ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Research Article

Impact of the Arterial Chemoreceptors on the Cardiopulmonary System

Robert S Fitzgerald[1,2,3]*, Gholam Abbas Dehghani[1] and Samara Kiihl[4]

[1]*Department of Environmental Health and Engineering, The Johns Hopkins University Medical Institutions, Baltimore, MD, USA*

[2]*Department of Physiology, The Johns Hopkins University Medical Institutions, Baltimore, MD, USA*

[3]*Department of Medicine, The Johns Hopkins University Medical Institutions, Baltimore, MD, USA*

[4]*Department of Biostatistics, The Johns Hopkins University Medical Institutions, Baltimore, MD, USA*

***Corresponding Author:** Robert S Fitzgerald, Department of Environmental Health and Engineering, The Johns Hopkins University Medical Institutions, Baltimore, MD, USA.

Received: February 11, 2021; **Published:** March 11, 2021

Abstract

The lung is the first cardiopulmonary organ to mediate the arrival of the organisms' most vital substrate from the external environment, oxygen. Many lung functions, controlled by the autonomic nervous system, are under the influence of sensors/receptors which govern the organism's response to the absence of oxygen. This study introduces a role for the less often reported arterial chemoreceptor, the aortic bodies, specifically their role in governing the resistance of the pulmonary vasculature.

Keywords: *Aortic Bodies; Hypoxemia; Sympathetic Nervous System*

Introduction

In this day of threats to the lungs a brief overview of how these organs are controlled from a physiological perspective seems pertinent. The carotid body (CB) is known to play a critical role in cardiopulmonary behavior. The CBs, located bilaterally near the bifurcation of the common carotid artery into its internal and external branches, exert their influence via the autonomic nervous system. More recent studies have pointed out the impact of the CBs on the cardiovascular system [6,7,18,23]. Hypoxemia in the form of a lowered PaO_2 is the more common stimulus for the CBs.

Two types of cells dominate the CBs, the glomus cell (GC, or Type I cell) which is the principal chemodetecting element and the Type II cell. Initially this cell was thought to be supportive only. But more recent studies point out a role for them in chemodetection [15,20].

A second set of chemoreceptors are the aortic bodies (ABs), sprayed across the arch of the aorta.

But there is quite a difference between the two. Whereas the CBs respond to a lowered PaO_2, the ABs respond both to decreases in PaO_2 and to carbon monoxide (CO), which lowers oxygen content (CaO_2), but not per se PaO_2.

Much speculation has surrounded the debate for this difference. A reasonable suggestion was blood flow. The metabolism of both chemoreceptor types is high. But blood flow through the CBs of cats has been measured to be > 2.1 L/min/100 gm tissue [4]. It is doubtful that the same variable has been measured in the ABs.

Stimulation of the CBs increases both the tidal volume of a breath and the frequency of breathing. Further, the FRC is increased [10]. Airway secretions and airway resistance are also increased consequent to CB stimulation [5,19]. The ABs have been much less explored. But recently two studies have appeared which explored the structures themselves [21,22]. This manuscript continues the analysis initiated in a previous study [6]. It emphasizes the significance of some data in that study, specifically on a role for the ABs in the cardiopulmonary system of a feline model.

Materials and Methods

The more important factors of the methods from that study [8] will be listed here so the reader is not forced to return to that original publication [6].

Preparation: One group of fifteen cats was used in four different conditions. Their average weight was approximately 4 Kg. The animals were initially sedated with ketamine (35 mg/Kg, ip), then anesthetized with sodium pentobarbital (30 mg/Kg, iv). A midline incision at the level of the trachea was made, and a tracheal cannula inserted. The animals were then paralyzed with succinylcholine (5mg/Kg and artificially ventilated via the endotracheal cannula. Depth of anesthesia was assessed by a positive medial canthal reflex in response to a mild toe pinch.

