Europace (2010) **12**, 155–157
doi:10.1093/europace/eup437

EDITORIAL

Heart rate and arrhythmic risk: old markers never die

Maria Teresa La Rovere*

Divisione di Cardiologia, Fondazione 'Salvatore Maugeri' IRCCS, Istituto Scientifico di Montescano, Montescano, 27040 Montescano, Pavia, Italy

This editorial refers to 'The relationship between high resting heart rate and ventricular arrhythmogenesis in patients referred to ambulatory 24 h electrocardiographic recording' by E.Z. Soliman *et al.*, on page 261.

The medical literature of the last 30 years has increasingly emphasized the role of elevated resting heart rate as an independent predictor of all-cause and cardiovascular mortality among men and women in the general population and in several pathological conditions, including coronary artery disease, myocardial infarction, and heart failure.[1] The independent contribution of heart rate to cardiovascular outcomes after adjustment for the effects of known risk factors has been clearly established in large series of apparently healthy subjects[2] and supports the recent re-appreciation of heart rate as a 'new' cardiovascular risk factor rather than a simple risk predictor reflecting other pathogenetic connections.[3]

Epidemiological evidence has also indicated that elevated heart rate reflects an increased propensity to sudden cardiac death in apparently healthy subjects.[4–6] In the Framingham Heart Study,[5] patients with the highest quintile of heart rate (>88 bpm) had a 5- and 2-fold higher risk of sudden death in men and in women, respectively, compared with subjects with heart rates <65 bpm. In the British Regional Heart Study,[6] a wide range of established risk factors for ischaemic heart disease have been examined in relation to sudden and non-sudden cardiac death in a cohort of 7735 middle-aged men with and without pre-existing ischaemic heart disease. Increased heart rate (>90 bpm) emerged as a potential specific factor for sudden cardiac death in that the significant association with cardiovascular mortality was largely due to increased risk of sudden cardiac death. Of interest, the magnitude of relative risk of sudden cardiac death was greater in individuals without pre-existing ischaemic heart disease. Similarly, in the Paris Prospective Study which included 7746 male subjects aged 42–53 years,[7] over a 23-year follow-up, the relative risk for sudden cardiac death significantly exceeded the relative risk for total mortality, cardiovascular death, and fatal myocardial infarction. Specifically, the risk in men with the highest quintile of heart rate (>75 bpm) was 3.8-fold than in those in the lowest quintile (<60 bpm), whereas risk for fatal myocardial infarction, cardiovascular, and total mortality was approximately twice greater. Moreover, when traditional risk factors, parental history of sudden death, and sports activity were entered into the survival model, resting heart rate remained independently related to sudden death but not to fatal myocardial infarction.

Although factors affecting heart rate are multiple, there is no doubt that neural influences, either central or reflex in nature, play a major role in determining heart rate. Under normal physiological conditions, resting heart rate is mainly under parasympathetic control as shown by a higher level of the 'intrinsic heart rate' observed after pharmacological blockade of autonomic influences (with atropine and propranolol).[8] Chronic imbalance of the autonomic nervous system characterized by activation of the sympathetic nervous system and/or diminished parasympathetic activity is a marker of an unhealthy cardiovascular system and is associated with increased risk of cardiovascular events and mortality.[9] Increased sympathetic activity elicited by acute myocardial ischaemia may be a trigger for life-threatening arrhythmias.[10] Moreover, in dogs with high spontaneous heart rate, acute myocardial ischaemia was likely to induce ventricular fibrillation, while ventricular fibrillation did not occur following administration of propranolol as well as in dogs with low spontaneous heart rate.[11]

There are several mechanisms by which increased heart rate may be detrimental to cardiac electrophysiology thus favouring the occurrence of ventricular tachyarrhythmias. Besides the already mentioned arrhythmogenic effects of the autonomic nervous system,[9] many of the electrophysiological properties of myocardial cells depend upon the cycle length. Increased heart rate may decrease action potential duration and effective refractory periods, slow conduction velocity and facilitate the occurrence of delayed afterdepolarizations and triggered activity in the presence of a diseased myocardium.[12]

Soliman *et al.*[13] explored the relation of resting heart rate and other electrocardiographic and clinical parameters that are related to ventricular arrhythmogenesis, namely heart rate variability, ventricular late potentials, and arrhythmia counts. All the subjects who had been referred for a 24 h Holter recording over 2

The opinions expressed in this article are not necessarily those of the Editors of the *Europace* or of the European Society of Cardiology.

