Sensing vascular distension in skeletal muscle by slow conducting afferent fibers: neurophysiological basis and implication for respiratory control

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Haouzi, Philippe, Bruno Chenuel, and Andrew Huszczuk. Sensing vascular distension in skeletal muscle by slow conducting afferent fibers. J Appl Physiol 96: 407–418, 2004; 10.1152/japplphysiol.00597.2003.—This review examines the evidence that skeletal muscles can sense the status of the peripheral vascular network through group III and IV muscle afferent fibers. The anatomic and neurophysiological basis for such a mechanism is the following: 1) significant portions of group III and IV afferent fibers have been found in the vicinity and the adventitia of the arterioles and the venules; 2) both of these groups of afferent fibers can respond to mechanical stimuli; 3) a population of group III and IV fibers stimulated during muscle contraction has been found to be inhibited to various degrees by arterial occlusion; and 4) more recently, direct evidence has been obtained showing that a part of the group IV muscle afferent fibers is stimulated by venous occlusion and by injection of vasodilatory agents. The physiological relevance of sensing local distension of the vascular network at venular level in the muscles is clearly different from that of the large veins, since the former can directly monitor the degree of tissue perfusion. The possible involvement of this sensing mechanism in respiratory control is discussed mainly in the light of the ventilatory effects of peripheral vascular occlusions during and after muscular exercise. It is proposed that this regulatory system anticipates the chemical changes that would occur in the arterial blood during increased metabolic load and attempts to minimize them by adjusting the level of ventilation to the level of muscle perfusion, thus matching the magnitudes of the peripheral and pulmonary gas exchange.

THE INCREASE IN OXYGEN DELIVERY TO THE MUSCLES, as well as the removal of CO₂ and heat, during muscular exercise relies on a complex interaction between the cardiovascular and the ventilatory gas exchange functions. Indeed, both systems are involved immediately and act in concert during exertion (14, 91) to minimize the acid-base perturbations in peripheral tissues by increasing local blood flow (36, 77) and to maintain arterial blood gas homeostasis by increasing alveolar ventilation in proportion to the rise in pulmonary oxygen uptake (V̇O₂) and in CO₂ output (V̇CO₂) (for review, see Refs. 13, 15, 87, 90). On the basis of this integrative view of the regulation of gas exchange in the body, a close link or coordination between the ventilatory and cardiovascular control systems has long been postulated (32, 53).

Two groups of mechanisms have been proposed to account for such a profound interplay between ventilatory and cardiovascular functions. The first group of mechanisms (see Refs. 16, 18, 91 for discussion) assumes that the cardiovascular and the respiratory responses are functionally linked through a parallel activation from either a peripheral, i.e., through muscular afferent signal (10, 45, 48, 57, 65, 82), or from a central origin (19, 53, 81). The second category of putative mechanisms proposes that some factor(s) proportional to the increased gas exchange rate during exercise (the product of blood flow and the volume of oxygen extracted or, more likely, the CO₂ produced) can trigger a ventilatory response with no chemical error signal at arterial level (13, 46, 87, 89, 90). The coupling between ventilation and factors related or proportional to the gas exchange rate is obvious when the changes in V̇O₂ and V̇CO₂ are dissociated from the motor act by imposing an exercise with fluctuating work rate (WR) at different frequencies (9). When the frequency of such a sinusoidally fluctuating WR increases, the amplitude of the minute ventilation (V̇E) response decreases and the phase lag increases, following V̇O₂ and V̇CO₂ responses, despite similar WR amplitude (see Refs. 9 and 91 for review). The search for a CO₂ flow-related control mechanism of respiration proportional to the flow of blood leaving the exercising tissues and located in the central circulation has, however, turned out to be rather inconclusive (see Ref. 90 for discussion). Neither the mechanoreceptors located in specific sites of the cardiovascular system, i.e., the right heart (42, 52, 83) or the pulmonary circulation (43, 55), nor the CO₂ or pH oscillations of the blood leaving the lungs (4, 94) seem to be capable of fully accounting...
for the isocapnic adjustment of ventilation to the rate of incoming CO2-loaded blood (5, 38, 39, 40, 44).

This review presents and discusses indirect and direct experimental evidence suggesting an alternative site of coupling between respiratory control and circulation. On the basis of animal and human studies, in which the peripheral circulation was altered at rest and during or after muscular exercise (29, 31, 37), it was considered that the change in volume of the postcapillary and/or venous network in the skeletal muscles produced by a vasodilation or by a venous blockade could affect Vt. These observations led us to look more carefully into the possibility that a source of ventilatory stimulation may reside in the skeletal muscles, transmitted by group III and IV muscle afferent fibers (for review, see Refs. 48, 63, 65) but acting through a circulatory-linked stimulus of a mechanical nature (27).

This paper first summarizes the neurophysiological and anatomic basis supporting the contention that skeletal muscles are equipped to sense the degree of distension of the peripheral vascular structures, primarily at the venular level. It then looks at how, from the data obtained by means of single-fiber recording, sensing local distension at the venular side of the peripheral vascular bed by individual fibers could be used in the central nervous system to monitor the recruitment of the postcapillary network, giving an image of blood flow changes.

