

REVIEW ARTICLE

PULMONARY BLOOD FLOW INCREMENT AND AUGMENTATION OF VENTILATION : A REVIEW OF MECHANISMS

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An augmentation of ventilation or hyperpnoea, typically accompanies all orders of exercise. It may be present as an accelerated rate or an increased depth of breathing. The first to examine this feature of exercise related hyperpnoea were Krogh and Lindhard (1), who observed that ventilation could increase even *before* exercise had begun. They found evidence that ventilation increased in subjects who 'were expecting to start exercising but had as yet not begun to do so'. They attributed this influence to 'an irradiation of impulses from the motor cortex rather than a reflex from the muscles'. In other words, a network of central neural pathways that controls ventilation, locomotion and automotive functions seems to be operative at the onset of exercise, with an increased ventilation during exercise being sustained by the activation of muscle afferents (Group III and IV) (2).

However, an important observation in exercising individuals is that despite an increase in ventilation, the end-tidal CO₂ (ETCO₂) does not fall i.e. the hyperpnoea of exercise is isocapneic and not hypocapneic. Although it is fairly well established that when subjects are made to hyperventilate voluntarily to the same magnitude, a rapid reduction in the end tidal CO₂, does indeed occur. Nevertheless, end-tidal CO₂ can

remain unchanged if perfusion were to increase just as rapidly as ventilation does. It is fairly well established that an increase in cardiac output is produced not only by maximal levels of exercise but also by submaximal ones (3). Even mere leg lifting leads to a significant increase in cardiac output in healthy subjects (4). Thus levels of cardiac output and respiration do bear a close relationship to each other.

Mills (5) was the first to systematically examine the influence, on the respiration of human subjects, of an increase in blood flow into the pulmonary circulation. He used a physiological model of increasing venous return. This was achieved by at first producing venous congestion by tying tourniquets around both the lower limbs and then releasing them suddenly by untying them all at once. This method of accumulating blood from the central circulation into the peripheral circulation has been used as an effective method for reducing ventricular load after a myocardial infarct (6, 7) and has been known since the observations of Danzer (8). Kountz et al. (9) studied the influence of this procedure in great detail noting its effect on the resultant venous and arterial pressures and on the cardiac output. On comparing its outcome in normal subjects with that of

patients with cardiac complaints, they recommended that it was indeed very useful in relieving paroxysmal cardiac dyspnoea after an acute myocardial infarction.

On releasing the accumulated blood in 85% of the subjects that he studied, Mills observed a simultaneous increase in ventilation. Evident with the first breath, it was either seen as (i) rapid shallow breathing or (ii) a series of deep breaths or (iii) a single large breath. A noteworthy increase in ventilation was similarly seen, rapidly accompanying an increase in cardiac output that occurred with leg lifting i.e. by another physiological model of increasing venous return (4). With this method, ventilation was augmented by about 36% and was produced by an obvious acceleration in breathing frequency rather than by an increase in the tidal volume.

I. ARTERIAL CHEMORECEPTORS

a. Accumulated metabolite

The most obvious stimulus for the increase in ventilation after the release of tourniquets, seemed possibly to be an accumulated metabolite, which on being released from the stagnant blood may have acted on the peripheral arterial chemoreceptors and given rise to the observed respiratory reflexes. Since Mills (5) did not find any correlation between the duration of the congestion and the magnitude of hyperpnoeic response, he concluded that a chemical was not a likely stimulus. Several years later, Innes et al (10) also came to a similar conclusion while studying the effect on ventilation, of restricting blood flow in the periphery, at the end of a given period of exercise.

b. Hypoxia of stagnant blood

In addition, two further observations made by Mills indicated that the augmentation of ventilation did not arise by the stimulation of the peripheral chemoreceptors. The first of these was that the hyperpnoeic response of subjects did not diminish when made to breathe pure oxygen. In a later study, using a similar physiological model of increased venous return, i.e. subjecting the lower body to negative pressure (LBNP) and then releasing it, Lawler et al. (11) also came to a similar conclusion. The influence of the release of LBNP on the breath by breath parameters of ventilation i.e. tidal volume (V_T) and breathing frequency (f_B), were similar whether the subjects breathed pure oxygen or just room air.