* Corresponding author. Tel: +39 0385 247290; fax: +39 0385 61386. Email: mtlarovere@fsm.it

years were considered for inclusion into analysis provided they had good quality resting ECG and Holter recordings for at least 12 h. Resting heart rate was obtained from a 10 s ECG before recording. The analysis included 867 patients of whom 57% were females. Less than 15% of patients had a history of coronary heart disease or heart failure and mean left ventricular ejection fraction was rather well preserved. After resting heart rate had been divided into quartiles, a significant association was found between increased heart rate and the prevalence of reduced heart rate variability, the presence of late potentials and ventricular arrhythmias. ST segment depression was also included in the analysis and showed a significant association with outcome. Although the strength of the association is not reported, these variables remained significant after adjustment for demographic risk factors and left ventricular ejection fraction.

Because of the lack of follow-up data, the predicted value of the observed association with outcome could not be confirmed. Moreover, newer measures reflecting electrophysiological properties, such as instability of ventricular repolarization—which may contribute to the development of ventricular tachycardia or ventricular fibrillation—have not been taken into account in the present study. Microvolt T-wave alternans, a marker of susceptibility to life-threatening arrhythmias, significantly depends on heart rate. In ambulatory ECG recordings, differences in MTWA values at times of higher heart rate were observed between patients who experienced cardiac arrest or arrhythmic death and matched controls.[14] Despite these limitations, the study by Soliman *et al.*[13] represents an additional contribution to the definitive entrenching of the concept of heart rate as a risk factor for life-threatening arrhythmias.

Furthermore, less immediately dangerous arrhythmias seem to be favoured by high heart rates. Indeed, elevated heart rate has been shown to affect not only ventricular but also atrial electrophysiology. In a recent *post hoc* analysis of the Losartan Intervention For End point reduction in hypertension (LIFE) study, Okin *et al.*[15] examined the relationship of heart rate changes over time in patients with hypertension and left ventricular hypertrophy on the risk of subsequent development of atrial fibrillation. In-treatment persistence or development of heart rate $\geq$84 bpm was associated with a 61% increased rate of atrial fibrillation after adjusting for baseline risk factors and changes in therapy.

Heart rate changes over years have been shown to have prognostic implications in apparently healthy individuals. Among 5138 asymptomatic working men, those with decreased heart rate during a 5-year observation period had a 14% lower risk of death after adjustments for confounding factors, including baseline heart rate at rest, whereas subjects with increased heart rate during the 5 years had a 19% increased mortality risk.[16]

Although heart rate is a simple clinical variable, a single measurement might be biased because of different conditions at sampling, physical, psychological, and environmental factors. Recommendations for the measurement of resting heart rate have been developed[17] for future trials. In specific populations, the limitation of a single measurement can be overcome by continuous measurements which can provide mean heart rate values over a longer time period.[18]

One fundamental issue is the distinction between the demonstration of a biological association linking a risk factor with prognosis and the practical demonstration that the marker can be used to select patients who may warrant treatment. The linear relationship between a reduction in heart rate and improved survival, observed in the studies of beta-blockers, provides strong evidence of the adverse effects of increased heart rate among patients with known heart disease.[19,20] Pure heart rate reduction with the I_f inhibitor ivabradine has been suggested to confer a benefit on cardiovascular outcomes in patients with elevated heart rate ($\geq$70 bpm) and left ventricular dysfunction,[21] although there was no measurable benefit of treatment on the primary endpoint in the entire study population. Sudden death was not included as a separate endpoint. The question is whether the pharmacological heart rate reduction might be beneficial in patients without cardiac disorders as well as to what extent the association between increased heart rate and sudden death in the general population might be primarily related to the underlying autonomic imbalance. Better understanding of the relationship between heart rate and arrhythmogenesis will help find new targets for interventions.