Finally, we shall examine and discuss how such receptive properties could prove to be a relatively simple mechanism that could contribute 1) to the ventilatory responses to acute changes in the status of the peripheral vascular bed in humans and animals, and 2) to the control of respiration during exercise and at rest.

ON THE RECEPTIVE PROPERTIES OF GROUP III AND IV AFFERENT FIBERS FROM MUSCLES AND TENDONS

Overview. Skeletal muscle afferent fibers are traditionally divided into four groups according to their conduction velocity and, therefore, their degree of myelination. Group I and II fibers are the largest myelinated fibers that innervate muscle spindle and tendon organs; their contribution to exercise hyperpnea has been suggested (7, 13, 23) but remains uncertain (35, 45, 48, 57, 82). It is only recently that the receptive properties of the group III and IV muscle afferent fibers (i.e., small myelinated or unmyelinated fibers) have been more carefully and systematically analyzed (33, 47, 49–51, 54, 59–61, 63). The traditional view is that 1) both of these types of muscle afferent fibers can trigger respiratory and circulatory responses (see Ref. 48 for review) and 2) the mechanical deformation of their receptive field (mechanoreception) during contraction (50, 51, 54, 61, 67), the accumulation of metabolic by-products of exercise (51, 61, 72, 74, 78), a local inflammation (60, 62, 63), and the rise in muscle temperature (33, 54, 59, 61) represent their main source of stimulation.

On the basis of the responses of a large number of muscle group III and IV receptors to these stimuli, different types of behaviors have been described (51, 63). A large number of receptors respond exclusively to noxious stimuli but not to contractions (22, 63) and are regarded as true nociceptors (60). Typically, these muscle nociceptors do not respond to light pressure or stretch, but they increase their discharge rate when noxious mechanical pressure is applied or when bradykinine is injected locally. Some of them also respond to thermal stimuli in the noxious range. Thus it was logically proposed that a population of group III and IV endings plays the physiological role of mediating muscle pain.

Other groups of receptors are activated by muscle contractions and some of the "metabolic products" released during exercise (51), whereas a significant number of group III and IV endings respond predominantly to mechanical stimuli (50, 51, 59, 63). The behavior of many of these two last groups of endings raises, however, intriguing questions as to the physiological factors that could activate them during or after contractions. These observations, which are presented in the following paragraphs, open up the possibility that, besides their response to the deformation (tension) of the muscles, alternative modes of mechanical stimulation exist for many of these endings.

What do we know about their mechanosensitivity? Mechanical stimulation, including stretching of the muscle or the muscle tendon and application of a direct pressure on the muscle, stimulates a variable proportion of group III and IV muscle afferent fibers. The percentage of fibers responding to mechanical stimulation varies considerably between group III and IV and between studies (51, 59, 61, 67). For example, whereas Paintal (67) found no group III endings responding to stretch, according to Mense and Stähnke (61), 43% of group III fibers are excited by stretching the tendon. They typically display an overshoot response followed by an adaptation. About 17% of group IV fibers are stretch-sensitive units, and they usually respond with a much slower time course.

There is no strict overlap between fibers responding to stretching and pressure (59, 61). A light pressure or squeeze applied to a muscle or tendon stimulates up to 19% of group IV and 44% of group III endings (59). Different figures were reported in other studies. For instance, Franz and Mense (22) found only 9–10% of low-pressure-sensitive group IV units [low-threshold (LT) units]. In all these studies, the number of group IV fibers responding to light pressure is definitely lower than for group III. It is worth noting that bradykinin, which is able to stimulate more than half of the group III and IV muscle afferent fibers, activates LT units without increasing their sensitivity to pressure (22, 63). Intriguingly, the increased activity of LT units induced by bradykinin typically remains below the level of activity triggered by a light pressure, even when large doses of bradykinin are used. This point will be discussed later.

The proportion of units responding to heavy or painful pressure caused by squeezing the muscle (high-threshold units) can be as high as 43% of group IV and 33% of group III fibers (59). Many of these endings are thus regarded as nociceptors due to the concordance with their response to injection of algesic agents (60, 62). Examples are shown in Fig. 1.

Effects of muscle contractions. The responses to contraction, which combines mechanical and chemical or metabolic factors, are difficult to summarize since they appear to be highly dependent on the type of contraction and the protocol chosen (49, 50, 59, 61).

During electrically induced rhythmic contractions (59, 61), it was shown that only a small portion of fibers is stimulated (from 23 to 36% for group III and from 19 to 31% for all group IV fibers), which intriguingly represents few of the actual mechanically sensitive units. Two types of behavior exist:
walking induced by hypothalamic locomotor center stimulation. They found that the light rhythmic contractions of the triceps surae muscles needed for walking were associated with the stimulation of a very large number of group III and IV fibers despite the low intensity of the contractions. The question remains as to the nature of the stimulus, which activates such a large proportion of group IV fibers despite very light contractions.

