EDITORIAL COMMENT

Carotid Body Denervation

Too Soon to Get Breathless About Heart Failure?*

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The carotid body chemoreceptors are the primary oxygen sensors in both humans and mammals (1). When arterial oxygen (O2) levels fall, they evoke a rise in minute ventilation that mirrors the O2 hemoglobin dissociation curve. When activated, they also evoke large increases in efferent sympathetic nerve activity (2). For many years, these physiological responses were thought to be mediated almost exclusively by arterial O2 partial pressure. Starting in the 1960s, carotid body ablation in humans was used as an experimental treatment for bronchial asthma and chronic obstructive pulmonary disease, but the procedure failed to produce significant benefits for patients. Recent evidence has emerged in animal models of congestive heart failure (CHF), demonstrating that chronic reductions in carotid body blood flow might sensitize the chemoreceptors to increase both their tonic activity and responses to hypoxia (3). In this context, at least some CHF patients have augmented ventilatory responses to hypoxia, showing that this phenomenon occurs in humans with CHF (4). The question then is does the enhanced activity of the carotid bodies contribute to the various forms of dyspnea and devastating sympathoexcitation seen in CHF (5)?

In this issue of the Journal, Del Rio et al. (6) induced myocardial infarction and subsequent CHF in rats and denervated the carotid bodies after the infarction in some of the animals. They found a host of improvements in autonomic, cardiac, and respiratory function and an improved survival rate 14 weeks after denervation when compared with CHF control subjects. These findings underscore the idea that the carotid bodies become overactive and contribute to the pathophysiology of CHF. The results of this study also raise several key ideas that are relevant to the treatment of heart failure, especially if carotid body denervation (CBD)

produces added benefits that are not associated with traditional therapies such as exercise training and medication.

Some benefits of CBD might be similar to exercise training in CHF (Fig. 1). Both might have similar effects on sympathetic activity. Exercise training in human (7) and animal (8) CHF models reduces sympathetic nerve activity to values observed in normal control subjects. Along these lines, Del Rio et al. (6) found that CBD restores the low-frequency component of systolic blood pressure variability (estimate of sympathetic tone to the vasculature) to values obtained by normal sham-operated rats. Similarly, both exercise training (9) and CBD improve cardiac vagal activity by augmenting the high-frequency component of heart rate variability. Baroreflex function also seems to be restored after exercise training (10) or CBD. Therefore, autonomic function is improved by both therapies. Additionally, both therapies positively impact cardiac remodeling (11) and normalize breathing patterns (12) after myocardial infarction. Like CBD in rats, exercise training in humans with CHF can also improve mortality (13). A critical question is does exercise training normalize carotid body responses in CHF patients? And if this occurs, does it play a role in the positive effects of training on sympathoexcitation in CHF?

Despite the potential similarities between exercise training and CBD on sympathetic outflow in CHF, it is unlikely that CBD provides similar widespread physiological gains achieved by exercise training in CHF (Fig. 1). These include improved exercise tolerance, endothelial function, peripheral blood flow, and various metabolic parameters. Furthermore, exercise training reduces CHF-related hospital visits (14). Although CBD seems tempting as a therapeutic tool in humans to improve CHF-related pathophysiology, we currently can only speculate about all the relevant physiological benefits/side effects that might be achieved or encountered in human trials with this therapy.

The CBD data from Del Rio et al. (6), along with the exercise training data noted in the preceding text, are consistent with ideas that sympathoinhibitory therapeutic strategies are critical in CHF. In this context, a notable success in the treatment of CHF has been the widespread adoption of beta-blocker therapy. There were hints that this therapy might be effective as early as the middle 1970s, but for a variety of reasons, it was not widely adopted until much later (15). More recent approaches to pharmacological sympathoinhibition with drugs like moxonidine have been less promising (16). However, the beta-blocker data, plus earlier data from hypertension trials, have shown that sympatholytic therapy is highly effective in reducing mortality (17). Along these lines, there is at least some evidence in the hypertension literature indicating that reflex increases in sympathetic outflow associated with lowering blood pressure might offset some of the mortality benefit associated with the lower pressure (18).

That said, do we need new and improved sympathoinhibitory drugs? In addition to being beneficial for classic CHF, would they be useful for the current wave of obesity-driven “resistant” hypertension that seems to be associated with high levels of sympathetic activity? Would they also be useful in the

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treatment of the emerging epidemic of diastolic dysfunction? Have we moved away from more renal-centric views of peripheral vasoconstriction to more central sympathetically driven mechanisms that require new treatment options (19)? Along these lines, sympatholytic device-based treatment for resistant hypertension has shown some promise, and there is discussion about its potential utility in CHF (16).

The findings by Del Rio et al. (6) are likely to increase enthusiasm for CBD as a possible therapeutic strategy in CHF as well as hypertension (20). However, is this warranted? The many potential consequences of CBD need to be addressed to ensure patient safety when performing normal activities (e.g., riding on a plane, traveling to altitude), considering the central role that the carotid body chemoreceptors play in maintaining arterial O₂ saturation during these challenges. Furthermore, patients with CHF have a number of comorbidities, such as respiratory diseases and obstructive sleep apnea, and CBD might worsen these conditions. Finally, ablation of the carotid body chemoreceptors might pose risks, including concurrent baroreceptor failure (21). All of these potential limitations need to be carefully considered before the carotid bodies become routine therapeutic targets in diseases like CHF that are associated with sympathoexcitation. More importantly, the search for sympatholytic therapies needs to be expanded while exercise training should continue to be prescribed.

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REFERENCES

17. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 1967;202:1028–34.

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