Conflict of interest: none declared.

References

1. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL *et al.* for the Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007;**50**:823–30.
2. Aboyans V, Criqui MH Can we improve cardiovascular risk prediction beyond risk equations in the physician's office? *J Clin Epidemiol* 2006;**59**:547–58.
3. Palatini P Elevated heart rate: a 'new' cardiovascular risk factor? *Prog Cardiovasc Dis* 2009;**52**:1–5.
4. Dyer AR, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM *et al.* Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic study. *Am J Epidemiol* 1980;**112**:736–49.
5. Kannel W, Kannel C, Paffenbarger RS, Cupples LA. Heart rate and cardiovascular mortality: the Framingham study. *Am Heart J* 1987;**113**:1489–94.
6. Wannamethee G, Shaper AG, Macfarlane PW, Walker M. Risk factors for sudden cardiac death in middle-aged British men. *Circulation* 1995;**91**:1749–56.
7. Jouven X, Zureik M, Desnos M, Guérot C, Ducimetierè P. Resting heart rate as a predictive factor for sudden death in middle-aged men. *Cardiovasc Res* 2001;**50**:373–8.
8. Katona PG, McLean M, Dighton DH, Guz A. Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest. *J Appl Physiol* 1982;**52**:1652–7.
9. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992;**85**(Suppl. 1):177–91.
10. Malliani A, Schwartz PJ, Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion. *Am J Physiol* 1969;**217**:703–9.
11. Reynolds RD, Calzadilla SD, Lee RJ. Spontaneous heart rate, propranolol, and ischemia-induced vetricula fibrillation in the dog. *Cardiovasc Res* 1978;**60**:738–46.
12. Janse MJ, Wit AL. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Physiol Rev* 1989;**69**:1049–169.
13. Soliman EZ, Elsalam MA, Li Y. The relationship between high resting heart rate and ventricular arrhythmogenesis in patients referred to ambulatory 24 h electrocardiographic recording. *Europace* 2010;**12**:261–5.
14. Verrier RL, Nearing BD, La Rovere MT, Pinna JD, Mittleman MA, Bigger JT Jr *et al.* Ambulatory ECG-based tracking of T-wave alternans in post-myocardial infarction patients to assess risk of cardiac arrest or arrhythmic death. *J Cardiovasc Electrophysiol* 2003;**14**:705–11.
15. Okin PM, Wachtell K, Kjedsen SE, Julius S, Lindholm LH, Dahlöf B *et al.* Incidence of atrial fibrillation in relation to changing heart rate over time in hypertensive patients: the LIFE study. *Circ Arrhythmia Electrophysiol* 2008;**1**:337–43.
16. Jouven X, Empana JP, Escolano S, Buyck JF, Tafflet M, Desnos M *et al.* Relation of heart rate at rest and long term (>20 years) death rate in initially healthy middle-aged men. *Am J Cardiol* 2009;**103**:279–83.

17. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G *et al.* ESH/ESC Task Force on the management of arterial hypertension. *J Hypertens* 2007;**25**:1751–62.
18. Ahmadi-Kashani M, Kessler DJ, Day J, Bunch TJ, Stolen KQ, Brown S *et al.* on behalf of the INTRINSIC RV Study Investigators. Heart rate predicts outcomes in an implantable cardioverter-defibrillator population. *Circulation* 2009;**120**:2040–5.
19. Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefit in post-myocardial infarction: a meta-regression of randomized clinical trials. *Eur Heart J* 2007;**28**:3012–9.
20. Lechat P, Hulot JS, Escolano S, Mallet A, Leizorovicz A, Werhlen-Grandjean M *et al.* on behalf of the CIBIS II Investigators. Heart rate and cardiac rhythm relationship with bisoprolol benefit in chronic heart failure in CIBIS II trial. *Circulation* 2001;**130**:1428–33.
21. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:807–16.