Catheters were placed in the:

- Femoral artery to measure arterial blood pressure and for drawing arterial blood samples.
- Femoral vein to allow further injections of anesthetic, $NaHCO_3$, glucose. Secondly, this catheter was advanced into the right atrium to measure pressure therein (Statham pressure transducer P-23De)
- A left lateral thoracotomy was performed at the fifth interspace.
- The pericardium was cut and the ascending aorta was gently separated from the pulmonary artery.
- An electromagnetic flow probe (Biotronex Laboratory Inc., 6.0 mm: connected to Biotronex Flowmeter, BL 620) was placed around the root of the aorta. Tests had been previously made to determine that this placement did not modify the aortic nerve activity. Calibration of probe was accomplished as previously described [6], yielding a straight line graph having a correlation coefficient of 0.99.
- A catheter was introduced into the left atrium via its appendage for measuring left atrial pressure (P-23 De).
- A catheter was introduced into the left ventricle for pressure measurements (P-23Db). The first derivative of ventricular pressure (LV dP/dtMAX) was recorded with a differentiator (SCM-2).
- A final catheter was introduced into the pulmonary artery, anchored with a small purse string on the surface of the artery for measuring pressure (P-23b). All pressures were referenced to the right atrium.
- Bilateral aortic depressor nerves (running adjacent to the vagus, and to a small degree having fibers mingling with the vagus) were isolated as much as possible, covered with pledgets of cotton previously soaked in Krebs Ringer bicarbonate solution. The area was then covered with a layer of mineral oil, and, when necessary, kept warm with a lamp.
- Temperature was monitored and kept constant between 37° and 39°C with a rectal probe and heating pad.

Variables measured

- Blood pressures in the organisms' various chambers were recorded on a polygraph (Electronics for Medicine).
- Chemical factors in arterial blood were measured through all phases of the preparation and experiment. PaO_2, $PaCO_2$, pHa were measured on a Radiometer BMS3MK2 blood gas analyzer. Oxygen saturation, hemoglobin concentration, and carboxyhemoglobin were measured with a CO-oximeter B (Instrumentation Laboratories #182).

Statistical evaluation tools

- Virtually all evaluations used the repeated measures analysis of variance (RMANOVA). If the data did not pass the Normality or Equal Variance Tests, the Repeated Measures Analysis of Variance on Ranks (RMANOVAR) was used.
- For the more complex analysis (needed for figure 2) a generalized least squares with autoregressive correlation for repeated measurements was used.

Experimental design

- This was based partly on some previous studies [9,14] which showed that both CBs and ABs increased neural output in response to a lowering of the PaO_2, but only the ABs responded to CO with an increased neural output.
- Ventilating the cat on 10% O_2 (Hypoxic Hypoxia: HHint). Ventilating the cat on CO (CO Hypoxia: COHint). Both ventilating sessions were done with the aortic depressor nerves intact. Cutting the bilateral aortic depressor nerves resects or excludes the aortic bodies from communicating with the nucleus tractus solitarii (NTS) and CNS. These challenges are labeled HHabr and COHabr.
- In summary the design has (1) both CBs and ABs sending increased neural output to the NTS (HHint), (2) only the CBs (HHabr), (3) only the ABs (COHint), neither CBs nor ABs (COH).

Protocol

1. As a precaution several experiments were done simply to determine if the cat could survive the extensive surgery and experimental steps. Based on these experiments, the data suggested three hours should be allowed for the cat to recover from the surgery.
2. A control period (time mark of 0') initiated the experiments in which aortic flow, right and left atrial pressure, arterial mean pressure were measured. Blood samples were drawn and measured for PaO_2, $PaCO_2$, Hb, pHa, and SaO_2 and values recorded (Table 1). The cats were then ventilated for 15 min on 10% O_2.
3. At the end of this period arterial blood samples were again withdrawn, measured and values recorded in table 1 (HHint).
4. Normoxic/normocapic conditions followed for one hour.
5. After a second control period the cat was ventilated for 15 min on carbon monoxide (COHint): 2% in air for the first 2 min (reducing SaO_2 to 50 - 60% and then 0.10% for the last 13 min reducing SaO_2 to 40 - 45%. Blood samples were drawn, measured, and values recorded, as above. This concluded the INTACT portion of the experiment.

