Hypertension Research (2010) 33, 876–877

www.nature.com/hr

COMMENTARY

Prolonged heart rate-corrected QT interval and cardiovascular risk in Asian populations

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Hypertension Research (2010) **33,** 876–877; doi:10.1038/hr.2010.116; published online 15 July 2010

The QT interval is the electrocardiographic representation of total ventricular electrical activity, the summation of ventricular depolarization and repolarization. The prolongation of heart rate-corrected QT-interval (QTc) duration remains the most traditional and widely used parameter reflecting abnormal ventricular repolarization. Abnormal ventricular repolarization is an established mechanism of arrhythmogenesis.[1] It has been shown in several population-based studies to constitute a risk marker of cardiovascular morbidity and mortality,[2,3] although its reliability is not generally accepted,[4] and it also has problems in measurement and interpretation.[5] Indeed, there is a continuous debate on the clinical significance of prolonged QTc interval measured in resting standard 12-lead ECG. QTc-interval prolongation has been associated with several unfavorable conditions: autonomic system imbalance and autonomic neuropathy, mutation of genes affecting cardiac ion channels involved in cardiac repolarization, nonconducting scar tissue resulting from myocardial infarction or slowly conducting tissues because of myocardial ischemia, hypokalemia and other electrolyte abnormalities, obesity and ventricular hypertrophy. Moreover, QTc-interval prolongation has been associated with several cardiovascular risk factors, including hiperinsulinemia, hyperglycemia and the conjunction of the metabolic syndrome. The association between prolonged QTc and cardiovascular risk factors implicated in atherosclerosis, and also the association with carotid intima-media thickness suggests that QTc-interval prolongation may be a marker of subclinical atherosclerosis.[6]

A recent qualitative overview[4] on the prognostic impact of prolonged QTc in population-based cohorts, encompassing seven prospective studies published until 2000, showed no consistent evidence for increased cardiovascular mortality risk and for sudden death, except maybe in patients with prior cardiovascular disease. Nevertheless, in more recent studies with occidental populations, including individuals of both genders, the prognostic influence of prolonged QTc interval beyond other established cardiovascular risk factors was reaffirmed. Dekker *et al.*[2] showed in black and white middle-aged men and women that QT-interval prolongation was a predictor for coronary heart disease events. Straus *et al.*[7] reported its prognostic influence in an older population for sudden cardiac death. However, Kim *et al.*[8] reported in Pima Indians that a prolonged QTc interval had no prognostic impact on cardiovascular mortality; the low proportion of baseline cardiovascular disease may have contributed, in part, to the lack of association in this study. Two other studies, one in postmenopausal women[3] and another in older man[9] showed the prognostic influence of QTc-interval length on coronary heart disease events and on cardiovascular morbidity and mortality, respectively.

Plausible explanations for differences in the prognostic impact of prolonged QTc interval among the studies are the occurrence of chance, bias and uncontrolled confounding variables. Chance could have a role, as most of the studies have insufficient statistical power to detect differences between the subgroups, and also gender differences. Moreover, differences among the results of the studies may be partially explained by differences in the outcomes, in studied populations, in classification of QTc interval and gender-specific QTc interval cutoff values used. Furthermore, in most studies, QTc prolongation was based on a single baseline ECG measurement; given the marked individual variability of QTc interval over the 24-h period, repeated measures may be necessary to detect confident associations. And, also relevant, one single ECG was related to outcomes that usually occurred many years later. Exposure to etiological factors during follow-up that may have lengthened QTc –interval, or interventions that could lead to shortening of QTc interval, were not accounted for. Differences in duration and completeness of follow-up may also account, at least in part, for the differences between the studies. Bias may also be present because of imprecise measurement of QTc interval and to differences in the prevalence of cardiovascular disease at baseline. Another aspect is the fact that most of the studies were not designed to investigate whether QTc prolongation was associated with cardiovascular morbidity and mortality and some variables not obtained or not adjusted for may have influenced the results.

