whether to compare groups at the equivalent absolute or relative workloads. Herein, we sought to determine respiratory muscle BFs and VCs in old and young rats exercising at the same absolute workload specifically because older and younger individuals perform daily tasks that are equivalent in absolute terms. This paradigm has previously been used to compare the effects of aging on cardiovascular responses to exercise (Lawrenson et al., 2003; Musch et al., 2004; Poole et al., 2003; Proctor et al., 1998). As aging results in a decline in $\dot{V}o_2max$ (Cartee and Farrar, 1987; Mazzeo et al., 1984), the same absolute workload in old rats likely results in a greater relative workload. Specifically, peak aerobic capacity has been found to decline ~10–20% in F344 rats (Cartee and Farrar, 1987; Mazzeo et al., 1984). Furthermore, the workload used herein elicits an oxygen uptake of 47–55 mL/min/kg (Brooks and White, 1978; Lawler et al., 1993; Musch et al., 1988). Thus, the old rats in the present investigation were estimated to be exercising at 71–83% of their $\dot{V}o_2max$, while the young rats were exercising at 63–73% of their $\dot{V}o_2max$ (assuming F344/BN rats exhibit a similar reduction in $\dot{V}o_2max$ as F344 rats). However, it is important to also note that the $\dot{V}o_2$ cost of running is 10–15% less in old (and also heavier) rats compared to young rats (Lawler et al., 1993; Schefer and Talan, 1996). Thus, the respiratory muscle BFs and VCs comparisons at absolute (rather than relative) workload should be considered when interpreting the findings of the present investigation.

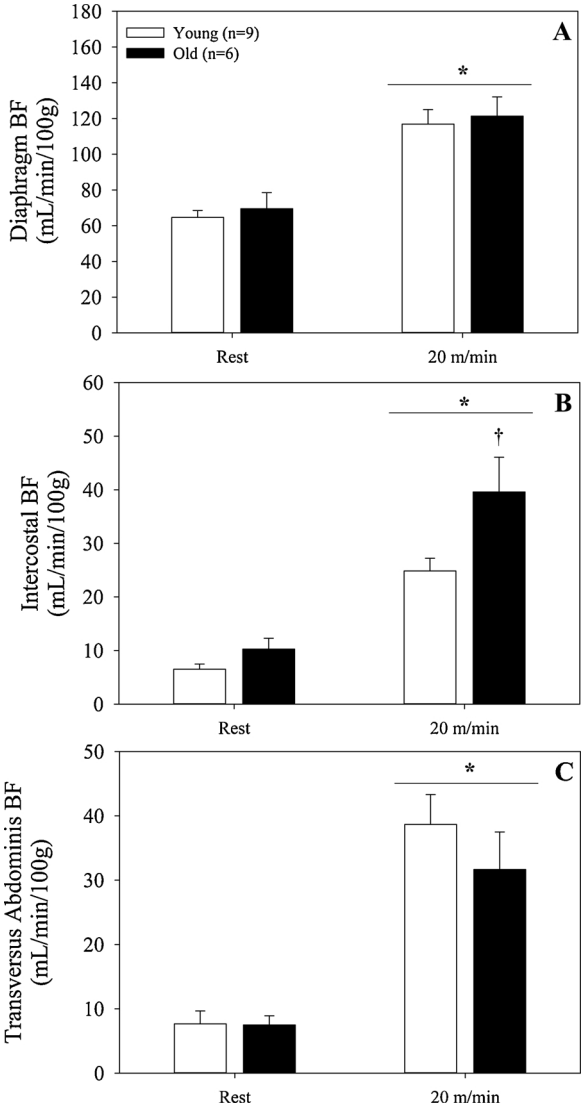

Fig. 1. Respiratory muscle blood flows (BFs) at rest and during submaximal exercise.
Diaphragm (A), intercostal (B), and transversus abdominis (C) BFs at rest and during submaximal exercise in young (white bar, n = 9) and old (black bar, n = 6) rats. Diaphragm, intercostal, and transversus abdominis BFs increased ($p < 0.01$) from rest to submaximal exercise. Old rats had greater intercostal BF during exercise compared to young rats ($p = 0.01$) *, significantly different from rest. †, significantly different from young rats.