The second and more significant observation made in this regard by Mills was that, if cyanide was injected in a vein just distal to the tourniquet and just before its release it produced a second and a more pronounced phase of accelerated breathing. The timing of the onset of this second phase suggested that it originated from peripheral chemoreceptors (12). The second period was approximately 2 seconds later and it was about the interval that it took subjects to smell ether when ether was injected into a vein just distal to the tourniquet, before its release.

c. Hypercapnia of stagnant blood

Just as there was a likelihood of the released hypoxic blood stimulating the arterial chemoreceptors, there was also the possibility of the hypercapnia of the stagnant blood exerting an influence on the chemoreceptors both peripheral and central. Lawler et al. (11) examined this by comparing the extent of increase in

ventilation of subjects who while being subjected to LBNP, also breathed gas mixtures which either consisted of a low percentage of CO₂ (1.25%) or a higher one (2.25%) in O₂ and were compared to a breath by breath measurement of (V_T) and breathing frequency (f_B), when the same subjects breathed either room air or almost pure oxygen (95%). An increase in ventilation when LBNP was released was evident in all cases as an increase in f_B more than an increase in V_T . However, the point to note was that the presence of hypercapnia, either a borderline increase over physiological levels or a greater one, could not account for the increase in ventilation that was seen with the above procedure. Ventilation was augmented to the same order as when the subject breathed pure oxygen or room air.

d. Pulmonary stretch receptors

The observation that the respiratory effect of releasing the accumulated blood was primarily seen during inspiration and that it could occur mid-expiration or even at the height of inspiration, seems to suggest strongly that this reflex was not mediated by the pulmonary stretch receptors (5).

II. VASCULAR FACTORS

Exercise physiologists studying the increase in ventilation that persists after exercise has ended, have also entertained the notion that this augmentation is related to a concomitant increase in cardiac output. This was at first shown in dogs by increasing cardiac output by injecting isoproterenol intravenously (13). Ventilation was enhanced almost immediately (the next breath) with the increase in heart rate and persisted for as long as the haemodynamic changes remained sustained. Furthermore,

hyperpnoea was not diminished by ventilating the dogs with pure oxygen (see above) or by removing the carotid bodies. A marked augmentation in ventilation was also seen in dogs who had pulmonary congestion and in whom an increase in pulmonary blood flow was produced by exercising them on a treadmill (14). This increase in ventilation was susceptible to cooling of the vagi - a procedure whereby the afferent impulses in these nerves are blocked (15).

Brown et al. (16) studied a situation in exercising subjects, which was opposite to the above and proved the same point. Essentially they used intravenous propranolol hydrochloride, a β -adrenergic blocker which decreases heart rate and cardiac output but does not influence oxygen consumption or arterial oxygen saturation. Under its influence heart rate fell by about 17% and ventilation (V_E) was reduced by about 9.6%.

WHAT DOES AN INCREASE IN BLOOD FLOW STIMULATE?

(a) Intrapulmonary CO₂ receptors

Accompanying the increase in cardiac output produced by leg-raising, was a significant increase in $EtCO_2$. Boone and Foley (4) considered the stimulation of possible carbon dioxide-sensitive sensory receptors in the pulmonary vasculature to be responsible for the respiratory reflexes seen. This question had also been addressed to earlier, by Green and Sheldon (17). Their results allow one to conclude that the presence of an increased CO₂ output, while ventilation was increasing linearly in response to an increasing pulmonary blood flow, produced an additive effect on the former.

(b) Pulmonary artery baroreceptors

Bianconi and Green (18) and Coleridge and Kidd (19, 20) showed that certain vagal endings in the wall of the pulmonary artery and its branches responded to an increase in the pulmonary artery pressure and could influence ventilation. These receptors came to be referred to as pulmonary artery baroreceptors. However, most studies did not find a correlation between the natural stimulus of these receptors, which was expected to be the pulmonary artery pulse pressure, and their responses.

