

## **2. Hereditary aspects of respiratory control in health and disease in humans**

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### **2.1 Introduction**

An early step toward discovery of heritable influences on ventilatory control was the finding of differences in the strength of ventilatory responses among human subjects. Here we review observations that these responses tended to be similar among family members and identical twins suggesting a role for heredity and that these effects were most evident for the ventilatory response to hypoxia than to hypercapnia. Findings in humans and animals suggest that the effect is largely on the strength of peripheral chemoreception.

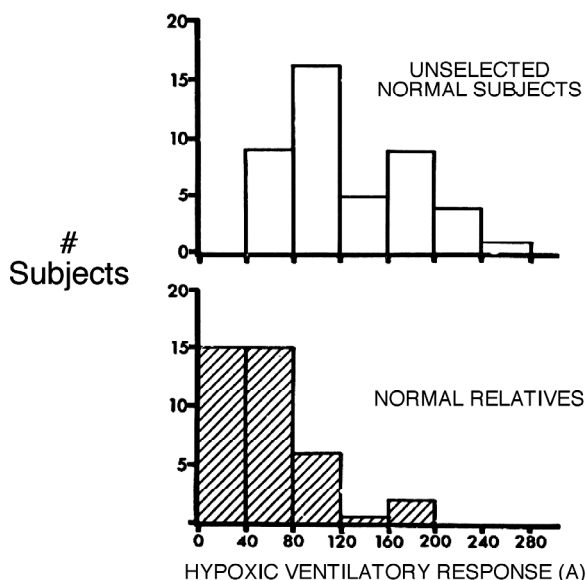
### **2.2 Inter-individual variation in human ventilatory control**

Among the earliest indications of variability in ventilatory response were the findings by Schaeffer [43] of inter-individual differences in the hypercapnic ventilatory response and the later observation by Beral and Read that hypercapnic ventilatory response was decreased in Enga tribesmen of New Guinea compared to Caucasians [6].

Because of the greater dependence of oxygenation on ventilation at high altitude than at sea level, some of the earliest differences in hypoxic ventilatory response were found among individuals with varied breathing and oxygen levels at altitude. Chiodi had found lesser ventilation among natives than sojourners at high altitude in the Andes [13], which lead to the observation by Severinghaus of profound decreases in hypoxic ventilatory response in Andean high altitude natives compared to those in newcomers [47]. The role of chronic hypoxia was under-

scored by the finding of similarly decreased hypoxic ventilatory responses in patients with life-long hypoxemia due to cyanotic congenital heart disease [48]. These findings suggested that hypoxia from birth might be required, but later studies found depressed hypoxic ventilatory response associated with chronic altitude exposure beginning later in life [11; 53].

Early measurements of the hypoxic ventilatory response were calculated from the increase in slope of hypercapnic ventilatory response at a single level of hypoxia compared to that in hyperoxia. The hypoxic response was thus often assessed from only two levels of oxygenation. Subsequently the development of oxygen tension sensors and improved oximeters with real-time control of end-tidal  $\text{PCO}_2$  levels during progressive induction of hypoxia permitted a continuous assessment of the response over a range of oxygen levels. The resulting improved precision afforded the opportunity to detect minor differences in hypoxic ventilatory response both within and among individuals [54].



**Fig. 1.** Upper panel: broad distribution of hypoxic ventilatory responses among normal unselected subjects. Responses were measured during progressive isocapnic hypoxia and expressed as the shape parameter A, an index of steepness of the hyperbolic response. Redrawn from [19]. Lower panel: responses in first degree relatives of endurance athletes, and healthy relatives of patients with idiopathic hypoventilation or chronically hypercapnic chronic obstructive pulmonary disease. The responses in relatives of subjects with low responses or of patients with hypoventilation are shifted to the low end of the spectrum. Drawn from [21]; [39]; [46]; [36]. Figure reproduced with permission from [56].

This led to studies, which showed wide variation of hypoxic ventilatory response among normal subjects at low altitude (Fig. 1, upper panel) [19; 36]. The responses, which measured the relationship of declining end-tidal oxygen tension to rising ventilation under isocapnic conditions, were assessed as the shape parameter, A, which indicates the steepness of the response. Responses spanned a

range broad of seven-fold and were distributed in a non-normal fashion with suggestion of a possibly bimodal configuration.