6. Transection of the bilateral aortic depressor nerves followed as the cat was being moderately hyperventilated on 95% O_2/5%CO_2 for one hour or more to facilitate the removal of CO. When SaO_2 had returned to control values, the animal was ventilated on room air (21%O_2 in N_2) for 15-20 min. Now the above steps 2, 3, 4, 5 were repeated in the abr animal. This concluded the experiment. (HHabr, COHabr).

7. Animals were sacrificed with an i.v. injection of Na Pentobarbital (50 mg/Kg). An absence of heart beat for 5 min signaled the end of life in the animal. Preparation of the cats and steps in the protocol were approved by the University's Animal Care and Use Committee which follows the National Institutes of Health's norms and guidelines for the care and use of animals.

Results

1. Table 1 records the strength of the hypoxic stimuli presented to the cats, as well as the relative constancy of pHa and $PaCO_2$.

2. A measurement of Cardiac Output (C.O.) was needed (Figure 1). The control level (0') was virtually identical in the four challenges at about 270 mL/min. The largest increase was during HHint where the 410 mL/min value was attained at about 4 min. During COHint the max of about 380 mL/min was reached at 13 min. During HHabr there was no significant difference between 3 min and 15 min (350 and377 mL/min. And during COHabr there was no significant differences among the time points from 0 to 15 min.

3. To compare the relative impact of the carotid and aortic chemoreceptors the values of cardiac output at each of the time points during the hypoxic exposures were measured and normalized to its own control and presented as a percent of its own control. A generalized least squares with autoregressive correlation for repeated measurements was the technique used to construct (Figure 2). The HHint trace (#1) is significantly greater than the HHabr trace (#2). The HHabr trace is significantly greater than the COHint trace (#3). C.O. during HHabr is significantly greater than C.O. during COHint at 3, 5, 7, and 10 min. And all traces are greater than when there is no input from the peripheral arterial chemoreceptors (COHabr; #4).

4. Mean arterial blood pressure was also measured (Figure 3). Once again the CV variable is most influenced in a period when both CBs and ABs are functioning to sustain homeostasis. Blood pressure decreases least when there is input to the SNS from both the CBs and ABs (HHint). And when there is no input to the SNS from either set of chemoreceptors (COHabr), blood pressure falls to the lowest level.

5. The total peripheral resistance was calculated also. In the face of systemic hypoxemia and the attendant systemic vasodilation the sympathetic nervous system (SNS) had a large challenge. When both sets of peripheral arterial chemoreceptors) were working to stimulate the SNS (HHint), the total peripheral resistance decreased least. But in response to the other three conditions (COHint, HHabr, COHabr) the total peripheral resistance produced traces which are statistically indistinguishable, though they tended to show a greater decrease in total vascular resistance.

6. The main purpose of this metaanalysis was to explore the activity of the ABs. Perhaps the most striking result occurs in the pulmonary vasculature (Figure 4). In the lung with tone (alveolar hypoxia is present), the data show in 8/9 time points the HH hypoxemia values (HHint) to be less than HHabr values at those time points. Red Dots are lower than paired Blue Dots. This suggests the ABs are exerting a depressive effect on the pulmonary vasculature. And if the nine time points are averaged to compare the total hypoxic time period for the two challenges, the average for HHint is significantly less than the average for the HHabr.

7. But when, presumably, there is only normoxic tone in the pulmonary vascular bed (COHint; there is no alveolar hypoxia) again a somewhat surprising pulmonary vasodilation occurs since all nine COHint values for pulmonary vascular resistances (red dots) are less than the corresponding COH abr values (blue dots). And again the average for the total period of COHint is significantly less than the average for the COHabr values. This seems to suggest that the ABs have a strong vasodilating impact on the pulmonary vasculature.