In later studies Kan et al. (21) showed a significant increase in breathing frequency on raising the pressure inside the pulmonary arteries. Ledsome et al. (22) reported similar results that further demonstrated that these reflexes were mediated through the vagus nerve. But, it is also imperative to point out that all of the above results were obtained within the range of pulmonary pressures that were not encountered physiologically.

A single most meaningful observation that dispelled the likely role of pulmonary artery baroreceptors in influencing ventilation was made by Lloyd (23) on vascularly isolated pulmonary artery and right ventricle. He concluded that unless the pressure was raised to 27–70 torr, to enable an increase in the blood flow to about 400 ml/min i.e. considerably higher than that encountered in the physiological range, no notable increase in the amplitude or rate of the phrenic nerve discharge could be achieved. Moreover, the increase in respiration was quite modest (increasing by 3–4 breaths/min) and Lloyd also suspected that the extreme distension of the pulmonary artery that was carried out in order to

achieve the required rise in the pulmonary artery pressure (PAP) may have occluded the systemic blood supply to the arterial chemoreceptors located on the innominate artery, lying just beneath it and consequently the increased ventilation occurred due to the resulting anoxia (24).

Recently, Hainsworth and co-workers (25, 26), have reiterated that a positive feedback or a 'feed-forward' mechanism originates from the pulmonary artery baroreceptors providing an increased respiratory drive. These recent demonstrations were aimed at determining the response of pulmonary artery baroreceptors to a range of distending pressures that are within the physiological range. They found that under experimental conditions when the chest is intact (unlike as in the earlier studies), the phasic negative intrathoracic pressure lowers the threshold pressure of the pulmonary pressure-baroreceptor response relationship. According to them, this implied that under normal conditions, these receptors would be responsive to the prevailing pulmonary artery pressures. However, these observations do not yield any evidence as to the extent of their stimulation when pressures were to increase further e.g. during exercise and pulmonary hypertension. Moreover, the following discrepancies between the responses of the pulmonary artery receptors themselves and the role attributed to them have to be resolved before one can conclude that the reflexes originating from them contribute to the hyperpnoea of exercise. One is a set of observations made by Bevan (27) on the respiratory acceleration seen in cats after injecting lobeline into the pulmonary artery and the other, more recently observed, is in patients of heart and heart and lung transplant (28). Bevan attributed the reflex

effects of lobeline injected seen within 2 sec to a stimulation of pulmonary baroreceptors. For such short latencies, one would have to assume that the sensory endings were in direct contact with the blood in the pulmonary artery, which not being likely, gives rise to the possibility of the origin of hyperpnoea from receptors from somewhere further downstream or from a site that is accessible from the capillary circulation (in so short an interval).

The observations that advocate the possible involvement of pulmonary baroreceptors, cannot, however, preclude the role of vagal receptors in the pulmonary bed, which must also experience the rise in pressure and an increase in flow. This was never more obvious in Bevan's study (27) and is discussed further in a later section.

c. Receptors near pulmonary capillaries

From the latency of response to the stimulus of releasing the occluded blood, Mills concluded that the site of origin of the hyperpnoea was located somewhere in the pulmonary capillaries. The following had been concluded from earlier experimentations: receptors in the pulmonary vascular bed gave rise to the marked tachypnoea that arose reflexly, as a result of multiple pulmonary embolism and also that it required intact vagi. This was supported by two key clinical observations that (i) pulmonary congestion was always accompanied by dyspnoea (29), and (ii) in cases of primary sclerosis of the pulmonary arteries there is no evidence of dyspnoea, suggesting that receptors proximal to the pulmonary arteries are not involved in the reflexes (30).

In 1955, Paintal (31) identified receptors near the pulmonary vasculature that were

located specifically near the alveoli and accessible only through the venous circulation. These, referred to as the juxtapulmonary capillary (J) receptors, are stimulated by certain drugs and chemicals (especially phenyl diguanide or PDG) injected intravenously and by an increase in interstitial volume (32, 33). A noteworthy stimulation of the J receptors is also produced by pulmonary congestion produced by phosgene gas (34). The respiratory reflex effects that they give rise to consist of tachypnoea followed by an apnoea or the two occurring in reverse sequence.