IMAGES IN ELECTROPHYSIOLOGY

doi:10.1093/europace/eup393
Online publish-ahead-of-print 17 December 2009

Intracardiac echocardiography identifies the substrate of left ventricular papillary muscle ectopy

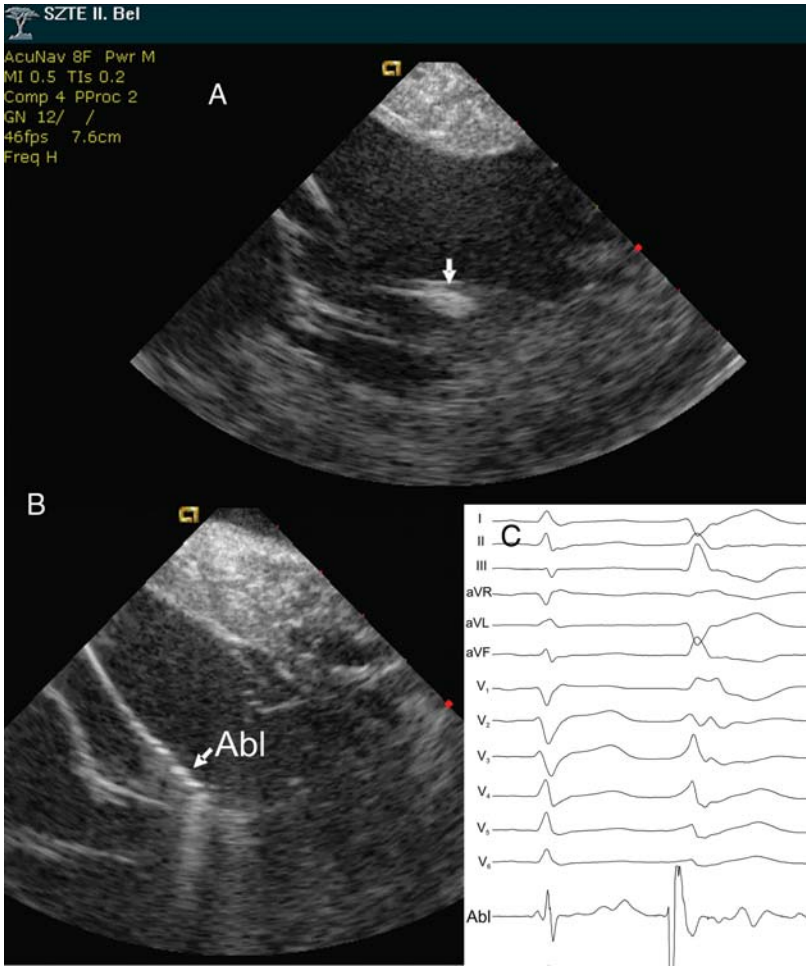
Róbert Pap*, Attila Makai, and László Sághy

2nd Department of Medicine and Cardiology Centre, University of Szeged, Korányi fasor 6, 6720 Szeged, Hungary

* Corresponding author. Tel: +36 62 544 901, Fax: +36 62 544 568, Email: pap.paprobert@gmail.com

A patient without organic heart disease underwent an electrophysiology study guided by phased-array intracardiac echocardiography (ICE) for frequent, premature ventricular contractions (PVCs) with right bundle branch block and right inferior axis morphology. During ICE interrogation of the left ventricle, a rounded, echogenic mass, 8 mm in diameter, was noted in the anterior head of the anterolateral papillary muscle (*panel A* and movie available as Supplementary material online), which subsequently was found to correspond to the site of earliest endocardial activation during PVCs (*panels B* and *C*) and successful irrigated radiofrequency ablation.

The origin of ventricular ectopy might be identified by ICE before mapping, in this case in the form of a focal tissue abnormality in the papillary muscle, likely similar to previously described delayed contrast enhancement in arrhythmogenic papillary muscle during magnetic resonance imaging.



Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.