n = 15	Intact				
Condition	**pHa**	**$PaCO_2$ (mmHg)**	**PaO_2 (mmHg)**	**SaO_2 (%)**	**Hb (gm%)**
Control	7.44 ± 0.02	33.8 ± 1.2	170.1 ± 4.0	99.0 ± 0.4	8.4 ± 0.5
HH (15 min)	7.36 ± 0.02	36.5 ± 1.1	28.1 ± 2.0*	43.7 ± 3.9*	9.7 ± 0.6
Control	7.42 ± 0.01	35.8 ± 1.0	121.0 ± 5.1	100.0 ± 0.0	8.5 ± 0.5
COH (15 min)	7.41 ± 0.02	34.3 ± 1.1	130.0 ± 5.1	44.8 ± 2.5*	9.0 ± 0.5
	Aortic bodies resected				
Control	7.49 ± 0.01	33.1 ± 0.9	124.1 ± 4.0	99.3 ± 0.3	7.6 ± 0.5
HH (15 min)	7.38 ± 0.02	34.3 ± 1.1	33.0 ± 3.1*	47.4 ± 4.0*	8.3 ± 0.6
Control	7.43 ± 0.02	35.1 ± 0.8	128.0 ± 5.1	99.1 ± 0.4	7.0 ± 0.5
COH (15 min)	7.39 ± 0.02	32.4 ± 1.7	125.0 ± 4.1	40.2 ± 3.7*	7.4 ± 0.5

Table 1: *Blood gas values for control before and during HH exposure and for control before and during COH exposure in cats before and after aortic nerve transection.*

**P ≤ 0.05.*

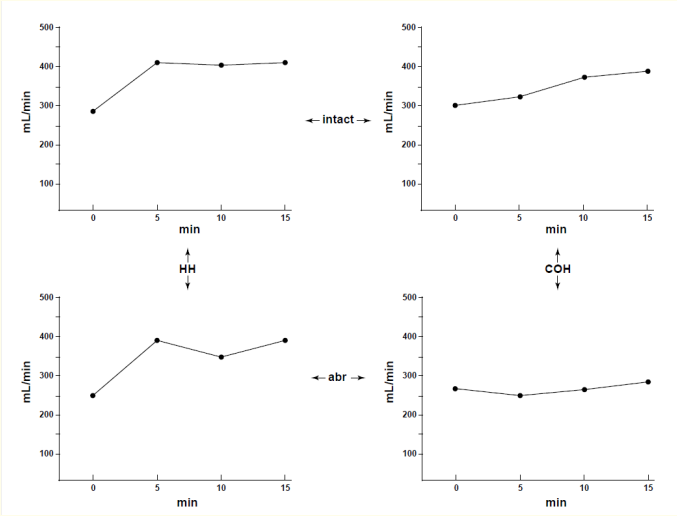

Figure 1: *Cardiac output (mL/min; n = 15). Top/left (HHint; CBs + ABs); values < 5 min are significantly less than values at 5 - 15 min. Bottom/left (HHabr; CBs only); values from about 3 - 5 min greater than those before (no difference 5 to 15 min. Top/right (COHint; ABs only) early values significantly less than 10 - 15 min values. Bottom/right (COHabr; neither CBs nor ABs) no significant difference among the time points.*

