Heart rate in chronic heart failure: an overlooked risk factor

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This editorial refers to 'Prognostic importance of temporal changes in resting heart rate in heart failure patients: an analysis of the CHARM program'[†], by A. Vazir et al., on page 669.

Introduction

Heart rate measured by palpation and more recently by auscultation has been used for centuries to assess the cardiovascular condition of patients (*Figure 1*). It is, however, only recently that the importance of heart rate measurement as a prognostic factor has been recognized in unselected healthy populations, patients with hypertension or coronary artery disease, after myocardial infarction, and in those with left ventricular dysfunction of ischaemic origin or heart failure with reduced ejection fraction.[1–5] Moreover, it has been shown that in patients with chronic heart failure, reduced ejection fraction, in sinus rhythm, and with an elevated heart rate ($\geq$ 70 b.p.m.) at baseline, the use of a pure heart rate-slowing agent, ivabradine, was associated with an improvement in cardiovascular outcomes.[6] This observation suggests that in heart failure with low ejection fraction, heart rate not only is a risk marker but also is a modifiable risk factor, unlike what was recently observed in coronary disease patients with preserved cardiac function.[7]

Vazir et al. now report that in the large cohort of 7599 patients enrolled in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity CHARM) programme, temporal changes in resting heart rate from the preceding visit as well as time-updated heart rate were associated with outcomes.[8] Any increase in heart rate of 5 b.p.m. from the preceding visit is associated with a 9% increase in the risk of all-cause mortality and 6% increase in the composite of cardiovascular death or hospitalization for heart failure and that time-updated heart rate is also associated with risk.

These results confirm and extend previous observations on the role of heart rate as a risk marker in heart failure.

The prognostic value of baseline heart rate is now well established in both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. It is assumed that increased heart rate might reflect sympathetic activity and progression of the disease or trigger potentially lethal arrhythmias.[9] In the placebo arm of the SHIFT trial, each increase of 5 b.p.m. was associated with a 16% increase in the risk of cardiovascular death or heart failure hospitalization.[10] In a previous analysis of the CHARM population, including patients with both reduced and preserved ejection fraction, any 10 b.p.m. increase in heart rate was associated with a 8% risk of all-cause mortality in patients without atrial fibrillation, regardless of ejection fraction.[11] A similar relationship was observed between increased heart rate and the risk of cardiovascular mortality or heart failure hospitalizations. This association was also demonstrated in the analysis of the I-Preserve population where all patients had an ejection fraction > 45%. In this analysis, each increase of 12 b.p.m. was associated with a 13% increase in the risk of cardiovascular death or heart failure hospitalization, with the exception of patients in atrial fibrillation.[12]

The analysis of Vazir et al.[8] shows that not only the resting baseline heart rate but also the change from the preceding visit is a powerful predictor of poor outcomes in a broad population of chronic heart failure patients with either preserved or reduced ejection fraction. It therefore suggests that the simple measure of this vital sign during the course of the disease should be a warning signal and should lead to treatment and follow-up intensification in order to improve outcomes. The predictive value of heart rate changes is further strengthened by the fact that it persists even after introduction of beta-blockers or adjustment of beta-blocker dose.

One interesting observation of Vazir's study is that unlike other studies where resting heart rate was measured by analysis of electrocardiographic tracings only, the ominous role of increased heart rate can also be determined by palpation or auscultation after 5 min of rest.

The study also shows that in patients with atrial fibrillation at baseline, there is a weaker correlation between heart rate at any time compared with patients in sinus rhythm. Previous observations in CHARM and in I-Preserve have indeed suggested that in this subgroup of patients baseline heart rate measurement is not predictive of outcome.[11,12] This is possibly related to the high instantaneous rate variability induced by atrial fibrillation which makes a short time assessment inaccurate. Here, the most recent value of heart rate remains

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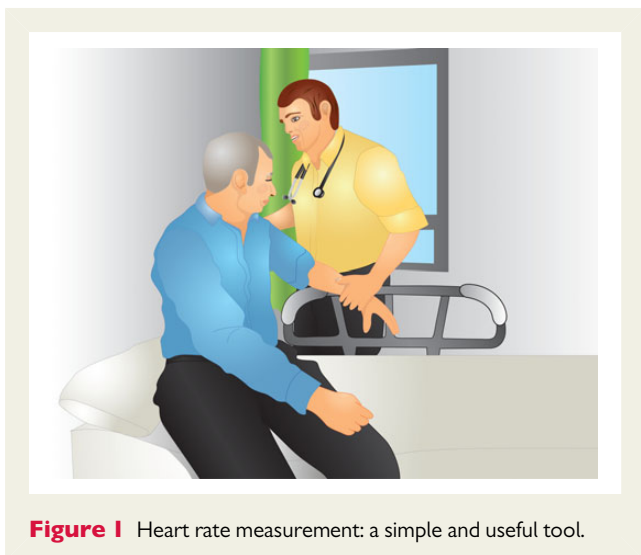
Figure 1 Heart rate measurement: a simple and useful tool.

predictive of outcomes possibly because it reflects better the '"heart rate load' over time than a single baseline measurement.