Aging promotes specific structural and functional adaptations of the pulmonary system culminating in breathing at higher lung volumes as well as augmented work of breathing and ventilatory responses during exercise (Brischetto et al., 1984; DeLorey and Babb, 1999; Johnson et al., 1994; Molgat-Seon et al., 2018a; Smith et al., 2018a). As a result, it has been speculated that respiratory muscle BF is elevated to meet these increased metabolic demands during exercise (Smith et al., 2018a). A recent study found that accessory respiratory muscle

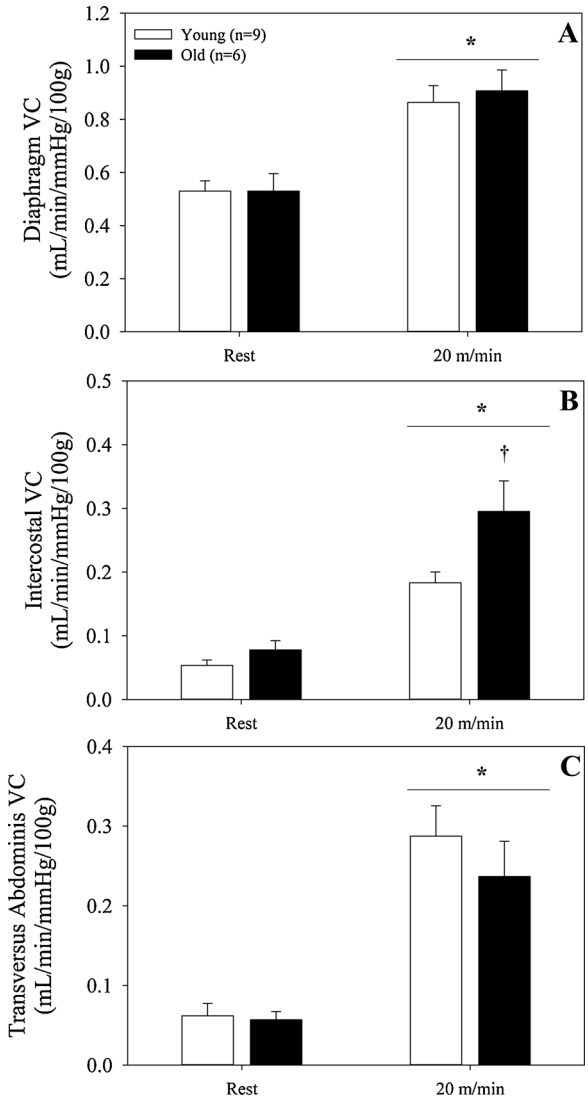

Fig. 2. Respiratory muscle vascular conductances (VCs) at rest and during submaximal exercise.
Diaphragm (A), intercostal (B), and transversus abdominis (C) VCs at rest and during submaximal exercise in young (white bar, n = 9) and old (black bar, n = 6) rats. Diaphragm, intercostal, and transversus abdominis VCs increased from rest to submaximal exercise. Intercostal VC was higher during submaximal exercise in old than young rats ($p < 0.01$). *, significantly different from rest. †, significantly different from young rats.

