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Highlights in clinical autonomic neurosciences: Insights into the Roles of the Carotid Body and Carotid Baroreceptor

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Cellular properties and chemosensory responses of the human carotid body. Ortega-Sáenz P, Pardal R, Levitsky K, Villadiego J, Muñoz-Manchado AB, Durán R, Bonilla-Henao V, Arias-Mayenco I, Sobrino V, Ordóñez A, Oliver M, Toledo-Aral JJ, López-Barneo J. (Sevilla, Spain). *J Physiol.* 2013;591:6157–6173

Article Summary:

The carotid body (CB) is the major peripheral arterial chemoreceptor in mammals that mediates the acute hyperventilatory response to hypoxia. The CB grows in response to sustained hypoxia and also participates in acclimatisation to chronic hypoxaemia. Knowledge of CB physiology at the cellular level has increased considerably in recent times thanks to studies performed on lower mammals, and rodents in particular. However, the functional characteristics of human CB cells remain practically unknown. The authors used tissue slices or enzymatically dispersed cells to determine the characteristics of human CB cells. The adult human CB parenchyma contains clusters of chemosensitive glomus (type I) and sustentacular (type II) cells as well as nestin-positive progenitor cells. This organ also expresses high levels of the dopaminotrophic glial cell line-derived neurotrophic factor (GDNF). They found that GDNF production and the number of progenitor and glomus cells were preserved in the CBs of human subjects of advanced age. Moreover, glomus cells exhibited voltage-dependent Na(+), Ca(2+) and K(+) currents that were qualitatively similar to those reported in lower mammals. These cells responded to hypoxia with an external Ca(2+)-dependent increase of cytosolic Ca(2+) and quantal catecholamine secretion, as reported for other mammalian species. Interestingly, human glomus cells are also responsive to hypoglycaemia and together these two stimuli can potentiate each other's effects. The chemosensory responses of glomus cells are also preserved at an advanced age. These new

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data on the cellular and molecular physiology of the CB pave the way for future pathophysiological studies involving this organ in humans.

Commentary:

The carotid body has long seemed intriguing, and yet very complicated. There has been a recent increase in interest about the important physiological role that the carotid body plays, and this article provides an interesting tutorial about the function of the human carotid body. The authors are to be applauded for conducting a difficult study. Most studies of the carotid body have occurred in rodents, because most humans are unwilling to give up their carotid bodies. These authors utilized a cadaveric donor program to harvest carotid bodies quickly post expiration.

The fundamental role of the carotid body is to function as a peripheral chemoreceptor. It is thought to primarily to mediate an increase in ventilation in response to hypoxia. It plays an important role in allowing adaptation to chronic hypoxemia, such as with certain chronic illnesses or in response to moving to high altitudes. In human carotid bodies, unlike rodents, the receptors have a similar response to hypoglycemia.

The human carotid body is located at the bifurcation of the common carotid artery. It is a very small ovoid organ that is immediately adjacent to the arterial adventitia. The authors report that the mean size is only 20 mm³, and that there is significant variability in the carotid body size between individuals and within individuals between the left and right side. The size of the carotid body is not age dependent.

The carotid bodies are organized into glomeruli with primarily 2 types of cells. The neuronal type I glomus cells are the "business cells" with secretory vesicles consisting largely dopamine and other neurotransmitter such as acetylcholine and ATP. There are also type II glia-like cells surrounding and supporting these glomeruli. The glomus cells are responsible for setting the oxygen tension and they function through the actions of a series of ion channels. For example, the closure of oxygen sensitive potassium channels in the setting of hypoxia can lead to initial membrane depolarization followed by calcium entry and ultimately the release of neurotransmitters in quanta. After initial membrane depolarization, there is a voltage-dependent inward current secondary to activation of both sodium and calcium channels, followed by large outward currents that result from multiple subtypes of voltage-dependent potassium channels.

A key feature of carotid bodies is that they can enlarge in response to sustained hypoxia. A sub-population of the type II cells can function as stem cells in response to sustained hypoxia and will begin the process of differentiation into both type-1 glomus cells, as well as other supporting cells. It is this ability to augment the number of cells that allows a carotid body to fulfill its fundamental homeostatic responsibilities such as the accommodation to high altitudes and the survival of patients with chronic hypoxemia due to cardiorespiratory diseases.

As with many regulatory mechanisms in the body, what he can start off as a beneficial homeostatic response can become counterproductive chronically. This has led to an interest

in modulating or decreasing the actions of the carotid body in conditions such as heart failure (as we will see in the next article). A better understanding of the role that specific ion channels play in the function of the carotid body could serve to provide targets for pharmacological modulation of carotid body function. Alternatively, there are many antiarrhythmic and antiepileptic medications that were primarily through the modulation of ion channels. It is possible that some of these medications may have "off target" affects on carotid body function.