**Effects of arterial occlusion during muscle contractions.** The effects of occluding the arterial supply to the contracting muscles on the activity of group III and IV muscle afferent fibers have been the subject of several studies (49, 61). This experimental approach was intended to mimic what may happen during very heavy exercise or in certain pathophysiological conditions associated with an extreme imbalance between oxygen supply and demand to trigger a muscle “chemoreflex” (45).

The response of group III and IV muscle afferent fibers to arterial occlusion is far from being unequivocal. During electrically induced rhythmic muscle contraction, Mense and Stahnke (61) found that a new group of fibers, predominantly belonging to group IV but different from Csm or Csx fibers, were stimulated by an acute reduction of the arterial supply to the contracting muscles (Fig. 2). This activation was intense and typically occurred after a 40- to 60-s delay, which might correspond to the delay after which contractions may become painful after a similar maneuver in humans.

However, if we look at the behavior of the Csm or Csx fiber responses, a very different picture emerges. The Csm and Csx fiber activity did not change during contraction with occlusion of the arterial supply and on several occasions decreased (Fig. 3). Although this phenomenon was associated with a reduction in muscle tension, a decrease in activity was also observed in the Csx fibers, which did not respond in proportion to the level of muscle tension (Fig. 3). Similar findings were reported during static contractions by Kaufman et al. (49). They found that 1) occluding the arterial supply to a contracting muscle increased the activity of units that were silent during normal contraction (7 of 22 “noncontraction sensitive” fibers); 2) in contrast to dynamic contractions (Fig. 3), some fibers already stimulated by a static contraction (mostly belonging to group IV) were more activated by ischemic contractions (10 of 32 “contraction sensitive” fibers); and 3) 19% of group III and IV fibers, which were activated during static contraction, had less action potentials when contractions were applied with a total impediment of the arterial supply. This occurred despite muscle tension and force being similar as in a freely perfused condition. It is also interesting to note that in the study of Adriani and Kaufman (2), the ischemic contractions on average did not increase the activity of the group IV muscle afferent that was stimulated during walking.

**Unanswered questions awaiting clarification.** The above description of the behavior of group III and IV mechanosensitive units raises several questions and remarks, which may be summarized as follows.

First, the distinction between LT and high-threshold units is derived from the response to mechanical pressure or to squeezing applied externally on the muscle. Such an experimental approach may underestimate the proportion of fibers responsive to light mechanical stimuli due to their deep location within the muscle. Heavy external stimuli may thus be needed.
additional stimulation of already activated fibers (49) related to noxious stimuli, may mask or even oppose the response of some of those endings that were stimulated during normal contraction but depressed during arterial occlusion. There is very little additional information on such an inhibitory response, and we are left with no explanation of the nature and the exact proportion of fibers that respond by reduced activity during contraction with an occluded circulation.

Finally, the question remains of what stimulates such a large number of group III and IV fibers during walking (1, 2, 68) when no metabolic factors appear to play a significant role and no excitatory effect is produced by local ischemia.

We shall propose and try to illustrate that some of these behaviors could be accounted for by fibers whose activity is related, through a purely mechanical factor, to the level of vascular distension. Such a mechanism of stimulation along with the location of the group III and IV muscle afferent fibers, i.e., their relationship with the venular vessels, offers an interesting receptive property for many mechanosensitive units as monitors of peripheral vascular network recruitment.

ON THE ANATOMIC LOCATION OF GROUP III AND IV MUSCLE AFFERENT ENDINGS IN THE MUSCLE

Very few studies have been done on the anatomic description of how group III and IV muscle afferent fibers “end” or rather “originate” in the muscle structures. One of the first systematic descriptions of the distal connections of free nerve endings was done by Stacey (79) in deafferentated and sympathectomized hindlimb muscles of the cat. He found that 1) 75% of the total sensory component consists of free nerve endings, 2) muscle afferents are traveling only along large intramuscular and vascular trunks (following the vascular tree), and 3) branching of unmyelinated nerve fibers is predominantly seen in the vascular nerve trunks that form anastomosing plexi closely associated with the branching arterioles and venules. The smaller nerve fibers produced by this division eventually leave the nerve trunk and the vascular vessels to end freely in the muscle. Intramuscular nerve trunks also branch to form free nerve endings in the muscle but appear to be fewer than those originating from the vascular trunks. Although there is a large range of termination sites within the muscle structures, many group III and IV fibers are found in the blood vessel adventitia, including the arterioles and venules. Some axon terminals lie both in the connective tissue and the adven-

to distort their receptive field, whereas a light stimulus would be sufficient if applied directly on it or in its immediate vicinity. Moreover, as pointed out by Mense (63), the direction of the deformation is of importance for several group IV fibers, which appear to possess “direction sensitivity.” The exact proportion of LT group III and IV fibers remains to be established with respect to these remarks.

Second, why does bradykinin stimulate the LT group III and IV fibers with an activity that is typically lower than that triggered by light mechanical pressure (22)? Can some of these endings be stimulated by a transduction mechanism other than a “metabolic” one, such as, for example, that resulting from the vascular effect of bradykinin, which relaxes vascular smooth muscles?

