JOURNAL CLUB

The baroreflex effectiveness index as an early marker of autonomic dysfunction in heart failure

Joseph C. Watso, Matthew C. Babcock, Kamila U. Migdal and Austin T. Robinson
Department of Kinesiology and Applied Physiology, University of Delaware, Newark, DE, USA
Email: jwatso@udel.edu

Heart failure (HF) is a major public health problem worldwide, associated with significant morbidity, mortality and healthcare expenditure (Roger, 2013). Excessive sympathetic nervous system activation occurs in HF, but the underlying mechanisms have not been fully characterized (Mosterd & Hoes, 2007). One potential factor in the pathophysiology of HF is altered baroreflex regulation. The baroreflex is essential in haemodynamic regulation, facilitating rapid adjustments in heart rate (HR) and sympathetic nerve activity to maintain arterial pressure (AP). Animal models demonstrate that baroreflex control of HR is reduced during HF, but whether alterations in baroreflex control of sympathetic nerve activity are similarly altered in HF remains equivocal. Thus, in a recent paper in *The Journal of Physiology*, Lataro *et al.* sought to determine if baroreflex control of renal sympathetic nerve activity (RSNA) was altered in a rodent model of early stage HF, induced by coronary ligation (Lataro *et al.* 2017).

Lataro and colleagues used three different approaches to investigate baroreflex control of RSNA: standard baroreflex gain analysis (AP *vs.* RSNA curve, which the authors term the barocurve); cross-spectral analysis (transfer function); and the sequence method. The gold standard of evaluating baroreflex function was carried out with bolus injections of phenylephrine, which causes a rise in AP, and nitroprusside, which causes a fall in AP. Baroreflex gain analysis was evaluated during the pharmacologically induced rise and fall of AP. Cross-spectral analysis and the sequence method evaluate baroreflex function near the operating point. The sequence method had previously been applied to assess spontaneous AP fluctuations and corresponding changes in heart rate to determine baroreflex sensitivity (BRS) and baroreflex effectiveness index (BEI). BEI quantifies the number of times the baroreflex is effective in mediating changes in HR in response to spontaneous AP changes (Di Rienzo *et al.* 2001). Surprisingly, Di Rienzo *et al.* reported that average 24-hour BEI was only 0.21 in healthy humans, indicating that the baroreflex responds to spontaneous AP changes with consequent changes in HR in 21% of cases. It has been speculated that the other 79% of cases may result from non-baroreflex mechanisms that might include central neural influences, humoral substances, chemoreflexes and respiration that may mask or interfere with baroreflex influence on HR (Di Rienzo *et al.* 2001). Sinoaortic denervation reduced BEI 89%, suggesting that the BEI is directly related to baroreflex function (Di Rienzo *et al.* 2001). Di Rienzo *et al.* recorded R–R interval to evaluate baroreflex control of HR, whereas in the present study Lataro *et al.* directly recorded RSNA to evaluate baroreflex control of sympathetic nerve activity. Here, BEI represents the fraction of spontaneous AP ramps that effectively elicited baroreflex-mediated changes in RSNA.

The traditional measures of baroreflex control of RSNA (barocurve and transfer function) did not appear to be altered in early HF rats; however, BEI as assessed by the sequence method was decreased in HF. This finding led the authors to conclude that the use of BEI provides an advantage over the traditional methods of assessing BRS alone (i.e. barocurve, transfer function and sequence methods). Therefore, BEI may be a more sensitive measure of altered sympathetic regulation in early HF, providing direct evidence of baroreflex function, as well as indirect evidence of non-baroreflex mechanisms that may be masking the normal baroreflex (AP–RSNA) relation. Taken together, the results from BRS and BEI may vary but provide complementary information to better understand overall baroreflex function in HF.

Data from humans also support using BEI in addition to traditional measures of BRS to provide a more comprehensive picture of reflex cardiovascular regulation. As stated earlier, Di Rienzo *et al.* reported that average 24-hour BEI (related to baroreflex-mediated changes in HR) was 0.21 in healthy humans. Interestingly, the present study reported a much higher BEI value (0.45) in the control rodents. It is currently unclear if these values represent differential control of HR *vs.* RSNA, differences between species, or a combination of the two. Recently, lower cardiovagal BEI was observed in moderate HF patients (cohort of predominantly New York Heart Association classes II and III). Additionally, BEI closely correlated with other clinical HF parameters, leading to the conclusion that the addition of BEI improves risk stratification in HF patients (Fernandes Serôdio *et al.* 2016). Taken together with these recent human data, the findings of Lataro *et al.* suggest that the use of BEI to assess baroreflex control of HR and sympathetic nerve activity may offer a more thorough characterization and stratification of HF patients.

The findings of Lataro *et al.* establish the groundwork for future research to address other questions related to baroreflex assessment and potential underlying mechanisms of autonomic dysregulation seen in HF. In HF, it is suspected that activation of the renin–angiotensin–aldosterone system within the brain may play a role (Zucker *et al.* 2009). Specifically, it has been demonstrated that higher angiotensin II (ANG II) concentrations in the brainstem result in reduced sensitivity of various sympathoinhibitory reflexes, including the arterial baroreflex. Lataro and colleagues assessed baroreflex sequences by regressing RSNA *vs.* AP for all sequences (up and down sequences). Considering the differential effects of ANG II on the baroreflex control of HR when AP is increasing *vs.* decreasing, future examination of up sequences *vs.* down sequences may reveal differences in baroreflex-mediated changes in sympathetic nerve activity. Other future murine studies of interest include using microinjections of ANG II to determine if central activation of the renin–angiotensin–aldosterone system evoke alterations in BEI. In addition, the ligation used by Lataro *et al.* for creating HF resulted in increased heart weight, cardiac weight index, left ventricular

 DOI: 10.1113/JP274664

diastolic pressure and lower $+dP/dt$, consistent with early HF. It is important to determine if BEI may provide a more comprehensive analysis along with other indices of impaired baroreflex regulation in more advanced stages of HF. Further studies assessing BEI represented by the fraction of spontaneous AP ramps that effectively elicit baroreflex-mediated changes in muscle sympathetic nerve activity in humans also appear to be warranted.

References

Di Rienzo M, Parati G, Castiglioni P, Tordi R, Mancia G & Pedotti A (2001). Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. *Am J Physiol Regul Integr Comp Physiol* **280**, R744–R751.

Fernandes Serôdio J, Martins Oliveira M, Matoso Laranjo S, Tavares C, Silva Cunha P, Abreu A, Branco L, Alves S, Rocha I & Cruz Ferreira R (2016). The arterial baroreflex effectiveness index in risk stratification of chronic heart failure patients who are candidates for cardiac resynchronization therapy. *Rev Port Cardiol* **35**, 343–350.

Lataro RM, Silva LEV, Silva CAA, Salgado HC & Fazan R Jr (2017). Baroreflex control of renal sympathetic nerve activity in early heart failure assessed by the sequence method. *J Physiol* **595**, 3319–3330.

Mosterd A & Hoes AW (2007). Clinical epidemiology of heart failure. *Heart* **93**, 1137–1146.

Roger VL (2013). Epidemiology of heart failure. *Circ Res* **113**, 646–659.

Zucker IH, Schultz HD, Patel KP, Wang W & Gao L (2009). Regulation of central angiotensin type 1 receptors and sympathetic outflow in heart failure. *Am J Physiol Heart Circ Physiol* **297**, H1557–H1566.

Additional information

Competing interests

None declared.

Acknowledgements

The authors would like to thank Dr William B. Farquhar and Dr Megan M. Wenner for their critical evaluation and feedback in the preparation of this Journal Club article.