But most importantly, in cats the activity of J receptors increases significantly (from a near zero resting value to 0.75 impulses/sec) when pulmonary blood flow is increased by 133%, i.e. twice cardiac output (35). This level of increase in their activity is normally seen accompanying an injection of phenyl diguanide that causes a 40–140% increase in ventilation (36). In addition to reflex respiratory acceleration, stimulation of J receptors in human subjects by injecting an alkaloid, lobeline intravenously, gives rise to certain sensations that are typically confined to the upper respiratory (chest) areas (37). The foregoing conclusion was inevitable as the respiratory reflexes and sensations occur within a few seconds of each other. Furthermore, they demonstrated quite clearly that the other predominant group of lung receptors—the pulmonary stretch receptors had no role to play in the perception of the lobeline-induced respiratory sensations.

Respiratory reflexes and sensations after pulmonary denervation

The above observations and conclusions have also been reaffirmed in patients who

had recent bi lateral lung transplants (28). In them, lobeline injected intravenously does not give rise, either to respiratory reflexes or to respiratory sensations in the same manner (qualitatively or quantitatively) as it does in normal subjects. Thus it is quite apparent that an intact pulmonary vagal innervation is vital for above mentioned respiratory reflexes to occur and the accompanying sensations to be felt. The presence of lobeline-induced sensations in heart transplant subjects, who were also studied similarly in this investigation provides further proof that they do not arise from any receptors in the region of the heart or from any major blood vessels arising from it.

It is crucial that we review the hypothesis put forward by Moore et al. (26) in the light of the above findings on lung and heart transplant patients. These investigators have assigned a central role to the pulmonary artery baroreceptors in influencing ventilation when stimulated by a rise in pulmonary artery pressure that is produced by the increased cardiac output during exercise.

Exercise studies after pulmonary denervation

It is fairly well established that the ventilatory response to exercise is exaggerated still further in patients with pulmonary hypertension (38, 39). Theodore et al (38) conducted an exercise study on patients with pulmonary hypertension, before and after they underwent heart-bilateral lung transplantation (HLT) and compared the data obtained from them with that from normals and those patients who had undergone only heart transplantation (HT). The criterion of the slope of minute ventilation over carbon dioxide production i.e. (VE/VO_2) was used to express a change

in the ventilatory response. They observed that in response to exercise, an increase in ventilation after HLT was much reduced compared to that obtained before surgery and in addition it was not too different from that of the normals. On the other hand, the increase in ventilation in response to exercise in HT patients was comparable to the values obtained before their surgery. Two obvious conclusions can be drawn from these finding: (i) cardiac receptors including pulmonary baroreceptors are not the site of origin of the augmented ventilation seen during exercise, and (ii) pulmonary sensory receptors are more likely to have been stimulated by a rise in pulmonary blood flow, although they had been deafferented in this situation. The important point to note was that the haemodynamic changes related to pulmonary hypertension were also no longer present.

In Theodore et al's (38) view since both pulmonary hypertension and pulmonary afferent innervation are absent in HLT and no augmentation of ventilation is recorded in response to exercise, this issue can only be resolved by conducting neurophysiological studies. One such study was the one undertaken by Butler et al. (28). In the foregoing account, it has been elaborated upon that in subjects with deafferented lungs (especially recent ones) – neither respiratory sensations nor respiratory reflexes are evoked by injecting lobeline i.v. These findings thus attribute this function to pulmonary sensory receptors albeit with intact innervation. The above conclusion is also supported by the observations of Pfeiffer et al. (40) on respiratory sensations evoked by loaded breathing in lung transplant subjects. The intensity of sensations (Borg scale score) in relation to

the stimulus provided in the form of increasing peak inspiratory mouth pressure - expressed as a correlation coefficient, was reduced in subjects after they had undergone lung transplantation. This was also accompanied by, as expected, reduced ventilatory response to loaded breathing.

From the various studies discussed, it is obvious that neither pulmonary baroreceptors which may be stimulated significantly by the increased blood flow nor pulmonary CO₂ receptors (?) that may be stimulated by the

increased CO₂ flow, are likely to mediate the increase in ventilation seen during exercise.