Third, the behavior of the fibers that 1) respond to contraction with a “long” time constant and 2) display a lower activity during contraction with an occlusion of the arterial supply is obviously incompatible with a metaboreception mechanism (Fig. 3). The violent activation by ischemic contractions of a different population of group III or IV fibers (61), or the

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Fig. 2. Examples of responses of group IV afferent fibers with receptive field in the triceps surae of the cat during electrically induced rhythmic contractions (A) and during static contractions (B and C). Responses were studied with freely perfused muscles (a) and during occlusion of the arterial supply to the triceps muscle (b). Note that, in A and B, endings belong to a population of receptors that is not stimulated during control contractions but is activated after a 40- to 60-s delay by ischemic contractions. In C, during static contractions, ischemia can magnify, after a delay, the response of some endings already stimulated. (A from Ref. 61 and B and C are from Ref. 47, with permission.)
lymphatic vessels running parallel to them. The cross-sectional vessels (for both groups), the arterioles (for bers end directly within the adventitia of the small venous papers, they found that a large proportion of tendon of sympathectomized cats in two reports. In both papers, they described in great detail the ultrastructure of group III and IV nerve terminals by Von Düring and Andres (84, 85). (From Ref. 79 with the permission of the Journal of Anatomy, see original for additional definitions.)

and Andres (84, 85) showed that the endings found in the adventitia of the arteries were mostly group III, whereas group IV endings were located close to the arterioles and, more importantly, close to the venular vessels.

Similarly, a large portion of group III afferent fibers innervating the Achilles tendon (3) forms lanceolate terminals in the collagenous and elastic fiber system of the adventitia of the small veins, suggesting that it is “the mechanical tension in the circumference of the vessel which may be registered.” Although group IV endings lack lanceolate profiles, many of them run in the direct neighborhood of venule vessels. In the case of both the muscles and the tendons, the remainder of group III and IV fibers can be found within the endoneurial tissue or in the connective tissue. Finally, some group III fibers have an arborization in the connective tissue surrounding the nerve vessel complex with an arrangement resembling the organ of Golgi-tendon, suggesting that they behave as mechanoreceptors.

**DIRECT EVIDENCE THAT GROUP III AND IV MUSCLE AFFERENT FIBERS RESPOND TO DISTENSION OF THE VASCULAR STRUCTURES**

Neural responses to vasodilatory agents and venous occlusion. All of the following data were obtained from the study of afferent impulses arising from endings in the triceps surae muscles in the cat (27). They were recorded from the L7 and S1 dorsal roots in anesthetized cats. Thirty-six group IV and 12 group III fibers were tested in response to an acute distension of the hindlimb venous system by means of an occlusion of the vena cava (Fig. 5). Twenty percent of the group IV and 16% of the group III fibers tested were stimulated during venous blockade (Fig. 5). In some fibers, the activity increased after a delay and remained ele-

Fig. 4. Schematic representation of the afferent innervation of deafferentated and sympathectomized skeletal muscle of the cat. Note that many group III and IV afferents fibers lie in association with arterioles (a.) and venous and ventral structures (v.). These observations have been confirmed by the description of the ultrastructure of group III and IV nerve terminals by Von Düring and Andres (84, 85). (From Ref. 79 with the permission of the Journal of Anatomy, see original for additional definitions.)

Fig. 5. Left: temporal profile of the cumulative histogram of the 7 group IV fibers and the 2 group III fibers (black area) originating in the triceps surae of the cat and responding to venous occlusion (top) and mean venous pressure (bottom). Right: examples of the effects of venous obstruction on the discharge of 1 group IV muscle afferent fiber (conduction velocity 1.3 m/s). A: histogram of activity. B: recording of the activity during time period depicted by the bracket. Thick horizontal bars indicate the period of venous obstruction. The activity of this fiber adapted during venous occlusion. The response to light probing of the belly of the muscle is shown in the inset (horizontal lines). (From Ref. 27, with permission.)
vated throughout the period of occlusion, whereas other fibers responded immediately and adapted to venous occlusion (Fig. 5). In addition, two of the fibers responding to venous occlusion, one belonging to group III and one to group IV, were studied 5–7 min after an injection of isoproterenol at different popliteal blood flow levels. The afferent activity triggered by the venous occlusion was directly proportional to blood flow rate before the obstruction (Fig. 6).

Out of a population of 67 slowly conducting afferent fibers, 31% of group IV and 15% of group III were stimulated by the vascular smooth muscle relaxant papaverine (2–2.5 mg/kg) (Fig. 7). Sixty two percent of the fibers responding to papaverine also responded to isoproterenol (50 μg/kg), and 57% of the fibers stimulated by papaverine also responded to venous occlusion, suggesting that over half of the fibers responding to vasodilatory agents had their receptive field in the vicinity of the venous or venular system. Finally, we observed that most of the group IV fibers that were excited during dynamic contractions of the triceps surae also responded to venous distension or to vasodilatory agents.

What could be monitored at the central nervous system level? As is the case in other mechanosensitive units, only the distortion of the receptive field of a given unit is encoded. Any form of mechanical distension within the vascularized space would therefore appear to constitute potential stimulus for such a receptor (venous occlusion, vasodilatory agent).