Carotid chemoreceptor ablation improves survival in heart failure: rescuing autonomic control of cardiorespiratory function. Del Rio R, Marcus NJ, Schultz HD. (Omaha, NE, USA). J Am Coll Cardiol. 2013;62:2422-2301

Article Summary:

Chronic heart failure (CHF) is a recognized health problem worldwide, and novel treatments are needed to better improve life quality and decrease mortality. Enhanced carotid chemoreflex drive from the carotid body (CB) is thought to contribute significantly to autonomic dysfunction, abnormal breathing patterns, and increased mortality in heart failure. This study sought to investigate whether selective ablation of the CB chemoreceptors improves cardiorespiratory control and survival during heart failure. Chronic heart failure was induced by coronary ligation in rats. Selective CB denervation was performed to remove carotid chemoreflex drive in the CHF state (16 weeks post-myocardial infarction). Indexes of autonomic and respiratory function were assessed in CB intact and CB denervated animals. CB denervation at 2 weeks post-myocardial infarction was performed to evaluate whether early CB ablation decreases the progression of left ventricular dysfunction, cardiac remodeling, and arrhythmic episodes and improves survival. The CHF rats developed increased CB chemoreflex drive and chronic central pre-sympathetic neuronal activation, increased indexes of elevated sympathetic outflow, increased breathing variability and apnea incidence, and desensitization of the baroreflex. Selective CB ablation reduced the central pre-sympathetic neuronal activation by 40%, normalized indexes of sympathetic outflow and baroreflex sensitivity, and reduced the incidence of apneas in CHF animals from 17 events/h to 8 events/h. When CB ablation was performed early, cardiac remodeling, deterioration of left ventricle ejection fraction, and cardiac arrhythmias were reduced. Most importantly, the rats that underwent early CB ablation exhibited an 85% survival rate compared with 45% survival in CHF rats without the intervention. Carotid chemoreceptors play a seminal role in the pathogenesis of heart failure, and their targeted ablation might be of therapeutic value to reduce cardiorespiratory dysfunction and improve survival during CHF.

Commentary:

Carotid body chemoreceptors are up-regulated in patients with heart failure. This can lead to higher sympathetic nervous system traffic, decreased baroreceptor sensitivity, and irregular breathing with an increase in the number of apneas and hypopnea. Del Rio et al. sought to determine whether some of these common heart failure manifestations could be improved, or even reversed, if the carotid body chemoreceptor overactivity were blunted.

Using a coronary artery ligation model of myocardial infarction and heart failure in rats, they performed a sham-controlled study of carotid body denervation 16 weeks post myocardial infarction using cryo-ablation. The authors argue that cryo-ablation allows for selective elimination of carotid body chemoreceptors without damaging the carotid baroreceptor, which is geographically proximate.

They found that the carotid body denervation led to a 40% decreased in neuronal activation in the rostral ventral lateral medulla (measured by c-fos staining), normalized sympathetic nervous system traffic, normalized cardiovagal baroreceptor sensitivity, and decreased apnea/hypopnea rates. Overall, carotid body denervation normalized “autonomic balance” in patients with heart failure.

They went on to study the effects of carotid body denervation 2 weeks post myocardial infarction (early) before a significant amount of ventricular remodeling has taken place. These results were even more remarkable. The group with the early denervation procedure had a better preserved left ventricular ejection fraction, a smaller left ventricular diastolic volume, less arrhythmia on telemetry, and most impressively increased survival at 16 weeks post-MI. The 16-week survival in the infarcted rats increased from 45% without the procedure up to 85% if this procedure was performed at 2 weeks.

This is a very important “proof of concept” study that carotid body ablation, in the setting of carotid body chemoreceptor overactivity and heart failure, favorably affects the normalization of sympathetic nerve traffic, baroreceptor sensitivity, and breathing. When this procedure was done early post MI, it also decreased ventricular remodeling, decreased post MI arrhythmia, and decreased the mortality rate in this population. While these study results are truly remarkable, it is worth noting that the study was done in the absence of “state-of-the-art” pharmacological therapy and a post MI setting. Further studies will be needed to see if the benefits of carotid body ablation will persist in the setting of contemporary therapies including beta-blocker and ACE inhibitor use (and possibly a cardiac rehabilitation program).

Importantly, these benefits were seen even though the procedure was done post MI. This is important if we want to consider translating this therapy to the clinic or to the hospital, which I expect will happen. There are already companies trying to develop the tools required for such a procedure in him in patients. As carotid body denervation moves forward toward human trials, another question that should be considered is what is the best approach to ablating the carotid body. Is a procedure required (such as was performed here) or could pharmacological therapies be developed to accomplish a similar goal less invasively?