activation (assessed via electromyography) was increased more in older than younger adults for a given ventilation during submaximal exercise (Molgat-Seon et al., 2018b). Furthermore, the optimal length of the length-tension relationship for the intercostals is near total lung capacity (Decramer, 1997; Decramer and De Troyer, 1984; Farkas et al., 1985), which is important as functional residual capacity is increased with aging (DeLorey and Babb, 1999), allowing for more advantageous respiratory pressure development by the intercostals. As the work of breathing and the ventilatory response are greater for a given workload with aging, we hypothesized that intercostal BF would be greater in old than young rats due to the greater contribution of the intercostals to the respiratory pressure generation. In the present study, we found that intercostal BF was ~60% greater in the old compared to the young rats during submaximal exercise (40 versus 25 mL/min/100 g). The submaximal exercise diaphragm BFs in the young (117 mL/min/100 g) and the old (121 mL/min/100 g) rats measured herein are in excellent agreement with those previously reported during submaximal exercise in young male and female rats (124 and 110–140 mL/min/100 g, respectively) (Sexton and Poole, 1995; Smith et al., 2017d), while substantially lower than those reported at maximal and supra-maximal exercise (283–360 mL/min/100 g) (Poole et al., 2000; Smith et al., 2017d). In contrast to the differences in intercostal BF, we found that diaphragm BF was not different between the old and young rats during submaximal exercise. We consider that this lack of difference in diaphragm BFs between age-groups may have been influenced by the relative contribution of the diaphragm to respiratory pressure development and the optimal length of the diaphragm during exercise. First, the relative contribution of the diaphragm to total respiratory pressure development declines with greater ventilation during exercise (Molgat-Seon et al., 2018b). Second, breathing at high lung volumes is disadvantageous for the diaphragm as the optimal muscle length is near function residual capacity (Decramer, 1997; Farkas et al., 1985). Thus, accessory respiratory muscles (e.g. intercostal muscles) are expected to contribute more to pulmonary function (i.e., total respiratory pressure development and work of breathing) than the diaphragm in regards to generating the aging-induced augmented exercise ventilatory response. Due to the inability to clearly dissect out the internal and external intercostals separately, it is not possible to resolve whether the greater intercostal BF in the old compared to young rats was due to elevated external and/or internal intercostal BF and future studies are necessary to clarify this. Taken together, these findings indicate that intercostal muscle BF is elevated with aging to meet the increased demands of the respiratory muscles during exercise.

These findings have important implications regarding the integrated response during severe intensity exercise. Specifically, a metaboreflex arising from the respiratory muscles is activated during exercise when cardiac output is limited. As a result, muscle sympathetic nerve activity and limb vascular resistance are elevated (Katayama et al., 2018; Smith et al., 2016; Smith et al., 2017b) redistributing blood flow from the locomotor to respiratory musculature (Harms et al., 1997; Olson et al., 2010; Smith et al., 2017c). Recently, we found that respiratory muscle metaboreflex activation led to similar cardiovascular consequences in younger and older men (Smith et al., 2017a). Future studies measuring absolute respiratory and locomotory muscle(s) blood flow coupled with cardiac output would provide an invaluable analysis of the respiratory muscle metaboreflex and its contribution to blood flow (re)distribution among vascular beds. Taken together, the present data support that the greater respiratory muscle cost of exercise with aging (due to a greater ventilatory response and work of breathing for a given ventilation) and thus BF response will result in earlier respiratory muscle metaboreflex activation in older than younger adults.

Several considerations are warranted in the present study. First, ventilation and respiratory mechanics were not measured directly herein. Although ventilation and work of breathing have been reported to be greater in older than younger adults (Brischetto et al., 1984; Johnson et al., 1994; Molgat-Seon et al., 2018a; Smith et al., 2018a), it would have been valuable to confirm that the old compared to young rats had greater ventilation and work of breathing during exercise. It is important to note that respiratory mechanics differ between humans and rats such that rats have a greater chest wall compliance and less resistance at rest compared to humans (Crosfill and Widdicombe, 1961). Second, the old rats were significantly heavier than the young rats. However, obesity per se has previously been shown not to influence the ventilatory response or work of breathing during exercise (deJong et al., 2008; DeLorey et al., 2005). Third, respiratory muscle weights were not reported; however, the respiratory muscle weights likely increased in parallel with age associated increases in body weight such that the ratios of respiratory muscles to body weight were not different between old and young rats (as reported for the diaphragm (Criswell et al., 2003; Powers et al., 1991)).

In conclusion, this is the first investigation to demonstrate that intercostal muscle BF and VC are augmented in older compared to young rats during submaximal exercise. These findings have important

implications regarding circulatory regulation during severe-intensity exercise in older adults. It remains to be determined if accessory muscle BFs are elevated during exercise in older humans.

Competing interests

The authors declare no competing interests.

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