The foregoing discussion inevitably strengthens Mills' observations made sixty years ago, that when pulmonary blood flow increases due to an increase in cardiac output (with exercise), it stimulates sensory receptors lying near the pulmonary vasculature, that reflexly augment ventilation. Further evidence in support may be provided by studies that include subjective data of responses.

REFERENCES

1. Krogh A, Lindhard J. The regulation of respiration and circulation during the initial stages of muscular work. *Journal of Physiology* 1913; 47: 112-136.
2. McCloskey DI, Mitchell JH. Reflex cardiovascular and respiratory responses originating in exercising muscle. *Journal of Physiology* 1972; 224: 173-186.
3. Åstrand P-O, Cuddy TE, Saltin B, Stenberg J. 1964. Cardiac output during submaximal and maximal work. *Journal of Applied Physiology* 1964; 10: 268-274.
4. Boone T, Foley M. Effect of venous return on respiratory response. *Journal of Sports Medicine and Physical Fitness*. 1991; 31: 249-256.
5. Mills JN. Hyperpnoea produced in man by sudden release of occluded blood. *Journal of Physiology* 1944; 103: 244-252.
6. Habak PA, Mark AL, Kioschos M, McRaven MD, Abboud FM. Effectiveness of congesting cuffs ("rotating tourniquets") in patients with left heart failure. *Circulation* 1974; 50: 366-371.
7. Klein HO, Brodsky E, Ninio R, Kaplinsky E & Di Segni E. The effect of venous occlusion with tourniquets on peripheral blood pooling and ventricular function. *Chest* 1993; 103: 521-527.
8. Danzer CS. The pathogenesis and treatment of dyspnoea in the light of recent experiments. *Annals of Internal Medicine* 1928; 2: 239-247.
9. Kountz WB, Smith JR, Wright ST. Observations on the effect of tourniquets on acute cardiac crises, normal subjects and chronic heart failure. *American Heart Journal*. 1932; 23: 624-636.
10. Innes JA, Solarte I, Huszczuk A, Yeh E, Whipp BJ, Wasserman K. Respiration during recovery from exercise: effects of trapping and release of femoral blood flow. *Journal of Applied Physiology* 1989; 67: 2608-2613.
11. Lawler JM, Cline CC, O'Kroy JA, Coast JR. Effects of inspired O₂ and CO₂ on ventilatory responses to LBNP-release and acute head-down tilt. *Aviation Space & Environment Medicine* 1995; 66: 751-756.
12. Robb GP, Weiss S. 1933. A method for the measurement of the velocity of the pulmonary and peripheral venous blood flow in man. *American Heart Journal* 1933; 8: 650-670.
13. Wasserman K, Whipp BJ, Castagna J. Cardiodynamic hyperpnoea: secondary to cardiac output increase. *Journal of Applied physiology* 1974; 36: 457-464.
14. Phillipson EA, Murphy E, Kozar LF, Schultze RK. Role of vagal stimuli in exercise ventilation in dogs with experimental pneumonitis. *Journal of Applied Physiology* 1975; 39: 76-85.
15. Phillipson EA, Hickey RF, Bainton CR, Nadel JA. Effect of vagal blockade on regulation of breathing in conscious dogs. *Journal of Applied Physiology* 1970; 27: 475-479.
16. Brown HV, Wasserman K, Whipp BJ. Effect of beta-adrenergic blockade during exercise on ventilation and gas exchange. *Journal of Physiology* 1976; 41: 886-892.
17. Green JF, Sheldon MI. Ventilatory changes associated with changes in pulmonary blood flow