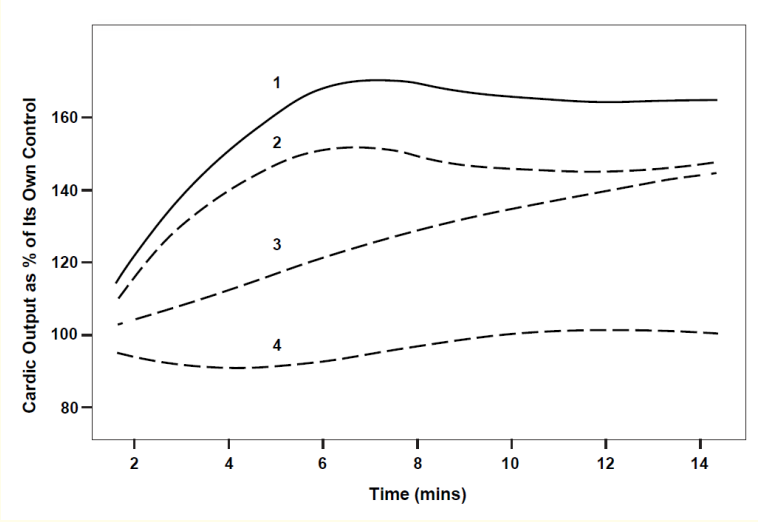

Figure 2: *Cardiac output (Values at time points [1 - 15 min] are % s of their own controls; n = 15). Panel allows comparison of values of the four treatments (as %s) seen together. Plot shows that the HHint challenge (trace #1) produces C.O. increases greater than when the CBs are acting alone (HHabr; trace #2). Trace #3 shows the less frequently reported impact of the ABs on cardiovascular control (COHint). From about 5 - 10 min Cardiac Output (C.O.) values of trace #2 (HHabr; CBs only) are significantly greater than trace #3 values (COHint; ABs only), Trace #2 (HHabr) becomes indistinguishable from trace #3 (ABs only) thereafter. Trace #4 (COHabr) shows no significant change throughout the 15 min.*

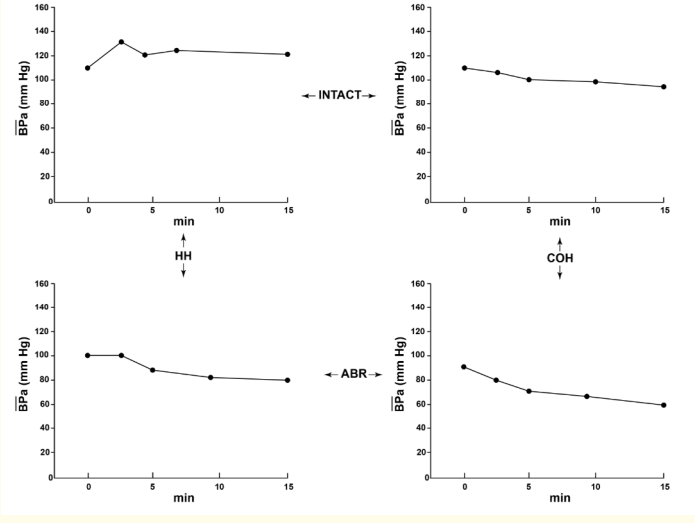

Figure 3: *Mean arterial blood pressure (mmHg; n = 15). Top/left (HHint; CBs + ABs); values start at ~110 mmHg, then rise to 130 mmHg, then drop to 120 mmHg. Bottom/left (HHabr; CBs only); values start from ~100 mmHg, but then gradually slide down to 80 mmHg. Top/right (COHint; ABs only) starting at ~112 mmHg values follow almost a straight line decrease to 92 mmHg. Bottom/right (COHabr; neither CBs nor ABs) values decrease from 90 to 60 mmHg. It is interesting to note that the only rise in mean BP in this preparation occurs when both sets of chemoreceptors are operating. Further, that the carotid sinus baroreceptors did not have more of an influence during COHabr is also curious.*

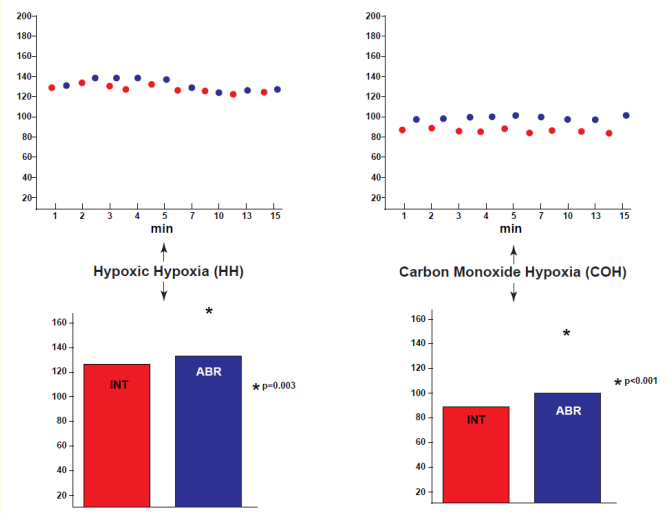

Figure 4: *Pulmonary vascular resistance (PPA/C.O = PVR). Values at time points normalized to their own control values. Left: In lung with increased vascular tone due to alveolar hypoxic vasoconstriction. PVR in eight of nine time points of the 15 min exposure with both CBs and ABs intact (red dot) was significantly less than the paired PVR value under abr conditions (blue dot). Right: In lung with normal tone (no alveolar hypoxia) PVR during the entire 15 min exposure to carbon monoxide was less in the intact preparation (ABs active; red dot) than in the abr preparation (blue dot); no peripheral chemoreceptor sending neural traffic to the NTS or CNS. Both plots show that the aortic bodies appear to be reducing PVR.*