In addition, hypoxic ventilatory responses at the high and low ends of the range seemed to be found in persons with particular attributes. Low responses were seen in patients with primary hypoventilation (Fig.1 lower panel) [21; 38].

Athletes, most notably those with success in endurance events were also found to have decreased hypoxic ventilatory response compared to non-athletic control subjects [7; 12; 31; 45] although one study found no decrease in marathoners [31]. It is not entirely clear whether decreased hypoxic ventilatory response in endurance athletes is endowed or acquired. Studies indicate that training of unconditioned subjects fails to lower hypoxic ventilatory response [30; 32] although other studies found a decrease [1; 23]. However, no studies have replicated the very long term conditioning of the typical athlete. As indicated below, studies of athlete's families suggest a preexistent contribution independent of training.

The strength of hypoxic ventilatory response has also been linked to performance at high altitude, with high hypoxic responses found in mountain climbers capable of unusually high altitude climbs [33; 44] and low responses in subjects with poor adaptation to altitude manifested as acute mountain sickness [4; 10; 34; 38] or high altitude pulmonary edema [4; 18; 20; 34].

## 2.3 Population and species differences

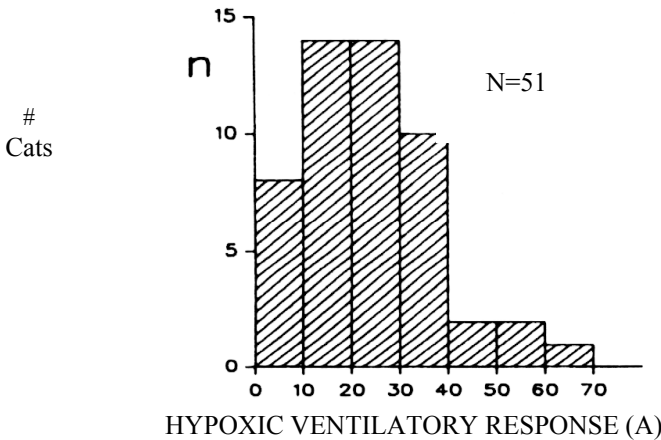
### 2.3.1 Studies in humans

Several reports describe differences in ventilatory control among geographically diverse populations. These include the early report of decreased hypercapnic ventilatory response among Enga tribesmen mentioned earlier. Much of the focus has been on the role of potential differences in hypoxic ventilatory response in relation to variation in adaptation to high altitude. Tibetans seem possessed of superior altitude adaptation and have higher hypoxic ventilatory response than Han Chinese and Andean Aymara [5; 56; 57]. Further, individuals of mixed Han-Tibetan ancestry have hypoxic ventilatory response greater than those of pure Han lineage pointing to a dominant effect of Tibetan ancestry [15]. The increased hypoxic ventilatory response of Tibetans reflects in part a resistance to the blunting effect of long-term hypoxic exposure on hypoxic ventilatory response, mentioned earlier, which is a common feature of other populations [37].

These population differences have commonly been considered to suggest genetic effects on ventilatory control, but a recent analysis suggested that they may be unrelated to genetic distance and may instead reflect differential adaptation to hypoxia [50].

### 2.3.2 Studies in animals

Differences in hypoxic ventilatory response have been found, both among, and within animal species. Decreased responses are found in species with excellent adaptation to high altitude. Bar-headed geese, which fly at exceptionally high altitude, have lower hypoxic ventilatory responses than the low altitude pekin duck [8]. This was seen in birds raised at low altitude and thus the lower response in the geese could not be ascribed to chronic hypoxic exposure. Variation has also been evident among strains in rats (see Chapter 9) and mice (see Chapter 10).



