Editorial

Eyeing Autonomic Dysregulation in Heart Failure

KHALIL MURAD, MD, MS, AND MARK E. DUNLAP, MD

Cleveland, OH

The autonomic nervous system plays an integral role in cardiovascular physiology, and autonomic dysregulation (AD) contributes to the pathophysiology of many cardiovascular disorders. AD in patients with heart failure (HF), consisting primarily of sympathetic up-regulation, parasympathetic down-regulation, and abnormal cardiovascular reflexes, is associated with poor outcomes, and has been the target of many interventional studies.[1]

Despite extensive research pertaining to AD in HF, its clinical utility is still hindered by many challenges, 3 of which are worth mentioning here. First, to date there is no reliable and practical method to accurately identify and quantitate AD in HF. The degree of activation of the sympathetic nervous system as measured by circulating plasma norepinephrine levels has been shown to portend worse prognosis in HF,[2] but the assay is sensitive to sample and laboratory variation and has not come into widespread clinical use. Heart rate variability (HRV) can be used as an indirect measure of parasympathetic control, and it has been shown to add prognostic predictive value in patients with left ventricular dysfunction after myocardial infarction.[3] However, techniques of measurement and lack of standardization have hampered its widespread clinical utility. More importantly, no interventions specifically targeting its use have been shown to improve clinical outcomes. HRV is also not feasible in patients with nonsinus rhythm or frequent ventricular ectopy.

Second, the causality of AD in HF has not been established. AD is present in several conditions known to be important precursors or comorbidities in HF, such as hypertension, diabetes, obesity, and obstructive sleep apnea. It remains unknown, however, if AD in these conditions contributes mechanistically to the development of HF and if modulating AD can prevent HF.

Third, with the exception of beta-blockade to block beta-adrenergic activation, interventions directed specifically at restoring normal autonomic regulation in patients with established HF thus far have had disappointing results, especially those directed at up-regulating parasympathetic tone. Despite encouraging studies in nonhuman animals, vagal stimulation invoked by various methods has failed to show benefit in humans with HF,[4,5] although an additional study is ongoing (NCT 03425422).

In the current issue of the *Journal*, Nozaki et al. introduce a novel method of assessing AD, the pupillary light reflex (PLR), and demonstrate its prognostic value in patients previously hospitalized with HF. The investigators found that reduced recovery time in PLR was associated with increased mortality. This association was independent from other known predictors of mortality in HF and added prognostic value to the Seattle Heart Failure Model (SHFM).[6]

The findings of this study confirm the established knowledge of the presence of AD in HF and its association with increased mortality. More importantly, the study introduces a potentially useful prognostic tool, namely the PLR recovery time, that could possibly be added to the battery of clinical prognostic tools in HF. Having said that, our enthusiasm for adopting this method for identifying and quantifying AD in HF is hindered by several caveats that should be mentioned here. First, the authors defined PLR recovery time as "time to 63% redilation" (after light stimulus). In the absence of reporting the physiologic correlate underlying this choice, the significance of using the 63% figure remains unclear. Second, this was a derivation cohort, and no intervention was performed to determine whether including this measure helps to target therapy, which would likely require serial prospective studies before and after intervention. Third, although it was a prospective study, no validation cohort was used to prospectively test the additive value to the SHFM to alter outcomes. Finally, the investigators noted that they "measured PLR to evaluate autonomic nervous function as an outcome of cardiac rehabilitation." However, such measures are not routine practice in cardiac rehabilitation programs in general, and they were not used in the only large-scale study of cardiac rehabilitation in patients with HF.[7] Therefore,

both the borderline significance underlying these findings in terms of affecting outcomes, as well as the logistics involved for measurement, render this a finding that is more of academic than practical interest.

Although various functions of the autonomic nervous system can be reflected by surrogate measures such as the PLR and HRV, the impact of AD on these physiologic processes is complex and may vary based on the underlying conditions leading to AD, its severity, and its interaction with other conditions. Therefore, impairment in various domains of PLR or HRV as surrogate measures of AD may not follow a simple linear relationship between AD and impaired PLR and HRV. Studies are needed to improve our understanding of the various processes leading to AD in HF and their impacts on the different components of PLR or different domains of HRV. This may help us to identify the most accurate surrogate measure to identify and quantify AD in HF, and ultimately to develop therapies targeting AD in HF to perhaps further improve HF outcomes.

Disclosures

None.

References

1. Zhang DY, Anderson AS. The sympathetic nervous system and heart failure. Cardiol Clin 2014;32:33–45.
2. Anand IS, Fisher LD, Chiang YT, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003;107:1278–83.
3. la Rovere MT, Pinna GD, Hohnloser SH, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. Circulation 2001;103:2072–7.
4. Gold MR, van Veldhuisen DJ, Hauptman PJ, et al. Vagus nerve stimulation for the treatment of heart failure: The INOVATE-HF Trial. J Am Coll Cardiol 2016;68:149–58.
5. Zannad F, de Ferrari GM, Tuinenburg AE, et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the Neural Cardiac Therapy for Heart Failure (NECTAR-HF) randomized controlled trial. Eur Heart J 2015;36:425–33.
6. Levy W, Mozaffarian D, Linker D, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113:1424–33.
7. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.