Discussion

The anesthetized, paralyzed, artificially ventilated preparations, having undergone extensive surgery, generated data the interpretation of which must be presented cautiously. The hypoxic hypoxia challenge would in the normal animal produce an increase in ventilation. This per se would generate mechanical changes in the lung which in turn would have an impact on cardiovascular variables; e.g. a decrease in downstream pressure for venous return. Further, since the ventilation would be exceeding the metabolism, $PaCO_2$ would fall. And this resulting decrease in $PaCO_2$ would attenuate the impact of hypoxia on the output of the mediating chemoreceptors. However, variations of preparations such as the one used in these studies have been found in several previous studies, especially in the older literature [1-3,8,11-13,16,17,24,25].

Nevertheless, caution remains the operative word in trying to interpret these results as if they were what would be seen in a normal animal under normal conditions. Their value is in opening up new ways to think about what is the most vital substrate needed by most organisms, oxygen, and the receptors or sensors by which the organism becomes aware that it is being challenged, and must respond autonomically and consciously.

One goal of this study was to explore the behavior of vascular resistance in several organs during various forms of hypoxemia with a variety of peripheral chemoreceptor involvement: With lowered PaO_2 both CBs and ABs would be increasing their neural output. If we disconnected the ABs from the CNS, only the CBs would be sending increased neural information to the CNS. Since the CBs do not increase their neural output to the CNS in response to CO, exposing the preparation to CO prompts only the ABs to increase their neural output to

the CNS. And upon transecting the aortic depressor nerves, no neural information would be proceeding as far as the CNS from the ABs. So, the resulting experimental design for a hypoxemic challenge would have [1]: both chemoreceptors involved (lowered PaO_2, intact CBs and ABs), [2]: only the CBs (loweredPaO_2, cut aortic depressor nerve), [3]: only the ABs (CO lowering O_2 content to same level as lowered PaO_2 did), [4]: none (CO, with aortic depressor nerve cut) before the hypoxemic challenge.

Some studies [16,17,25] have reported that the CBs attenuated the well-known hypoxic pulmonary vasoconstriction. We have also seen that a selective perfusion of the CBs could vasodilate the pulmonary vasculature [8].

This meta-analysis shows that by subtracting one set of arterial chemoreceptors (the ABs) produces a higher pulmonary vascular resistance. In the abr preparations (in both high and low tone pulmonary vasculature) there was a higher value for PVR. Hence, the ABs must have been producing a vasodilation in the pulmonary vasculature.

Conclusion

In conclusion the sum of the data show that the second set of arterial chemoreceptors, the ABs, also seem to be responsible for pulmonary vasodilation. The data as a whole shows emphatically that the ABs produce a decrease in pulmonary vascular resistance. Nevertheless, this interpretation is offered with a note of caution.

Bibliography

1. Browse NJ and Shepherd JT. "Response of veins of canine limb to aortic and carotid chemoreceptor stimulation". *American Journal of Physiology* 210 (1966): 1435-1441.

2. Carmody JJ and Scott MJ. "Respiratory and cardiovascular responses to prolonged stimulation of the carotid body chemoreceptors in the cat". *Australian Journal of Experimental Biology and Medical Science* 52 (1974): 271-283.

3. Daly I deB and Daly M deB. "The effects of stimulation of the carotid body chemoreceptors on pulmonary vascular resistance in the dog". *The Journal of Physiology* 182 (1957): 436-446.

4. Daly M deB., *et al.* "Observations on the volume of blood flow and oxygen utilization of the carotid body in the cat". *The Journal of Physiology* 125 (1954): 67-89.