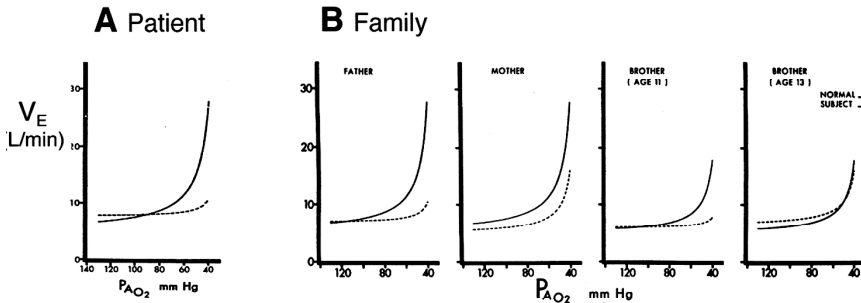
**Fig. 2.** Interindividual variation in ventilatory response to isocapnic hypoxia among cats. Hypoxic responses are expressed as the shape parameter A, an index of steepness of the hyperbolic response of ventilation to decrease in oxygen tension. Responses were assessed during wakefulness with plethysmographic techniques and were found to be reproducible on repeat testing on several days indicating stable differences among cats. Data from [52].

A study of hypoxic ventilatory response in awake cats showed a large range of responses similar to that seen in humans (Fig. 2) [52]. Repeat measurements on separate days were similar for individual cats indicating stable inter-individual differences.

## 2.4 Familial clusters

In the early 1970's Hudgel observed a young asthmatic patient with frequent episodes of hypoventilation and severe hypoxemia, which seemed disproportionate to his mild airway obstruction [21]. Studies of the patient's ventilatory responses during asthmatic remission showed profoundly decreased hypoxic response with a normal response to hypercapnia indicating that the low hypoxic response was not attributable to ventilatory limitation. Studies of the patient's par-

ents and siblings who were in good health, found a family cluster of low hypoxic, but normal hypercapnic responses (Fig. 3). Similar findings were seen in studies of a second case of unexplained hypoventilation in which first degree relatives had low hypoxic ventilatory responses with no depression of the hypercapnic ventilatory response [36].



**Fig. 3.** Panel A: decreased hypoxic ventilatory response to isocapnic hypoxia in a patient with hypoventilation (dashed line), compared to average control value (solid line). Panel B: decreased responses in the patient's healthy parents and siblings (dashed line) compared to average control values of similar age. Data from [21], reproduced with permission from [56].

As mentioned earlier, low values of hypoxic ventilatory response are found in endurance athletes. A study of families of runners who had won events of a mile or longer at the state or higher levels showed clusters of low hypoxic responses in the runner's nonathletic parents and siblings (Fig. 4) [46]. The findings suggest that decreased hypoxic ventilatory response may be a pre-existent attribute of individuals capable of endurance exercise. Reasons for such linkage are unclear. It might be that this reflects a general cellular ability to maintain normal metabolic function with less metabolic error signal at lower oxygen tensions manifested as lesser ventilatory stimulation and better skeletal muscle function at lower oxygen tensions in blood and skeletal muscle.

Differences in hypoxic ventilatory response have also been found among families of patients with chronic obstructive pulmonary disease (COPD). Observations were stimulated by the variation in chronic stable ventilatory status among patients with COPD. It has long been apparent that such patients span a ventilatory spectrum ranging from individuals who chronically maintain nearly normal ventilation (pink puffers or fighters) to those with chronic hypoventilation (blue bloaters or non-fighters) [41; 42]. Early studies had shown that  $\text{PaCO}_2$  in stable COPD patients was not clearly explained by the severity of airway obstruction, but was associated with decreased ventilatory effort response to hypercapnia (measured as respiratory work or occlusion pressure) [28; 35]. Hypoxic ventilatory responses measured as occlusion pressure were found to be lower in COPD patients with hypoxemia than in those who remained well oxygenated with similar degree of airways obstruction [9].