Such a mechanism offers the possibility of encoding both the effects of muscle contraction through intramuscular pressure changes (24, 50, 94) and the distension of the venular system (29, 37, 56, 66) during the relaxing phase, thereby monitoring the activity of the veno-muscular pump. From the study described in the previous paragraph, it is reasonable to assume that the fibers, which were stimulated during the venous occlusion, have their receptive field close to the venular side of the microcirculation and respond to the deformation of the venular end of the muscle vasculature. However, such a receptive property may have different physiological implications besides simply monitoring the distension of vascular structures (large veins) (11, 64) because it offers the possibility of encoding the change in peripheral flow. Indeed, a common effect of venous occlusion and vasodilatation, produced physiologically or pharmacologically, is the recruitment, the presurization, and the distension of the venular end of the vascular bed despite the decrease in perfusion pressure in the latter, as shown by Fronek and Zweifach (20).

Sensing the distension of the venular structures by individual fibers in the muscles during peripheral vasodilatation could therefore transmit to the central nervous system an image of the changes in vascular conductance or of the extent of vascular bed perfusion and thus of blood flow. The close relation between the change in conductance and the level of local metabolism could therefore place muscle circulation as a key site of mediation between the regulation of respiration and circulation and peripheral gas exchange.

**IMPLICATION FOR THE RESPIRATORY CONTROL**

Ventilatory effects of a total or arterial occlusion during and after a dynamic muscular exercise. The ventilatory effects of impeding the arterial blood supply to the limbs during or after a muscular exercise have been the subject of considerable controversy. Since Dejours et al.’s classical study was published in 1955 (12), there have been extensive reports that total obstruction of the peripheral circulation, i.e., arterial and venous occlusion, after the cessation of a dynamic exercise speeds up the normal ventilatory decline toward resting levels. Such a reduction in \( V_{\text{E}} \) has been observed during the recovery from light, moderate, or heavy constant WR exercises in humans (26, 28, 41, 73) and in animals (37), leading all of these authors to conclude that intramuscular chemoreception alone does not play a significant role in exercise hyperpnea, i.e., in the absence of muscle contractions (Fig. 8). In addition, the kinetics and magnitude of the drop in \( V_{\text{E}} \) induced by the occlusion could not be explained by the changes in the chemical content of the venous or arterial blood occurring during the vascular obstruction. Indeed, the decrease in the \( V_{\text{E}} \) response during the occlusion is immediate (i.e., beginning at the first breath) (28, 41, 73), was not affected by hyperoxia (41), and

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**Fig. 6.** Effects of venous obstruction on the discharge of 1 group IV muscle afferent (●) and 1 group III (○) fiber originating in the triceps surae of the cat at different flow levels after an injection of isoproterenol. For these 2 fibers, the higher the level of flow before occlusion the greater the neural response to venous distension (personal observation).

**Fig. 7.** Examples of the effects of a bolus intra-aortic injection of papaverine (2.5 mg/kg) on the discharge rate of 2 different group IV muscle afferents of the triceps surae muscles of the cat. A: histogram of activity. B: popliteal blood flow. C: arterial blood pressure (ABP) and recording of the activity during time period depicted by the bracket (D). Vertical arrows indicate the time of injection. Note that the fiber shown at left responds immediately as soon as blood flow increases, and the activity remains elevated as long as the peripheral conductance (blood flow on ABP ratio) is high despite flow returning to the preinjection level. This pattern of response was observed in 1/2 of the responding fibers. In contrast, there is no immediate excitation of the fiber shown at right. This afferent fiber responds after a delay, which was associated with a second rise in blood flow. (From Ref. 27, with permission.)
could not be accounted for by the effects on the arterial chemoreceptors of trapping then releasing metabolites such as CO₂, lactate, or K⁺ (28). Finally, the magnitude of the ventilatory deficit during occlusion was found to be proportional to the level of WR (28). To our knowledge, the only exception is the study of Stanley et al. (80), who reported a stimulation of V̇E during total vascular occlusion but with occlusions performed when the subjects were still contracting their muscles. Total circulatory occlusion (75) applied during rhythmic muscle contractions in humans is painful, or at best unpleasant, and in our experience gives extremely variable responses between subjects. As already pointed out by Dejours (13), the physiological relevance of looking at the effects of V̇E while impeding the arterial supply during exercise in humans is questionable, because the ensuing pain stimuli will elicit a different population of fibers, which does not necessarily play a role in freely perfused muscles (61). This may also be the case during muscle ischemia after static contractions (69) since, according to neurophysiological data, such a maneuver stimulates a new population of fibers (see also Fig. 2). Although this approach is often used to recruit group III and IV endings to activate the sympathetic nervous system and respiration (see Ref. 48 for review), it is of little help to determine the relevant factors affecting muscle ending activity when the contractions are not painful, like during moderate exercise.