I look forward to seeing how this therapy develops over the next few years.

Dissection of carotid sinus hypersensitivity: the timing of vagal and vasodepressor effects and the effect of body position. Krediet CT, Jardine

DL, Wieling W. (Amsterdam, The Netherlands and Christchurch, New Zealand). Clin Sci (Lond). 2011;121:389–396

Article Summary:

The authors assessed the timing of vagal and sympathetic factors that mediate hypotension during CSM (carotid sinus massage) in patients with carotid sinus hypersensitivity. They hypothesized that a fall in cardiac output would precede vasodepression, and that vasodepression would be exaggerated by head-up tilt. They performed pulse contour analyses on blood pressure recordings during CSM in syncope patients during supine rest and head-up tilt. In a subset, they simultaneously recorded muscle sympathetic nerve activity supine. During supine rest, systolic blood pressure decreased from 150 ± 7 mmHg to 107 ± 7 mmHg ($P < 0.001$) and heart rate from 64 ± 2 to 39 ± 3 beats/min ($P < 0.01$). Cardiac output decreased with heart rate to nadir ($66 \pm 6\%$ of baseline), 3.1 ± 0.4 s after onset of bradycardia. In contrast, total peripheral resistance reached nadir ($77 \pm 3\%$ of baseline) after 11 ± 1 s. During head-up-tilt, systolic blood pressure fell from 149 ± 10 to 90 ± 11 mmHg and heart rate decreased from 73 ± 4 beats/min to 60 ± 7 beats/min. Compared with supine rest, cardiac output nadir was lower ($60 \pm 8\%$ compared with $83 \pm 4\%$, $P < 0.05$), whereas total peripheral resistance nadir was similar ($81 \pm 6\%$ compared with $80 \pm 3\%$). The time to nadir from the onset of bradycardia did not differ from supine rest. At the onset of bradycardia there was an immediate withdrawal of muscle-sympathetic nerve activity while total peripheral resistance decay occurred much later (6–8 s). The hemodynamic changes following CSM have a distinct temporal pattern that is characterized by an initial fall in cardiac output (driven by heart rate), followed by a later fall in total peripheral resistance, even though sympathetic withdrawal is immediate. This pattern is independent of body position.

Commentary:

Carotid sinus hypersensitivity is often defined by the response to carotid sinus massage (CSM) in combination with the reproduction of clinical symptoms. The European Society of Cardiology guidelines define a cardioinhibitory response as a cardiac pause lasting ≥ 3 seconds and a vasodepressor response as a drop in systolic blood pressure of ≥ 50 mmHg. The guidelines emphasized the importance of performing CSM with the patient upright, if the supine CSM was not positive. Multiple studies have shown that upright CSM has higher test sensitivity than supine CSM. The presumption has been that the vasodilatory response is more difficult to bring out with the patient supine. With upright posture, one can see more hypotension due to a more marked reduction in total peripheral resistance.

Krediet et al. report on careful review of several patients from 2 centers that were studied with careful physiologic monitoring during and after CSM. In the supine vasodepressor subgroup, the nadir cardiac output (largely reflecting a drop in stroke volume) is reached in about 3 seconds following CSM onset. However, the nadir total peripheral resistance is not reached until 11 seconds following CSM onset. A subgroup of the patients underwent microneurography during the procedure, and sympathetic nerve traffic stopped immediately at the start of the heart rate decline. So it appears that the alterations in sympathetic and

parasympathetic function occurred very rapidly, but there is a neurovascular "lag time" of 6–8 seconds before the vascular resistance "bottoms out".

A similar phenomenon was noted in the cardioinhibitory subgroup. The authors looked at how quickly cardiac output and vascular resistance recovered with the return heartbeat following the pause. Cardiac output recovered to normal or overshoot within 1–2 seconds, whereas the total peripheral resistance did not recover back to baseline for 5–10 seconds after the return heartbeat. There is again this evidence of a "lag time", this time for the recovery of vascular resistance recovery, as opposed to a decrease in vascular resistance.

The authors studied a subgroup of the patients studied both supine and upright. Contrary to conventional wisdom, the total peripheral resistance drop was not different between the 2 body positions. Rather, the cardiac output nadir was significantly lower with upright posture. These data suggest that upright posture (or head up tilt) with carotid sinus massage does not augment a vasodilatory or vasodepressor response, but rather that upright posture lowers the stroke volume and cardiac output (compared with the supine posture) and this "unmasks" a vasodepressor response.

These data suggest that strategies to augment stroke volume might be useful in carotid sinus hypersensitivity patients with a vasodepressor response. These strategies could include blood volume expansion, the use of abdominal binders, or pharmacological vasoconstrictors such as midodrine HCl.