Pulmonary blood flow and its distribution in highly trained endurance athletes and healthy control subjects

Ilkka Heinonen,1,2,4 Anna M. Savolainen,1 Chunlei Han,1 Jukka Kemppainen,1,3 Vesa Oikonen,1 Matti Luotolahti,3 Dirk J. Duncker,4 Daphne Merkus,4 Juhani Knuuti,1 and Kari K. Kalliokoski1

1Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland; 2Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku and Turku University Hospital, Turku, Finland; 3Department of Clinical Physiology and Nuclear Medicine, University of Turku and Turku University Hospital, Turku, Finland; 4Division of Experimental Cardiology, Thoraxcenter, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

Submitted 7 June 2012; accepted in final form 28 November 2012

THE LUNGS PROVIDE THE SITE for the first step for oxygenation of blood to be supplied to other organs in the body. While the lungs of healthy young individuals are usually not regarded as a limiting factor for endurance performance, emerging evidence suggests that it may affect performance in some highly trained endurance athletes (EA) (1, 11). As reviewed recently (1), these limiting factors are 1) restriction of cardiac output by excessive intrathoracic pressure fluctuations; 2) exhaustion of respiratory muscles and vasoconstrictor reflexes that arise; and 3) arterial desaturation due to high metabolic requirements and subsequent increase in core temperature and metabolic acidosis. Despite these possible limitations, however, athletes can still cope with the highest cardiac outputs that humans can reach, and their pulmonary circulation, therefore, may be equipped with acquired and/or inherent (genetic) structural and functional adaptations. However, differences in pulmonary blood flow (PBF), and its large-scale distribution and small-scale heterogeneity between athletes and matched untrained subjects, remain incompletely understood.

Absolute PBF is not controlled by the lungs themselves, but rather is determined by right ventricular output equaling systemic cardiac output. Since resting cardiac output is usually equal or even slightly lower in athletes compared with untrained subjects, an increase in total PBF at rest in athletes can be excluded as an adaptation to training. Interestingly, while large-scale PBF distribution is largely determined by gravitational influences, PBF heterogeneity is not influenced by overall blood flow level (7) and, although vasoregulatory mechanisms may also contribute, can be largely considered to reflect differences in blood flow distribution and vascular capacity at the capillary level in the lungs (15, 17–20, 25). PBF heterogeneity, which can be assessed noninvasively in humans by positron emission tomography (30, 41, 45), may thus provide an interesting tool to investigate possible structural and functional adaptations in athletes’ lungs. Consequently, we determined here PBF, its distribution, and heterogeneity in highly trained EA and matched healthy control (C) subjects. We hypothesized to observe similar overall PBF values, but more uniform blood flow distribution in athletes, particularly during adenosine infusion.

METHODS

Subjects. Twenty healthy men volunteered for the study (Table 1). Ten of them were highly trained EA, and 10 were untrained C men. The subjects were apparently healthy, as determined by health questionnaire and medical screening by a doctor, in addition to pre-ECG evaluation. The subjects were not under any medication and were normotensive nonsmokers with no history of hypercholesterolemia and no family history of coronary disease. The purpose, nature, and potential risks were verbally explained to the subjects before they gave their written, informed consent to participate. The study was performed according to the Declaration of Helsinki and was approved by the Ethical Committee of the Hospital District of South-Western Finland.

The EA participants in the study were cross-country skiers, who also trained and competed in other endurance sport events, such as running, cycling, and orienteering. The training volume of their last training season was, on average, 626 ± 181 h in a year. The EA had been training on a regular basis for 12.3 ± 2.9 yr, 8.7 ± 1.4 times, and 12.8 ± 1.5 h/wk, primarily in endurance exercise at various intensi-
Table 1. Characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>EA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>25.7 ± 4.2</td>
<td>24.6 ± 3.6</td>
<td>0.54</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179.3 ± 6.6</td>
<td>182.3 ± 7.5</td>
<td>0.35</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.1 ± 7.0</td>
<td>78.1 ± 6.6</td>
<td>1</td>
</tr>
<tr>
<td>BML, kg/m2</td>
<td>24.4 ± 2.9</td>
<td>23.4 ± 0.9</td>
<td>0.33</td>
</tr>
<tr>
<td>BSA, m2</td>
<td>1.97 ± 0.09</td>
<td>1.99 ± 0.13</td>
<td>0.60</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>19.0 ± 3.9</td>
<td>9.7 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Powermax, W</td>
<td>271 ± 35</td>
<td>367 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V02max, ml·kg·min⁻¹</td>
<td>46.2 ± 3.2</td>
<td>61.7 ± 5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V02max, l/min</td>
<td>3.5 ± 0.3</td>
<td>4.7 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD. C, control subjects; EA, endurance athletes; BML, body mass index; BSA, body surface area; Powermax, highest workload in maximal O2 consumption (V02max) test.