5. Davis B., *et al.* "Hypoxemia reflexly increases secretion from tracheal submucosal glands in dogs". *Journal of Applied Physiology* 52 (1982): 1416-1419.

6. Fitzgerald RS., *et al.* "Autonomic control of the cardiovascular system in the cat". *Auton Neur: Bas and Clin.* 174 (2013): 21-30.

7. Fitzgerald RS., *et al.* "Organismal responses to hypoxemic challenges". *Advances in Experimental Medicine and Biology* 860 (2015): 101-113.

8. Fitzgerald RS., *et al.* "Peripheral chemoreceptor modulation of the pulmonary vasculature in the cat". *Journal of Applied Physiology* 73 (1993): 20-29.

9. Fitzgerald RS and Traystman RJ. "Peripheral chemoreceptors and the cerebral vascular response to hypoxemia". *Federation Proceedings* 39 (1980): 2674-2676.

10. Garfinkel F and Fitzgerald RS. "The effect of hyperoxia, hypoxia and hyper-capnia on FRC and occlusion pressure in human subjects". *Respiratory Physiology* 33 (1978): 241-250.

11. Krasney JA. "Effect of sinoaortic denervation on regional circulatory responses to cyanide". *American Journal of Physiology* 218 (1970): 556-563.

12. Krasney JA. "Cardiovascular responses to cyanide in awake sinoaortic denervated dogs". *American Journal of Physiology* 220 (1971): 1361-1368.

13. Krasney JA., *et al.* "Cardiovascular responses to arterial hypoxia in awake sinoaortic denervated dogs". *Journal of Applied Physiology* 35 (1973): 733-738.

14. Lahiri S., *et al.* "Relative responses of the aortic body and carotid body chemoreceptors to carboxyhemoglobinemia". *Journal of Applied Physiology* 50 (1981): 580-586.

15. Leonard EM., *et al.* "Evidence for protein kinase involvement in the 5-HT-[Ca2+]I - pannexin-1 signalling pathway in type II glial cells of the rat carotid body". *Experimental Physiology* 104 (2019): 244-253.

16. Levitzky MG. "Chemoreceptor stimulation and hypoxic pulmonary vasoconstriction in conscious dogs". *Respiratory Physiology* 37 (1979): 151-160.

17. Levitzky MG., *et al.* "Chemoreceptor influence on pulmonary blood flow during unilateral hypoxia in dogs". *Respiratory Physiology* 31 (1977): 345-356.

18. Marshaii JM. "Peripheral chemoreceptors and cardiovascular regulation". *Physiological Reviews* 74 (1994): 543-594.

19. Nadel JA and Widdicombe JG. "Effect of changes in blood gas tensions and carotid sinus pressure on tracheal volume and total lung resistance to airflow". *The Journal of Physiology* 163 (1962): 13-33.

20. Nurse CA., *et al.* "Role of glial-like type II cells as paracrine modulators of carotid body chemoreception". *The Physiological Genomics* 50 (2018): 255-262.

21. Piskuric NA and Nurse CA. "Effects of chemostimuli on $[Ca^{2+}]_I$ responses of rat aortic body type I cells and endogenous local neurons: Comparison with carotid body cells". *The Journal of Physiology* 590.9 (2012): 2121-2135.

22. Piskuric NA., *et al.* "Confocal immunofluorescence study of rat aortic body chemoreceptors and associated neurons in situ and in vitro". *The Journal of Comparative Neurology* 519 (2011): 856-877.

23. Schultz HD., *et al.* "Mechanisms of carotid body chemoreflex dysfunction during heart failure". *Experimental Physiology* 100.2 (2015): 124-129.

24. Stern S and Braun K. "Effect of chemoreceptor stimulation on the pulmonary veins". *American Journal of Physiology* 210 (1966): 535-539.

25. Wilson LB and Levitzky MG. "Chemoreflex blunting of hypoxic pulmonary vasoconstriction is vagally mediated". *Journal of Applied Physiology* 66 (1989): 782-791.

Volume 10 Issue 4 March 2021