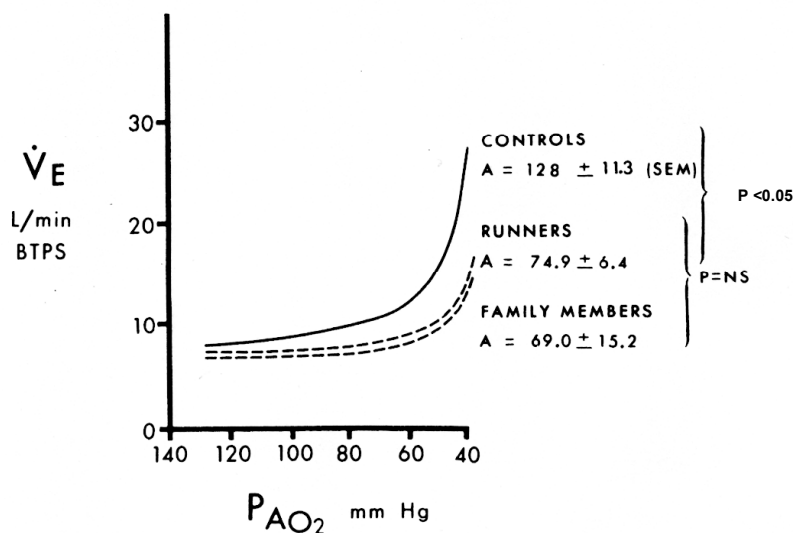


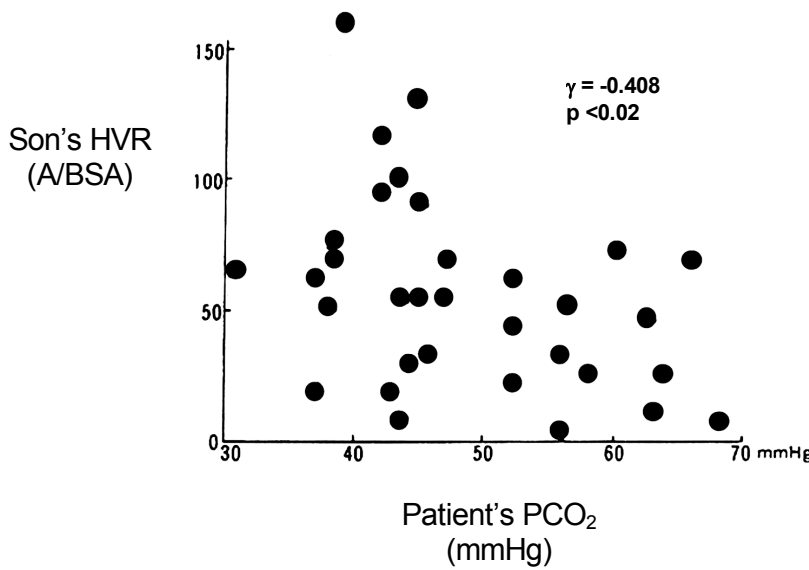
Fig. 4. Depressed values for hypoxic ventilatory response in endurance runners and their healthy, non-athletic parents and siblings. Reproduced with permission from [46].

The possibility that familial factors might contribute to differences in stable ventilation in patients with COPD was explored in studies of families of hypercapnic and normocapnic patients. Healthy offspring of patients with chronic hypoventilation showed lower hypoxic ventilatory response than those of patients with similar airway obstruction who maintained normal ventilation (Fig. 5) [16; 24; 39].

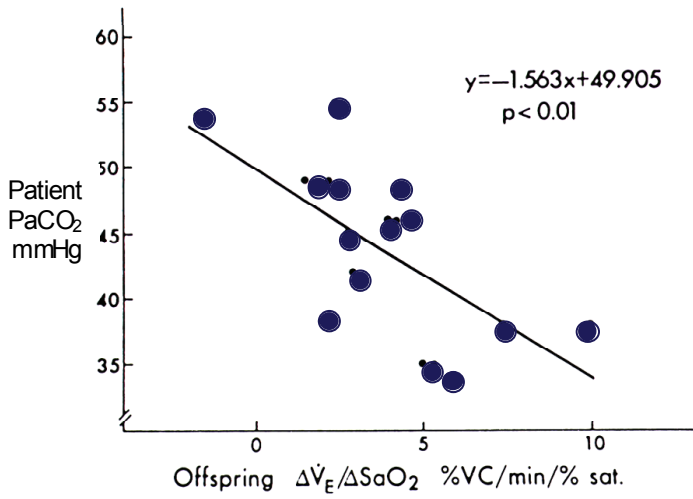
Further, the extent of hypoventilation (measured as  $\text{PaCO}_2$ ) during acute exacerbations of airways obstruction in COPD patients was inversely related to the strength of the hypoxic response of their offspring (Fig. 6) [24]. In these studies the linkage of ventilatory responses of offspring to the ventilatory status of the patients was mainly, or exclusively, to the hypoxic response with little or no relationship evident for the response to hypercapnia. Overall, these findings pointed to familial determinants of the hypoxic ventilatory response and of ventilation in the face of chronic airway obstruction.