Adenosine elevated PBF ~2.6-fold, but mean blood flow at rest and during adenosine stimulation was similar between the groups in the whole lung segment (Fig. 2) and its ventral and dorsal parts (Fig. 3). There was a marked gravitational influence on general PBF distribution so that, in this supine body posture, a clear dorsal dominance compared with ventral areas (Fig. 3, and Fig. 1 for general illustration) was observed, both at rest and during adenosine infusion (both P < 0.001).

Fig. 1. Representative cross-sectional parametric PET image from the middle of the thorax region while subject is supine and at rest. Lung regions of interests are also illustrated.
Table 2. Hemodynamic variables during the PET measurements

<table>
<thead>
<tr>
<th></th>
<th>Baseline (C)</th>
<th>Baseline (EA)</th>
<th>Ado (C)</th>
<th>Ado (EA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>59 ± 8</td>
<td>47 ± 7†</td>
<td>103 ± 11†</td>
<td>80 ± 9†</td>
</tr>
<tr>
<td>BPs, mmHg</td>
<td>115 ± 11</td>
<td>123 ± 7*</td>
<td>117 ± 10</td>
<td>127 ± 8*</td>
</tr>
<tr>
<td>BPd, mmHg</td>
<td>68 ± 7</td>
<td>64 ± 5</td>
<td>67 ± 8</td>
<td>66 ± 5</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>84 ± 8</td>
<td>84 ± 4</td>
<td>84 ± 9</td>
<td>86 ± 5</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.6 ± 0.9</td>
<td>5.8 ± 1.1</td>
<td>9.2 ± 1.2†</td>
<td>8.8 ± 1.2†</td>
</tr>
</tbody>
</table>

Values are means ± SD. Ado, adenosine; HR, heart rate; BPs, systolic blood pressure; BPd, diastolic blood pressure; MAP, mean arterial blood pressure. *P < 0.001, †P < 0.001 and ‡P < 0.05; however, Ado induced no changes in BPs, BPd, and MAP, but EA had higher BPs and lower HR in every measurement compared with C.

Training status had no influence on this distribution difference between dorsal and ventral parts at the absolute blood flow level. However, PBF heterogeneity in the whole lung segment was reduced from rest to adenosine infusion in athletes (P < 0.05), while it remained unchanged in healthy C (P = 0.4) (Fig. 2). The decrease in heterogeneity in athletes was largely attributable to the dorsal part, where blood flow tended to become less heterogeneous (P = 0.06) (Fig. 3), while it remained unchanged in the ventral part (Fig. 3). As was the case with mean blood flow, blood flow heterogeneity was also markedly lower in the high-perfusion dorsal areas at rest and during adenosine infusion in all subjects (P < 0.001).

DISCUSSION

The present study shows that, although highly trained EA do not have supranormal absolute PBF or altered regional PBF distribution, they show reduced microvascular blood flow heterogeneity in response to pharmacological vasodilation. The latter finding could be interpreted to represent increased capillary reserve, which is more extensively recruitable in athletes than in matched healthy control subjects. This extravascular capacity may act during exercise to limit an excessive increase in pulmonary artery pressure during strenuous exercise. However, these vascular adaptations in athletes may also inadvertently contribute to the exaggerated arterial desaturation that is often observed in highly trained athletes during maximal exercise.