However, studies in Asian populations are scarcer.[10,11] The first one reported in an elderly Japanese population without cardiovascular disease at baseline (3543 individuals, 64% women, mean age 65 years) that QTc-interval prolongation (>440 ms) was an independent risk marker for cardiovascular and coronary heart disease mortality, whereas no gender difference on the effects of QTc interval on mortality was observed. On the other hand, Maebuchi *et al.*,[11] in this issue of the Journal, showed also in a Japanese

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population (2439 individuals, 59% women, mean age 58 years) that prolonged QTc interval was associated with the future development of cardiovascular disease, coronary heart disease and stroke, independent of other traditional risk factors, only in males. The reasons for differences of prognostic impact of prolonged QTc interval between genders in the second study are not clearly apparent. Conflicting results may be explained, in part, by differences in the outcomes (only fatal events were evaluated in the first study[10]), and by differences in selected populations. Indeed, individuals in this study were younger and had a lower prevalence of prolonged QTc interval, particularly in women, than individuals enrolled in the first cohort. Nonetheless, the fact that the present study had a longer follow-up and a greater number of events than the earlier study indicates that it probably had enough power to have detected any significant effect of QTc-interval prolongation on cardiovascular outcomes in women, if it actually exists. However, even using higher QTc interval cutoff values for women ($\geqslant$450 and $\geqslant$460 ms), no significant association was observed. Other possible explanations for the controversial finding of a lack of association between QTc-interval prolongation and cardiovascular events in women have been discussed by Mabeuchi *et al.*[11] Possibly, it may be easier to show the prognostic influence of prolonged QTc interval in older postmenopausal women than in younger females.

Most relevant, this prospective long-term follow-up study further supports the concept of a quantitative approach to electrocardiography and provides evidence that ventricular repolarization prolongation, assessed by a prolonged QTc-interval duration, represents an important risk marker for future cardiovascular morbidity and mortality also in Asian populations, above and beyond other traditional cardiovascular risk factors. Hence, QTc-interval measurement is an inexpensive, easily accessible and noninvasive tool that may contribute to improve cardiovascular risk stratification also in these populations.

ACKNOWLEDGEMENTS

CRL Cardoso has research grants from Conselho Brasileiro de Desenvolvimento Científico e Tecnológico (CNPq) and from Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

1 Kuo CS, Reddy CP, Munakata K, Surawicz B. Mechanism of ventricular arrhythmias caused by increased dispersion of repolarization. *Eur Heart J* 1985; **6**: 63–70.
2 Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women. The ARIC study. *J Am Coll Cardiol* 2004; **43**: 565–571.
3 Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women. The women's health initiative. *Circulation* 2006; **113**: 473–480.
4 Montanez A, Ruskin JN, Hebert PR, Lamas GA, Hennekens CH. Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population. *Arch Intern Med* 2004; **164**: 943–948.
5 Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is 'normal'. *J Cardiovasc Electrophysiol* 2006; **17**: 333–336.
6 Festa A, D'Agostino R, Rautaharju P, O'Leary DH, Rewers M, Mykkänen L, Haffner SM. Is QT interval a marker of subclinical atherosclerosis in nondiabetic subjects? The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke* 1999; **30**: 1566–1571.
7 Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol* 2006; **47**: 362–367.
8 Kim NH, Pavkov ME, Nelson RG, Hanson RL, Bennett PH, Curtis JM, Sievers ML, Knowler WC. The separate and joint effects of prolonged QT interval and heart rate on mortality. *Atherosclerosis* 2010; **209**: 539–544.
9 Sohaib SM, Papacosta O, Morris RW, Macfarlane PW, Whincup PH. Length of the QT interval: determinants and prognostic implications in a population-based prospective study of older men. *J Electrocardiol* 2008; **41**: 704–710.
10 Nakanishi S, Yamada M, Hattori N, Suzuki G. Relation between QT duration and mortality in an elderly Japanese population. *Am J Cardiol* 2004; **93**: 1182–1185.
11 Maebuchi D, Arima H, Doi Y, Ninomya T, Yonemoto K, Tanizaki Y, Kubo M, Hata J, Matsumura K, Iida M, Kiyohara Y. QT interval prolongation and the risks of stroke and coronary heart disease in a general Japanese population: the Hisayama study. *Hypertens Res* 2010; **33**: 916–921.