Familial clustering of decreased hypoxic ventilatory responses has also been found in relation to patients with sleep apnea (see Chapter 8), but not with patients with the obesity hypoventilation syndrome [22].

When combined, hypoxic responses in first degree relatives of endurance athletes and patients with hypoventilation show a distribution is strongly shifted to lower end of the broad spectrum seen in the general population (Fig. 1, lower panel). These familial effects on the hypoxic response seemed to be quite strong given that they were evident with small groups of subjects.



**Fig. 5.** Familial influence on ventilation in COPD. Ventilation in the COPD patients is correlated with the hypoxic response of their healthy offspring. Hypoxic responses are plotted as the shape parameter A, an index of steepness of the hyperbolic response normalized for body surface area (BSA). Drawn from [24] and reproduced with permission from [56].



**Fig. 6.** Familial influence on ventilation in patients with COPD. Alveolar ventilation measured as  $PaCO_2$  in patients during acute exacerbation of COPD is correlated with hypoxic ventilatory response of their offspring. Ventilatory responses were measured as the slope of the linear response of increasing ventilation ( $\dot{V}_E$ ) to decreasing arterial oxygen saturation ( $SaO_2$ ) normalised for vital capacity (VC). (Drawn from data of [16] and reproduced from [56].

## 2.5 Genetics vs. environment

Population and familial differences in ventilatory control could reflect either environmental or genetic mechanisms. To explore this issue studies were undertaken to compare responses among monozygotic and dizygotic twins. The approach was to compare similarity of responses between the two members of a twin pair (within-pair variance) for the two classes of twins. The extent to which there is greater similarity of responses within pairs of monozygotic (identical) twins, measured as within-pair variance, compared to that of dizygotic (fraternal) twins is taken as an indicator of genetic contribution. Studies by the Denver, Hokkaido and Edinburgh groups found greater concordance within adult monozygotic than in dizygotic twins suggesting a genetic contribution to the hypoxic response [14; 24; 29] (Fig. 7). Similar concordance was found in infant monozygotic twins [51]. Findings for the hypercapnic response among twins varied. No genetic effect was evident in work by the Denver investigators [14] and by Arkinstall [3], while two studies by the Hokkaido group indicated a genetic contribution [24; 25]. However, these latter findings were complicated by measurement of some of the hypercapnic responses at euoxic oxygen tensions of 90 mmHg, rather than under the usual hyperoxia conditions, which might have added a "hypoxic" contribution to the hypercapnic response. Ultimately the investigators did a direct comparison of hypercapnic responses during euoxia and hyperoxia and found a genetic effect for the hypercapnic response only in hypoxia and agreed that a genetic influence on the response to "pure", hyperoxic, hypercapnia was likely small or absent [27].

In studies of families and of twins, coherence of hypoxic ventilatory responses were evident with very small group sizes suggesting a strong heritable effect.

## 2.6 Locus of hereditary effects

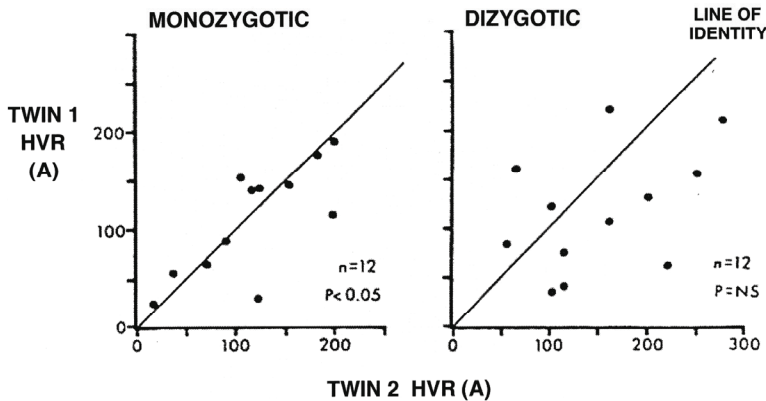
Hereditary influences on the hypoxic ventilatory response could reflect an influence on chemosensitivity, on central nervous system processing of chemoreceptor signals, or on respiratory mechanics.