- in dogs. *Journal of Applied Physiology* 1983; 54: 997-1002.
18. Bianconi R, Green JH. Pulmonary baroreceptors in the cat. *Archives Italia Biologica* 1959; 97: 305-315.
 19. Coleridge JCG, Kidd C. Electrophysiological evidence of baroreceptors in the pulmonary artery of the dog. *Journal of Physiology* 1960; 150: 319-331.
 20. Coleridge JCG, Kidd C. Relationship between pulmonary arterial pressure and impulse activity in pulmonary arterial baroreceptor fibres. *Journal of Physiology* 1961; 158: 197-210.
 21. Kan WO, Ledsome JR, Bolter CP. Pulmonary arterial distension and activity in phrenic nerve of anaesthetized dogs. *Journal of Applied Physiology* 1979; 46: 625-631.
 22. Ledsome JR, Kan WO, Bolter CP. Respiratory and cardiovascular responses to temperatures changes in the perfused pulmonary arteries of the dog. *Canadian Journal of Physiology & Pharmacology* 1981; 59: 493-499.
 23. Lloyd TC. Jr. Effect on breathing of acute pressure rise in pulmonary artery and right ventricle. *Journal of Applied Physiology* 1984; 57: 110-116.
 24. Lloyd TC. Jr. Control of breathing in anaesthetized dogs by a left heart baroreflex. *Journal of Applied Physiology* 1986; 61: 2095-2101.
 25. Moore JP, Hainsworth R, Drinkhill MJ. Pulmonary arterial distension and vagal afferent nerve activity in anaesthetized dogs. *Journal of Physiology* 2004a; 553: 805-814.
 26. Moore JP, Hainsworth R, Drinkhill MJ. Phasic negative intrathoracic pressures enhance the vascular responses to stimulation of pulmonary arterial baroreceptors in closed chest anaesthetized dogs. *Journal of Physiology* 2004b; 553: 815-824.
 27. Bevan JA. Action of Lobeline and Capsaicine on afferent endings in the pulmonary artery of the cat. *Circulation Research* 1962; 10: 792-797.
 28. Butler JE, Anand A, Crawford MR, Glanville AR, McKenzie DK, Paintal AS, Taylor JL, Gandevia SC. Changes in respiratory sensations induced by lobeline after human bilateral lung transplantation. *Journal of Physiology* 2001; 534: 583-593.
 29. Weiss S, Robb GP. Cardiac Asthma (paroxymal cardiac dypnoea). *Journal of American Medical Association* 1933; 100: 1841-1846.
 30. East T. Pulmonary hypertension. *British Heart Journal* 1940; 2: 189-200.
 31. Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of these receptors to phenyl diguanide, potato starch, 5-hydroxytryptamine and nicotine, and their role in respiratory and cardiovascular reflexes. *Quarterly Journal of Experimental Physiology* 1955; 40: 89-111.
 32. Paintal AS. Mechanism of stimulation of type J pulmonary receptors. *Journal of Physiology* 1969; 203: 511-532.
 33. Paintal AS. Vagal sensory receptors and their reflex effects. *Physiological Reviews* 1973; 53: 159-227.
 34. Anand A, Paintal AS, Whitteridge D. Mechanisms underlying enhanced responses of J receptors of cats to excitants in pulmonary oedema. *Journal of Physiology* 1993; 471: 535-547.
 35. Anand A, Paintal AS. Reflex effects following selective stimulation of J receptors in the cat. *Journal of Physiology* 1980; 29: 553-572.
 36. Anand A, Loeschke HH, Marek W, Paintal AS. Significance of the respiratory drive by impulses from J receptors. *Journal of Physiology* 1982; 325: 14.
 37. Raj H, Singh, VK, Anand, A, Paintal, AS. Sensory origin of lobeline-induced sensations : a correlative study in man and cat. *Journal of Physiology* 1995; 482: 235-246.
 38. Theodore J, Robin ED, Morris AJR, Burke CM, Jamieson MB, VanKessel A, Stinson EB, Shumway NE. Augmented Ventilatory response to exercise in pulmonary hypertension. *Chest* 1986; 89: 39-44.
 39. Schwaiblmair M, Reichenspurner H, Muller C et al. Cardiopulmonary Exercise testing before and after lung and heart-lung transplantation. *American Journal of Respiratory and Critical Care Medicine* 1999; 159: 1277-1283.
 40. Peiffer C, Silbert D, Cerrina J, Laduri FL, Dartvelle P, Chaplier A, Herve P. Respiratory sensation related to resistive loads in lung transplant recipients. *American Journal of Respiration & Critical Care Medicine* 1996; 154: 924-930