The pulmonary microvasculature differs in many respects from other microvascular beds in the systemic circulation (3, 37, 40, 42, 44). For instance, total PBF is not controlled by lungs themselves, but is determined by right ventricular output, which equals systemic cardiac output. Consequently, it is not surprising that athletes and our fit C subjects showed similar resting and adenosine-induced PBF, because cardiac output values were also similar between the groups. However, PBF is higher in athletes during maximal exercise due to the higher cardiac output. Importantly, effective gas exchange that is needed particularly during high-intensity exercise does not depend on only absolute PBF, but especially its distribution in the lungs, which could possibly be affected by training status.

The striking regional differences in PBF have been recognized ever since West et al. (51) found that the rate of removal of inhaled 15O-labeled carbon dioxide was much slower from the apex of the upright lung than from the base (51). Since these differences between apex and base were abolished in the supine position, gravity was clearly the culprit, although non-gravitational factors may also contribute (18, 23). Several studies have investigated the distribution of PBF by noninvasive imaging methods in supine vs. upright (43), in hypoxia (2, 8), and after exercise in athletes (5). However, direct comparison of PBF distribution between highly trained EA and C has, to the best of our knowledge, been lacking. The present study, however, shows that, when studied in supine position, both athletes and matched untrained subjects show a similar marked dorsal dominance (almost three times higher than ventral area) of PBF. PBF also increased similarly in both regions in both groups in response to adenosine infusion. Hence, it appears that gravitation, rather than training status, influences blood flow distribution toward dorsal and ventral areas of the lungs. Interestingly, however, PBF heterogeneity (as studied by standard deviation of blood flow values in PET image voxels within the ROI, divided by the mean blood flow within the same ROI) was affected differently between athletes and C. Thus overall blood flow heterogeneity, which is in the whole lung segment, was reduced by adenosine infusion only in athletes, which was principally due to a trend toward a lower flow heterogeneity in the dorsal area of the lung, as it remained unchanged in the ventral part. In contrast, blood flow heterogeneity in untrained subjects was not affected by adenosine in any of the lung areas studied.

Since PBF heterogeneity can be largely generalized to reflect differences in blood flow distribution and vascular capacity in...
the lungs at the capillary level (15, 17–20, 25), there is at least one possible explanation why blood flow heterogeneity is diminished in athletes in response to pharmacological vasodilation. While we are not aware of studies that have demonstrated higher alveolar capillarity in endurance-trained animals, our data could be interpreted to suggest that the reduced heterogeneity may be the due to a higher capillary reserve, which is more extensively recruitable in athletes than in matched healthy C subjects. This extensive capillary bed, which is likely recruited by high pulmonary arterial pressure that athletes can reach when exercising maximally (42), may aid in limiting the increase in pulmonary artery pressure further. Whether these vascular adaptations (be it intrinsic or acquired) blunt or aggravate the arterial desaturation frequently observed in athletes is presently unknown. Thus it could be argued that the adaptations provide some extra reserve for blood flow and diffusion surface needed during strenuous maximal exercise or in hypoxia (42, 50). This would allow larger increases in pulmonary blood volume (35) and thus oxygen diffusion to counteract reduced red blood cell transit times during strenuous exercise, which limit the widening of alveolar-to-arterial oxygen pressure. Conversely, there is evidence that ventilation-perfusion equality is more easily disturbed in athletes (10, 12, 16, 26–29, 36, 46, 47, 52). Thus PBF is not principally actively regulated, but controlled largely by right-side cardiac output, with high pulmonary arterial pressure being the driving force. Consequently, during maximal exertion, blood flow may “escape” to unfavorable vascular regions (26–29) that appear to be more extensive in athletes, thereby contributing to the widening of alveolar-to-arterial oxygen tension. Future studies are required to determine whether the observed vascular adaptations are beneficial or detrimental.

Limitations. The present study has a number of limitations. First, we did not measure pulmonary arterial pressure, and thus could not calculate pulmonary vascular resistance. Intravenous administration or direct infusion of adenosine into the pulmonary artery leads to unchanged (31) or reduced pulmonary vascular resistance (48). Conversely, animal studies indicate that exercise training does not modify pulmonary arterial vasoreactivity or pulmonary artery pressure at rest (21, 22, 32). Taken together, these observations suggest that PBF would appear to provide a reasonable noninvasive measure of pulmonary vascular function and structure to compare EA and C subjects.

