ESC European Society of Cardiology

European Journal of Cardiovascular Nursing (2024) **23**, e75–e76
https://doi.org/10.1093/eurjcn/zvae003

INVITED COMMENTARY

Marathon not sprint: fatigue and early symptoms detected with sympathetic dysfunction in patients with heart failure

Angela Durante *

Department of Translational Medicine, University of Eastern Piedmont Amedeo Avogadro, Via Solaroli 17, Palazzo Bellini, Room P89b, 28100 Novara, Italy

Received 29 December 2023; accepted 2 January 2024; published 16 January 2024

This invited commentary refers to 'Sympathetic dysfunction is associated with worse fatigue and early and subtle symptoms in heart failure: An exploratory sex-stratified analysis', by N. Stutsman *et al.*, https://doi.org/10.1093/eurjcn/zvad121.

Evidence indicates that dysfunction of the sympathetic nervous system is crucial in the development of heart failure (HF). This takes the form of persistent and adverse activation of sympathetic outflows to the heart and kidneys.[1] The sympathetic nervous system in HF is overactivated and stimulates the heart to contract more vigorously and more frequently.[2] It constitutes a compensation system that, however, exhausts the heart muscle in the long run. Adrenalin and noradrenalin are the effectors of this sympathetic hyperactivity. Metaphorically speaking, we could compare the heart to a sick mule forced to work uphill; the owner, to make it walk further, whips it (imagine the whip as the sympathetic system: adrenalin and noradrenalin). Initially, the mule works harder but eventually exhausts all the strength. However, a previous study suggests that hyperactivity of the sympathetic nervous system is associated with immune/inflammatory variables, occurs frequently before the onset of HF, and is present in HF with a maintained left ventricular ejection fraction (LVEF) [diastolic HF or heart failure with preserved ejection fraction (HFpEF)]. Plasma levels of catecholamine norepinephrine (NE), which is a strong indicator of a poor prognosis in HF, can be used to evaluate sympathetic function.[3] Furthermore, concomitant non-cardiac morbidities can increase sympathetic nervous system activity in HF, and genetic and demographic variables can alter it.[4] And it is precisely on the latter two assumptions that the article by Stutsman *et al.* is based, namely the association between catecholamine metabolites, resulting from sympathetic dysfunction, and physical symptoms perceived by patients with HF and the sex differences related to this association.[5] Therefore, it is important to know more about the symptom-related aspects because symptoms are the most noticeable part of the disease for patients who attribute the negative impact on their quality of life due to their symptoms.

Fatigue and early/subtle physical symptoms

In a recent meta-synthesis, fatigue in patients with HF was identified as distressing, predominant in many aspects of patient life, and related to clinical and patient-reported outcomes.[6] The same article pointed out that knowledge of the physiological aspects of fatigue in HF is inadequate, which affects our ability to treat and prevent the condition. Although many therapies are not available to reduce fatigue in patients with HF, they are needed to improve patient outcomes and quality of life. The results of the article by Stutsman and colleagues are informative about these issues by identifying sympathetic dysfunction as associated with worse fatigue.

Stronger association: more fragile women

The observed association was more pronounced in women compared with men. Regrettably, there is a dearth of literature on sex-linked dysmorphisms and their pathophysiological effects. Significant knowledge gaps exist about sex-specific mechanisms, such as the best pharmacological dosages for women and the criteria specific to a given sex for device therapy. A review of 740 completed cardiovascular clinical trials conducted between 2010 and 2017 found that women represent roughly 38% of the total participants.[7] Numerous studies that have investigated the enrolment of women in randomized controlled trials (RCTs) for HF since 2000 have found that the percentage of women enrolled has fluctuated between 21% and 29%.[8] Therefore, so far, treatment guidelines are based primarily on data from men. Certainly, further studies are needed to expand knowledge about the pathophysiological mechanisms to treat the subtle and early-stage symptoms of decompensation. The study by Stutsman and colleagues paves the way for new investigations, including genetic differences.

Acknowledgements

I would like to express our gratitude to the authors of the study "Sympathetic dysfunction is associated with worse fatigue and early and subtle symptoms in heart failure: An exploratory sex-stratified analysis" and the patients involved in their studies.

Funding

None declared.

Conflict of interest: none declared.

Data availability

Not applicable.

* Corresponding author. Tel: +39 0321660567, Email: angela.durante89@gmail.com

References

1. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J* 2012;**33**:1058–1066.
2. Gronda E, Dusi V, D'Elia E, Iacoviello M, Benvenuto E, Vanoli E. Sympathetic activation in heart failure. *Eur Heart J Suppl* 2022;**24**:E4–E11.
3. Minatoguchi S. Heart failure and its treatment from the perspective of sympathetic nerve activity. *J Cardiol* 2022;**79**:691–697.
4. Triposkiadis F, Briasoulis A, Kitai T, Magouliotis D, Athanasiou T, Skoularigis J, *et al.* The sympathetic nervous system in heart failure revisited. *Heart Fail Revs* 2023. doi:10.1007/s10741-023-10345-y
5. Stutsman NHB, Pavlovic N, Jurgens CY, Woodward WR, Lee CS, Denfeld QE. Sympathetic dysfunction is associated with worse fatigue and early and subtle symptoms in heart failure: an exploratory sex-stratified analysis. *Eur J Cardiovasc Nurs* 2024;**23**:532–539.
6. Pavlovic NV, Gilotra NA, Lee CS, Ndumele C, Mammos D, Dennisonhimmelfarb C, *et al.* Fatigue in persons with heart failure: a systematic literature review and meta-synthesis using the biopsychosocial model of health. *J Card Fail* 2022;**28**:283–315.
7. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation* 2020;**141**:540–548.
8. Parwani PJ, Spall HGCV, Mamas M. Representation of women in heart failure trials: does it matter? *Heart* 2022;**108**:1508–1509.