Studies in humans and animals indicate a dominant influence on responses to hypoxia rather than to hypercapnia suggesting an effect on peripheral chemosensitivity. The lack of clear effect on the hypercapnic response limits the likelihood that respiratory mechanics account for the findings. The role of an effect on peripheral chemosensitivity is further supported by a study in adult female twins, which showed a genetic influence on a rapid test, consisting of the administration of two breaths of oxygen during steady state hypoxia, pointing to an effect on fast-responding peripheral chemosensitivity [2]. Similar findings were evident in infant twins, in whom a single breath oxygen test showed greater concordance among monozygotic twins [51].

These effects could reflect influences either the peripheral chemoreceptor (carotid body) *per se* or on the central translation of chemoreceptor input into ven-

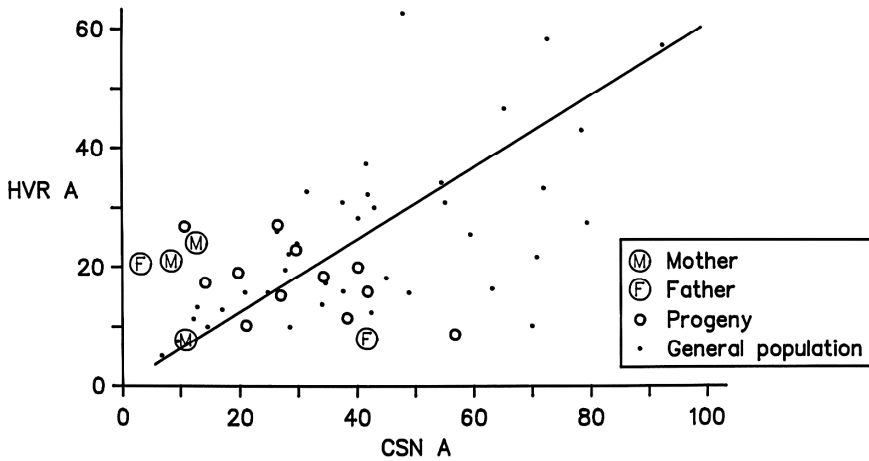


tilatory output. This was explored in cats, which as mentioned show a broad range of interindividual differences in hypoxic response. Simultaneous measurement of carotid sinus nerve and ventilatory responses to hypoxia showed that the responses were correlated, suggesting that differences in carotid body hypoxic sensitivity were contributors to variation of the hypoxic ventilatory response (Fig. 8) [52].



**Fig. 7.** Hypoxic ventilatory responses (HVR), plotted as the shape parameter A, measured within pairs of monozygotic (left panel) and dizygotic (right panel) twins. The data are plotted in relation to the line of identity (solid line). The findings show greater similarity of hypoxic ventilatory response within pairs of monozygotic than is dizygotic twins suggesting a genetic influence on the response. Reproduced from [14].