The second limitation is that we could not directly measure stroke volume during the adenosine stress test. Hence, we estimated cardiac output during adenosine by multiplying heart rate during adenosine with resting stroke volume. Although there is evidence that adenosine produces a small increase in stroke volume (13), there is no evidence to suggest that these responses differ between trained and untrained subjects. Importantly, the estimation did not influence our PBF measurements, as these were directly measured using PET. Moreover,

![Fig. 3. Lung blood flow (top) and blood flow heterogeneity (bottom) in the ventral (left) and dorsal (right) parts of the lung in C and EA. Values are means ± SD. ***P < 0.001, both C and EA compared with baseline. Mean blood flow was always higher and heterogeneity and lower in dorsal part compared with ventral part in all subjects (both P < 0.001).](attachment:image.png)
PBFs were obtained during quite modest increase in cardiac output, and it is plausible that differences are even more exaggerated during maximal exercise when cardiac output is markedly higher in athletes.

A third limitation is that we included only men. Since the structure of the lungs appears to differ between men and women (24, 39), the effect of sex on general distribution of PBF and its distribution and their response to acute and chronic exercise in women warrants further study.

The fourth limitation is that we did not obtain measures of lung volumes and pulmonary function. Thus we cannot ex-clude that a difference in lung size between athletes and C subjects may have contributed to the results, as the size of the lungs may affect the ability of the lung to accommodate the increased in PBF. The extent this might happen remains, however, unknown. Moreover, our results are direct measure-ments from lungs rather than derived from measures of lung size and cardiac output, meaning that reported blood flow values per milliliter of tissue are irrespective of lung size. There is also some evidence from animal studies that lung volume-to-body weight ratio is increased in high-capacity runner rats (33), which results from lower body weight in athletic rats. In this regard, these findings from human pulmo-nary circulation that are irrespective of lung size are likely to provide some elucidation for the current collection of evidence that only lungs do not change in response to exercise training (9, 49). Thus also the adult lung appears to be a modifiable organ (6), if trained hard enough.

Finally, it has recently been suggested, based on the agitated contrast method, that there are direct arteriovenous shunts in the human pulmonary vasculature, which are opened when cardiac output and pulmonary arterial pressure are increased, either pharmacologically (4), or especially in response to exercise (14, 34, 38). While PET cannot provide greater insights to this topic due to inherent characteristics of the radio-water tracer that can measure only capillary level blood flow, it is also known that the pulmonary transit of agitated contrast is not associated with arterial desaturation (34, 35), and high-flow-high-pressure-driven dilated pulmonary capil-laries rather than true pulmonary shunts likely explain the positive appearance of contrast during exercise (35). Moreover, it has recently been suggested that it might be mostly capillary distension rather than recruitment that accounts for larger vascular reserve with increasing fitness of the untrained sub-jects (35). However, while this might be mostly the case in untrained subjects, the results from the present study suggest that, in highly trained athletes, capillary recruitment might also be present.

Conclusions. The present study shows that EA do not to have supranormal absolute PBFs at rest and during pharmacolog-ical vasodilation and also shows normal gravitation-induced PBF distribution between dorsal and ventral parts of the lung. However, athletes, but not untrained subjects, show a reduction in blood flow heterogeneity in response to pharmacological vasodilation. These observations could be interpreted to sug-gest an increase in capillary reserve, which is more extensively recruitable in athletes than in matched healthy C subjects. Future studies in exercise-trained animals are required to con-firm this concept, by direct determination of pulmonary capil-larity density.

ACKNOWLEDGMENTS

This study was conducted within the Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research, supported by the Academy of Finland, University of Turku, Turku University Hospital, and Abo Academy. The authors thank the contribution of the personnel of the Turku PET Centre for excellent assistance during the study.

GRANTS

The present study was financially supported by The Ministry of Education of State of Finland, Academy of Finland, The Finnish Cultural Foundation and its South-Western Fund, The Finnish Sport Research Foundation, and the Hospital District of Southwestern Finland.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