Impeding the arterial supply for 60 s at the onset of dynamic contractions in anesthetized dogs blunts the normal ventilatory response (37), as illustrated in Fig. 9. This suggests that before the time of ~1 min, which is needed to stimulate new group III and IV endings during ischemic contractions (47, 61), is reached, the ventilatory effect of impeding the arterial supply to contracting muscles is not a stimulation of breathing but an inhibition. Similar conclusions may be drawn from the study of patients with severe peripheral vascular disease of the lower extremities exercising below their pain threshold (30). Due to the lack of vascular adaptation during muscle contractions, these patients have a delayed VO₂ rise consistently associated with a virtually abolished ventilatory response, despite local ischemia (Fig. 10).

Ventilatory effects of predominant venous blockade. To clarify the mechanisms of the reduction in V̇E produced by an arterial or total vascular occlusion at the onset of, and during recovery from, a constant WR exercise, several studies have tried to dissociate the effects related to the reduction in venous return from the limbs from those consequent to the decrease in peripheral perfusion pressure (9, 26, 29, 56). This was achieved by preventing the rise in pulmonary gas exchange during a metabolic challenge by blocking the venous return without affecting the arterial supply.

Animal studies. Impeding, by intravascular occluders, the circulation either from (venous side) or to (arterial side) the hindlimbs of resting sheep (29) and during electrically induced muscle contractions in dogs (37) leads to opposite ventilatory

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**Fig. 8.** Example of the breath-by-breath minute ventilation (V̇E; A), O₂ consumption (VO₂; B), and end-tidal Pco₂ (Patm; C) data obtained in 1 subject during control recovery (●) from a constant work rate cycloergometer exercise above the lactate threshold and recovery with cuffs inflated for 2 min around the upper thigh at a pressure of 200 Torr (○). The first arrow indicates the cessation of exercise and the moment of cuff inflation; the second arrow indicates the occlusion release. Note that V̇E decline was sped up during cuff occlusion despite expected accumulation of metabolites in the muscle circulation. (From Ref. 28, with permission from Elsevier.)

**Fig. 9.** V̇E and VO₂ responses to electrically induced muscle contractions in anaesthetized dogs in control condition (●) and during occlusion of the iliac arteries (○). The arrow indicates the onset of exercise. Occlusion was maintained during the period depicted by the horizontal bar. Note that impedence of the arterial supply to the contracting muscles reduces the magnitude of the V̇E response to exercise. (From Ref. 37, with permission from Elsevier.)
outcomes. Indeed, despite a similar reduction in VO₂ resulting from obstructing the caudal vena cava or the distal abdominal aorta in anesthetized sheep, ventilation typically rises in the former and decreases in the latter. Similarly, preventing the normal increase in VO₂ at the onset of electrically induced hindlimb muscle contractions in dogs blunts the normal ventilatory response to this type of exercise, whereas releasing the arterial occlusion with an obstructed venous return provoked a hypocapnic stimulation of VE despite no or little contamination of the central circulation downstream of the occlusion (Fig. 11). Because the VE changes occurred either with a VE-to-tocarotid blood pressure ratio out of proportion to the ventilatory component of the arterial baroreflex (29) or with no change in systemic blood pressure (37), it was postulated that circulatory factors acting in concert with, but independently of, the arterial baroreflex (8, 34, 76) depress VE during impediment of the arterial supply to hyperemic muscles and stimulate ventilation when the venous return is obstructed (see Can we reconcile these observations? for additional discussion).

Human studies. In humans, it is much more difficult to distinguish between the effects of a venous and arterial occlusion. Several studies have highlighted that partial impediment of blood flow with lower body positive pressure applied through a pressurized chamber (17, 92) stimulates ventilation. However, any manipulation of the circulation applied during muscle contraction in humans may elicit unspecific nociceptive reflexes, which are not necessarily involved in freely perfused muscles (see discussion on muscle afferent fibers). The separation between metabolic and purely mechanical factors in the resulting VE stimulation is therefore difficult to establish.

An approach that could avoid this problem is to look at the relationship between the pulmonary gas exchange rate and ventilation without muscle contractions. This can be achieved by analyzing the relationship between the delayed rise in VE, VO₂, and VCO₂ triggered by an “impulse” disturbance in the form of a short burst (10–15 s) of a supramaximal exercise. The rise in VO₂, VCO₂, and VE triggered by this “impulse forcing” occurs well after cessation of the contractions (Ref. 21; for review, see Refs. 90, 91). On the basis of the principle of linearity, an impulse forcing, which can be regarded as the first derivative of a constant WR exercise, is expected to trigger delayed ventilatory and metabolic responses, which follow the temporal profile of the first derivative of the response to a step exercise. Indeed, the traditional VE phases I and II (3) are replaced by a sudden and transient increase in VE for a few breaths followed by clearly delayed rises in pulmonary gas exchange and VE (phase II imp), which subside exponentially (21, 25). The second phase of the VE response, therefore, occurs at a time (>20 s into recovery) when neither cortical and subcortical drive to the spinal motoneurons nor muscular contraction-related information is operating. Yet, the VE response is that expected from a step exercise and follows the change in pulmonary gas exchange.