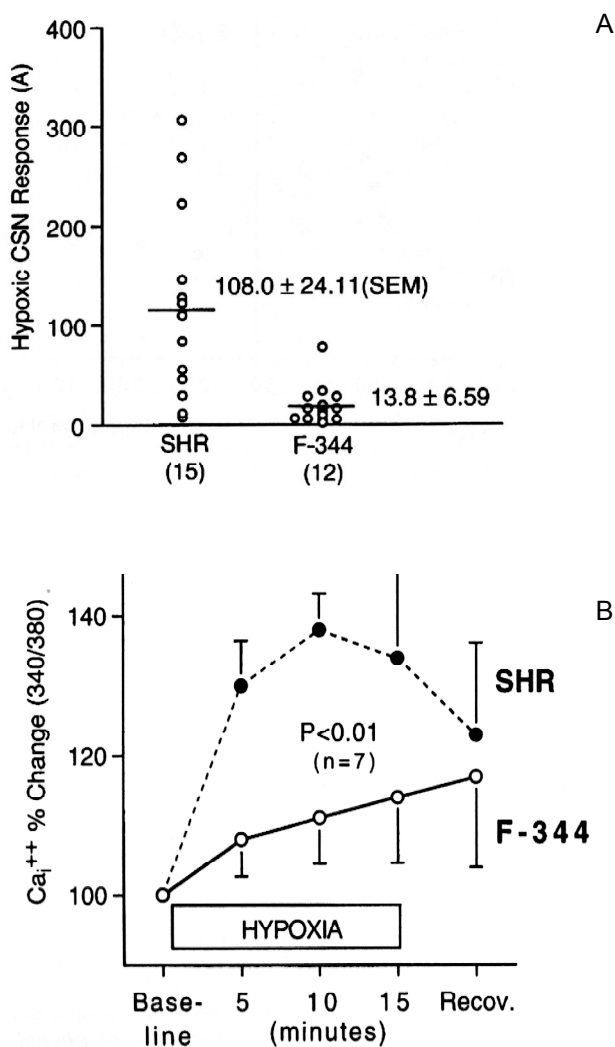
Further, the ratio of ventilatory to carotid sinus nerve response was unchanged over the broad range of hypoxic ventilatory responses indicating that differences in central nervous system translation of peripheral chemoreceptor activity to ventilation were unlikely factors. Thus it appears that among cats the variation in hypoxic ventilatory response is most likely a reflection of variable peripheral chemosensitivity. To explore the potential heritability of this effect, we began a breeding colony to study the offspring of high and low responder cats. Unfortunately the effort was aborted by high costs, but studies were completed in 12 offspring of low responders. It was found that both the ventilatory and carotid sinus nerve responses of the offspring tended to cluster at the low end of the range of hypoxic responses with values similar to those of their parents (J. Weil, unpublished data), (Fig. 8).



**Fig. 8.** Ventilatory and carotid sinus nerve responses to hypoxia in cats (filled circles). The wide distribution of ventilatory response shows correlation with carotid sinus nerve responses suggesting a role of varied hypoxic sensitivity of the carotid body in the variation in ventilatory response. Similarity of responses in low responder parents (open circles M & F) and their offspring (open circles) suggests an hereditary effect. From [52] and unpublished data.

These effects on the response of the carotid body could reflect variation in intrinsic chemosensitivity or the influence of neural or humoral modulation. This was addressed in a comparison of strains of rats which found that carotid sinus nerve responses to hypoxia were greater in the spontaneously hypertensive (SHR) than in the Fischer 344 (F344) strain (Fig. 9, panel A) [55]. Hypoxic responses measured in isolated carotid bodies by fluorometric measures of carotid body cytosolic free calcium in response to hypoxic superfusion showed greater response in the SHR strain (Fig. 9, panel B). The findings suggest the existence of inter-strain differences in intrinsic hypoxic chemosensitivity. Thus, collectively the findings are consistent with a possible role of genetically directed effects on intrinsic chemosensitivity in variation of hypoxic ventilatory response. However, the extent to which these findings in animals apply to human variation in hypoxic ventilatory response remains uncertain.

There is little information concerning the question of which specific genes might be involved in variation of hypoxic ventilatory response. Studies in rats suggest possible roles for genes on chromosomes 9 and 18 in differences among Dahl Salt Sensitive and Brown Norway strains [17] and in mice a role for genes on chromosome 9 possibly reflecting effects on dopamine D2 receptor or acetylcholine nicotinic receptor expression have been suggested [49].



**Fig. 9.** Panel A: carotid sinus nerve responses to hypoxia are greater in SHR than in F344 rats. Panel B: isolated carotid bodies show greater responses to superfusion hypoxia measured as the increase in cytosolic free calcium. Reproduced [55].

## 2.7 Conclusion

Ventilatory control shows considerable variation among individual humans. Familial influences are evident in the similarity of ventilatory responses among first degree relatives and a genetic effect is indicated by concordance within identical twins. These factors have their predominant effects on the ventilatory response to hypoxia rather than to the response to hypercapnia. This suggests that heritable influences may act on peripheral chemosensitivity. Studies of inter-individual variation in hypoxic ventilatory responses in animals show correlation with carotid body responses, which appear to reflect intrinsic differences in hypoxic sensitivity. Finally, variation in the hypoxic ventilatory response seems related to ventilatory adaptation and function in exposure to high altitude, in endurance athletics and in chronic obstructive pulmonary disease.

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