Clinical Research in Cardiology (2019) 108:1410–1411
https://doi.org/10.1007/s00392-019-01487-x

LETTER TO THE EDITORS

Reply to the letter "The role of heart rate in the assessment of cardiac autonomic modulation with heart rate variability"

Claudia Arab[1] · Luiz Carlos Marques Vanderlei[2] · Laércio da Silva Paiva[3] · Yori Gidron[4] · Celso Ferreira[1]

Received: 25 April 2019 / Accepted: 29 April 2019 / Published online: 28 May 2019

Sirs:

We received a letter about our recently published article [1]. Plaza-Florido et al. have suggested evaluations due to the importance of heart rate (HR) in the assessment of cardiac autonomic modulation with heart rate variability (HRV). The suggestions were about the influence of HR on HRV, which could impact our observed results.

In fact, we did not include HR as one of the predictor covariates in the multivariate models. No HR-adjustments were performed in the statistical analyses, as they proposed. However, we performed the exact same protocol of HRV measurement and analysis in all subjects, regardless of one's HR. As HR has been suggested as predictor of mortality in both healthy [2] and cancer patients [3], HR was used in our subsequent study as dependent variable in a regression model (See on page 930). The results showed that advanced breast cancer ($\beta = -0.13$, $p < 0.001$) and BMI ($\beta = 0.007$, $p = 0.015$) were associated with resting heart rate ($R^2 = 0.24$, $p < 0.001$).

We understood the concern pointed out by the authors and re-ran the analyses predicting patients' HRV, corrected for HR. In this new analysis, after controlling for HR, menopausal status was no longer associated with RMSSD ($R^2 = 0.19$, $p = 0.001$; advanced breast cancer $\beta = -0.006$, $p = 0.017$; age $\beta = -0.0007$, $p < 0.001$; menopausal status $\beta = 0.007$, $p = 0.08$), and advanced stage was no longer associated with SDNN ($R^2 = 0.10$, p = 0.006; advanced breast cancer $\beta = -0.004$, $p = 0.120$; age $\beta = -0.0004$, $p < 0.003$). After controlling for HR, the fact that tumor stage is no longer correlated with SDNN while it is still correlated with RMSSD could be partly explained by the fact that HR is mostly sympathetically driven, and SDNN is a global index (i.e. parasympathetic and also sympathetically driven). In contrast, RMSSD is more purely a vagal parasympathetic index, thus its prediction may be less affected by controlling for HR [4]. Therefore, controlling for HR did not alter our main finding that cancer severity is related to lower vagally dependent HRV. This is in line with two studies showing that HRV may have a stronger prognostic role in cancer than does HR. One study on HRV and the colon cancer tumor marker CEA found that while HR only tended to predict future CEA levels, HRV was a significant and independent predict of CEA [5]. In the study by De Couck et al. [6], the prognostic role of HRV was not adjusted for HR because among all confounders, only stage, radiotherapy, hormonal treatment, age and baseline prostate-specific antigen (PSA) were related to PSA levels, and HR did not predict PSA.

We are thankful for the letter. This discussion extends perspectives for future investigations.

This reply refers to the article available at https://doi.org/10.1007/s00392-019-01486-y.

✉ Claudia Arab
ac.arabclaudia@gmail.com

1 Escola Paulista de Medicina, Departamento de Medicina, Disciplina de Cardiologia, Hospital São Paulo, Universidade Federal de São Paulo, 715 Napoleão de Barros St, São Paulo, SP 04024-002, Brazil

2 Faculdade de Ciência e Tecnologia, Departamento de Fisioterapia, Universidade Estadual Paulista Júlio de Mesquita Filho, 305 Roberto Símonsen St, Presidente Prudente, SP 19060-900, Brazil

3 Laboratório de Epidemiologia e Análise de Dados, Centro Universitário Saúde ABC, 2000 Lauro Gomes Av, Santo André, SP 09060-870, Brazil

4 Sciences Cognitives et Sciences Affectives-SCALab, Universités de Lille, Rue du barreau, BP 60149, 59653 Villeneuve d'Ascq Cedex, France

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest None declared.

References

1. Arab C et al (2018) Cardiac autonomic modulation impairments in advanced breast cancer patients. Clin Res Cardiol. https://doi.org/10.1007/s00392-018-1264-9
2. Anker MS et al (2016) Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study. Eur J Heart Fail 18(12):1524–1534
3. Lee DH et al (2016) Resting heart rate as a prognostic factor for mortality in patients with breast cancer. Breast Cancer Res Treat 159(2):375–384
4. Lombardi F (2011) Origin of heart rate variability and turbulence: an appraisal of autonomic modulation of cardiovascular function. Front Physiol 2:95
5. Mouton C et al (2012) The relationship between heart rate variability and time-course of carcinoembryonic antigen in colorectal cancer. Auton Neurosci 166(1):96–99
6. De Couck M, van Brummelen D, Schallier D, De Grève J, Gidron Y (2013) The relationship between vagal nerve activity and clinical outcomes in prostate and non-small cell lung cancer patients. Oncol Rep 30(5):2435–2441