This approach offers the opportunity to study the ventilatory response to exercise while the body is in the peculiar state of being at rest but behaving as if exercising from the metabolic and circulatory point of view (increased cardiac output and high muscle blood flow). Total occlusion of hindlimb circulation during the phase II imp produced a significant reduction in the delayed rise of VE, which normally occurred 20–25 s after the cessation of the contractions (26). In contrast, cuff inflation at a level predominantly impeding venous return while partially maintaining the arterial supply reduced the rise in pulmonary gas exchange in a proportion similar to that during total obstruction but with no reduction in ventilation (Fig. 12).

Can we reconcile these observations? All the above observations support the contention that, when pain or discomfort is prevented, i.e., without nociceptive afferent information being evoked, occlusion of the arterial supply to the muscles during or after contractions depresses ventilation in contrast to what would have been expected from the respiratory muscle metaboreflex. Like the behavior of certain group III and IV endings stimulated during contractions but inhibited by occlusion.

Fig. 10. Changes (Δ) in VE (A), VO₂ (B), and PETCO₂ (C; means ± SE) in 6 normal subjects (left) and 7 patients with very severe vascular disease of the lower extremities (right) during walking. Exercise starts at time 0. Note that VE: phase I is virtually abolished in the patients despite normal locomotor activity. (From Ref. 30, with permission from Elsevier.)

Fig. 11. Example of the ventilatory effects of the occlusion of the iliac arteries and veins at the cessation of an electrically induced hindlimb muscle contraction in 1 anesthetized dog. At the cessation of the contractions (second vertical arrow), both the arterial and venous balloons are inflated (first and second horizontal bar, respectively). The arterial balloon is deflated at the first vertical line, whereas venous return from the hindlimb is kept blocked. This produces a rise in ventilation despite the drop in PETCO₂ and the lack of sustained change in systemic blood pressure (BP). When the venous balloon is deflated, note that VE decreases despite the ensuing hypercapnia. PETCO₂ is PCO₂ at the airways. (From Ref. 37, with permission from Elsevier.)
If the reduction in \( \dot{V}e \) during total or arterial occlusion were to be explained by the “mechanical” consequences of the drop in peripheral pressure, this would imply that an afferent signal of a circulatory nature is indeed operative in physiological conditions and does contribute to the normal control of exercise hyperpnea.

The description of the ventilatory response to a constant WR exercise of moderate intensity is that, after an initial increase by several liters per minute, \( \dot{V}e \) phase I (13, 14, 16) ventilation rises exponentially (\( \dot{V}e \) phase II) toward a steady state, which is reached within 3 min (89, 91). The most striking observation is that ventilation appears to very closely follow \( \dot{V}CO_2 \) measured at the mouth (90). The result of such a coupling is that arterial \( PCO_2 \) does not increase during a dynamic exercise (13, 15, 91), suggesting a feed-forward rather than a feedback regulatory mechanism. Similar conclusions can be drawn from the responses to other types of input forcing such as a sinusoidal (9) or an impulse exercise (26, 91).

As already briefly discussed in the introduction, many different concepts have been proposed to account for \( \dot{V}e \) temporal profile during a dynamic exercise, from a parallel activation of locomotion and respiration with a short-term potentiation phenomenon (18) to feed-forward peripheral factors related or proportional to the metabolic rate at the muscle or at the central circulation levels (15, 18, 87, 90). Although any rapid neural signal originating from supraspinal sites or arising from the muscles could account for \( \dot{V}e \) phase I, it is difficult to reconcile most of the observations made on this initial response with a signal strictly related to the motor act. For example Bell et al. (6) found that passive exercise produces a significant \( \dot{V}e \) phase I only when passive movements were associated with an immediate increase in pulmonary \( VO_2 \) and \( VC02 \). Similarly, the blunted initial ventilatory phase I response in the supine position (88), as well as the dramatic reduction in this phase in patients with impeded arterial supply to the lower extremities (30), suggest that even during this initial phase, factors unrelated to the motor effects of the contractions or their command are involved (Figs. 9 and 10). The known temporal profile of the muscle blood flow changes (58, 71, 77, 86), i.e., with its abrupt increase, is compatible with the immediate rise in ventilation (phase I) when exercise is started from rest (Fig. 13) and could perfectly account for the above observation, i.e., a phase that can be affected by the magnitude of vascular response to contractions. It is worth noting that muscle blood flow does increase during passive movements (71).

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**Fig. 12.** Effects on ventilation and \( VO_2 \) of suprasystolic vascular occlusion (left) and partial occlusion (right) applied for 90 s just after the cessation of an impulse change in work rate (400 W for 12 s). Data are means ± SD of 12 tests performed in 6 subjects. The control tests are shown in thick lines, whereas the occlusion tests are shown in dotted lines. The period of exercise is indicated by the 2 vertical dotted lines. The period of occlusion is depicted by the thick horizontal bar. Note that, despite similar reduction in \( VO_2 \) during total and partial (venous) occlusion, ventilation is dramatically depressed during total occlusion but not during partial occlusion. (From Ref. 26, with permission.)