There are few examples of serial measurements of heart rate as markers of risk in cardiovascular conditions: one study showed an association with mortality in a hypertensive population, whereas an analysis of the ON TARGET/TRANSCEND trials pooling 31 531 patients at high cardiovascular risk showed that in trial average heart rate was independently associated with cardiovascular events and mortality.[13,14] The current analysis suggests that regular assessment of heart rate also provides useful prognostic information in chronic heart failure.

Finally, the study of Vazir et al. shows that lowering heart rate is associated with a lower risk even after adjustment for beta-blocker dose, and brings another piece of evidence for heart rate being a modifiable risk factor in chronic heart failure.

This study raises two important questions. If an increased heart rate is observed during the follow-up of a patient with heart failure, which heart rate-lowering agent should be used and what should be the target to reach in order to improve outcomes? In the study of Vazir et al., only 55% of the patients were receiving beta-blockers at baseline and, although the paper provides no information, it is very likely that most patients who experienced a drop in heart rate during follow-up were introduced a beta-blocker or were up-titrated to a higher dose. In SHIFT, the ivabradine outcome trial, a vast majority of the patients were receiving a beta-blocker (90%) and therefore no direct comparison of the potential advantages of the two heart rate-lowering strategies can be made. Therefore, the recommended strategy should be in line with international guidelines which advise to start with a beta-blocker and consider the addition of ivabradine in patients remaining symptomatic, in sinus rhythm, and with a heart rate of $>$ 70 b.p.m.[15] The only analysis on the optimal target heart rate derives from SHIFT where the patients treated by ivabradine who reached a heart rate of $<$ 60 b.p.m. at 4 weeks after randomization had the best outcome.

Conclusion

In conclusion, Vazir et al. demonstrate in a broad population of chronic heart failure with reduced or preserved heart failure that regular assessment of heart rate is predictive of outcomes, and can identify patients at high risk of death or hospitalization. This simple and inexpensive

evaluation of the '"heart rate burden' should therefore be put into practice as a standard procedure. Whether more sophisticated assessment of heart rate by remote monitoring devices can further improve risk prediction in individual patients is an open question. In the meantime, doctors should pay more attention to palpation, auscultation, or electrocardiogram for the regular follow-up of heart failure patients.

References

1. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham study. *Am Heart J* 1987;**113**:1489–1494.
2. Palatini P, Thijs L, Staessen JA, Fagard RH, Bulpitt CJ, Clement DL, de Leeuw PW, Jaaskivi M, Leonetti G, Nachev C, O'Brien ET, Parati G, Rodicio JL, Roman E, Sarti C, Tuomilehto J. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension.* Arch Intern Med 2002;**162**:2313–2321.
3. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* 2005;**26**:967–974.
4. Bangalore S, Messerli FH, Ou FS, Tamis-Holland J, Palazzo A, Roe MT, Hong MK, Peterson ED; CRUSADE Investigators. The association of admission heart rate and in-hospital cardiovascular events in patients with non ST-segment elevation acute coronary syndromes: results from 135164 patients in the CRUSADE quality improvement initiative. *Eur Heart J* 2010;**31**:552–560.
5. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, BEAUTIFUL investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008;**372**:817–821.
6. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, Investigators S. Ivabradine and outcomes in chronic heart falure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
7. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R for the SIGNIFY Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014;**371**:1091–1099.
8. Vazir A, Claggett B, Jhund P, Castagno D, Skali H, Yusuf S, Swedberg K, Granger CB, McMurray JJV, Pfeffer M, Solomon SD. Prognostic importance of temporal changes in resting heart rate in heart failure patients: an analysis of the CHARM program. *Eur Heart J* 2015;**36**:669–675.
9. Palatini P, Julius S. Elevated heart rate: a major risk factor for cardiovascular disease. *Clin Exp Hypertens* 2004;**26**:637–644.
10. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, Investigators S. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomized placebo-controlled trial. *Lancet* 2010;**376**:886–94.
11. Castagno D, Skali H, Takeuchi M, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pfeffer MA, McMurray JJ, Solomon SD, Investigators C. Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) program. *J Am Coll Cardiol* 2012;**59**:1785–1795.
12. Bohm M, Perez A, Jhund PS, Reil JC, Komajda M, Zile MR, McKelvie RS, Anand IS, Massie BM, Carson PE, McMurray JJV, on behalf of the I-Preserve Committees and Investigators. Relationship between heart rate and mortality and morbidity in the irbesartan patients with heart failure and preserved systolic function trial (I-Preserve). *Eur J Heart Failure* 2014;**16**:778–787.
13. Paul L, Hastie CE, Li WS, Harrow C, Muir S, Connell JM, Dominiczak AF, McInnes GT, Padmanabhan S. Resting heart rate pattern during follow-up and mortality in hypertensive patients. *Hypertension* 2010;**55**:567–574.
14. Lonn EM, Rambihar S, Gao P, Florian F, Custodis-Karen S, Teo KK, Yusuf S, Böhm M. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. *Clin Res Cardiol* 2014;**103**:149–159.
15. Authors/Task Force Members : McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk C, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–1847.