**Fig. 13.** Mean \( VO_2 \) (dotted line) and leg blood flow (solid line) responses to a constant work rate exercise in supine position (40 W). Note the immediate increase in blood flow (as soon as the exercise starts) and the exponential increase in blood flow preceding, but resembling, \( V02 \) phase II and reaching a steady state within 2 min. (From Ref. 58, with permission.)
The second (exponential) rise in \( \dot{V}_{E} \) (phase II) has a 50- to 60-s time constant and follows the exponential like increase in \( \dot{V}_{O_2} \) and \( \dot{V}_{CO_2} \). This phase was first proposed to be humorally mediated (13), but no satisfactory candidate has been found yet to account for this response. Because even in the absence of feedback information, ventilation can increase exponentially in response to a steady stimulus (see Ref. 18 for review), \( \dot{V}_{E} \) phase II has been suggested to be explained by the intrinsic properties of the respiratory neurons responsible for a short-term potentiation phenomenon. This phenomenon was proposed to slow and magnify the effects of a centrally mediated stimulus to breathe, which was immediate and, therefore, had no measurable time constant (19). According to such a model, it would be difficult for the ventilatory outcome to follow \( \dot{V}_{O_2} \) and \( \dot{V}_{CO_2} \); the original signal having no relationship with any of these factors being proportional to the motor act. In addition, results obtained from both sinusoidal and impulse exercise do not support a significant contribution of a system producing a parallel activation of respiration and locomotion during \( \dot{V}_{E} \) phase II (Refs. 9, 25, 26, and Ref. 90 for discussion). It should, however, be kept in mind that a short-term potentiation phenomenon has also been described during the stimulation of the sciatic or the sinus nerves (see Ref. 18 for review). This mechanism could therefore slow the ventilatory outcome resulting from any rapid signal coming from a peripheral source. Muscle blood flow phase II has a response faster than, but with a similar temporal profile as, \( \dot{V}_{O_2} \) measured at the mouth (Fig. 13) and thus faster than the \( \dot{V}_{E} \) response. Its time constant has been reported to be between 28 and 39 s, depending on the position of the body (58). The interaction of the contractions and the local vascular response (which has an exponential pattern similar to that of gas exchange) could produce a signal resulting in a temporal profile compatible with the ventilatory outcome after the filtering and amplifying effects of a short-term potentiation phenomenon at the brain stem level. We propose such a model as a possible way through which ventilation could follow the change in pulmonary gas exchange by anticipating these changes through a peripheral signal of circulatory nature proportional to the local flow of blood.

Worthy of note is that a large proportion of group IV muscle afferent fibers (>50%) has a background resting activity (22, 63). As pointed out by Menese (63), this activity may result from an artifact, since recording the activity of afferent fibers requires the muscle to be exposed surgically. This involves removal of the skin and many hours of performing various types of mechanical manipulations. However, this resting activity is not suppressed by acetylsalicylic acid and thus might not be due to the experimental conditions, which could cause muscle inflammation (62). The functional significance of such a resting activity is therefore unknown. It has been postulated (63) that some of these endings could be cold-sensitive receptors that may display a high level of background activity at normal muscle temperature. This remains to be demonstrated. It is possible that several factors may account for this resting activity, and it could be interesting to determine whether some of these fibers may simply be affected by the degree of resting perfusion pressure or the level of vascular conductance by injecting a powerful vasoconstrictor agent intra-arterially. The question of whether such a background activity, considering the total mass of skeletal muscle of the body, could represent a tonic input to the bulbar respiratory neurons and contribute to the drive to breathe should be clarified.

CONCLUSIONS AND PERSPECTIVES

On the basis of the foregoing observations, we are inclined to propose the following conclusions.

One of the pathways through which the control of breathing may follow varying states of metabolic challenge could be based on neural monitoring of the peripheral vascular events.

The volume of blood occupying the vascular space, likely at venular level in the muscles, is a physiological entity, which is sensed and could constitute the stimulus. The proposed mechanism is therefore of “plethysmometric” nature.

Such a system implies that factors affecting this vascular blood volume due to humoral, mechanical, or circulatory reasons will affect the ventilatory outcome.

The reflex effects of such a system can be masked or opposed by the recruitment of a large population of new fibers during ischemic contractions experimentally produced by affecting the arterial supply. Great care, therefore, should be taken about this issue in all studies dealing with respiratory control and muscle ischemia when transposing conclusions to the behavior of muscle afferent fibers in freely perfused muscles.

Future studies should clarify 1) the effects of combining peripheral vascular distension and muscle contraction on the afferent traffic of slowly conducting afferent fibers during the contracting and the relaxing phases; 2) the interaction of such a system with the arterial baroreflex, allowing the monitoring of both the arterial pressure through the arterial baroreceptors and the degree of recruitment of the muscle peripheral vascular bed [recent results from Potts et al. (70) on the key role played by the nucleus tractus solitarii in the interaction between mechanosensitive muscle afferents and the arterial baroreflex confirm the reality of such an interaction during exercise]; 3) the effects of a specific peripheral vasoconstriction induced pharmacologically during muscular exercise on respiratory control and the afferent neural traffic from the muscles; 4) the implications of such a system on the control of breathing in patients with an increased load to venous return, such as in right heart insufficiency; and 5) the possible role of the resting activity of these endings as a tonic drive to breathe.

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REFERENCES


VASCULAR DISTENSION IN SKELETAL MUSCLE


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