shortening (13%) of the IVRT, a 22% decrease in the mitral E-wave deceleration time, and a 25% increase in the mitral E-wave velocity. In the patients with LQT3, bradycardia may protect their hearts from developing overt diastolic dysfunction.

Similarly, in an animal model that mimics LQT2, we observed that the prolongation of the LV monophasic action potential duration (APD) and QTc interval caused by the IKr blocker clofilium was associated with a delay in LV relaxation (unpublished data). This finding is consistent with those reported in LV myocytes isolated from failing canine and human hearts where prolongation of APD is accompanies by abnormal intracellular Ca2+ transients and twitch contractions that are characterized by a phasic (spike) and tonic (domelike) component. Similar to the results of Moss study, shortening of the APD of these failing myocytes suppresses EADs and abrogates the tonic component of the intracellular Ca2+ transients and twitch contraction without affecting the phasic component.

Prolonged contraction/systole and delayed relaxation may also affect myocardial blood flow. Coronary blood flow is minimal during systole and reaches a maximum during the initial relaxation phase coincident with the IVRT period. Directly relevant to this issue is the work of Mayet's group using wave intensity analysis of coronary blood flow. They showed that during ventricular relaxation the relief of myocardial compression of the coronary microcirculation generates a 'backward travelling suction wave' that becomes the dominant driver of the increase in coronary blood flow in diastole. This wave generated by the rapid ventricular relaxation pulls blood into the microcirculation. Therefore, it is conceivable that patients with prolonged ventricular repolarization have a reduced 'suction wave' and thereby reduced diastolic coronary flow. This condition may also apply to acquired diseases wherein ventricular repolarization is slowed (e.g. heart failure and left ventricular hypertrophy).

In summary, we agree with De Ferrari and Schwartz that evidence is accumulating that abnormal ventricular repolarization due to ion channelopathies may not only cause a 'pure electrical disease' but also affects contractile function and possibly impairs myocardial perfusion. Whether a compromised myocardial perfusion contributes to the symptoms or the risk for cardiac events in patients with LQTS remains to be established.

References


Luiz Belardinelli
Head of Cardiovascular Therapeutics
Gilead Sciences
Palo Alto, CA 94304
USA
Tel: +1 650 384 8526
Fax: +1 650 475 0450
Email: luiz.belardinelli@gilead.com

Arvinder Dhalla
Department of Biology
Gilead Sciences
Palo Alto, CA
USA

John Shryock
Department of Biology
Gilead Sciences
Palo Alto, CA
USA

doi:10.1093/eurheartj/ehp445
Online publish-ahead-of-print 20 October 2009

Abnormal left ventricular relaxation in patients with long QT syndrome: reply

We appreciate the interest and comments from Dr Belardinelli et al. regarding the accumulating evidence of cardiac contraction abnormalities in long QT syndrome (LQTS) patients. The study referred to from Moss et al. showed slowed ventricular relaxation in LQT3 patients which was, to some extent, reversed by ranolazine-induced shortening of action potential duration (APD). The patients with LQT3 differ genetically and clinically from LQT1 and LQT2 patients who constituted the majority of our patients, but nevertheless the study by Moss et al. represents an important and valuable link between electrical and mechanical dysfunction in LQTS patients.

In our study, contraction abnormalities were most evident in LQT1 and LQT2 patients with arrhythmic events compared with silent mutation carriers. This implies that the degree of the electrical defects may be translated into mechanical dysfunction. We note with interest that ‘dys synchrony score’ used by Moss et al. was reduced by ranolazine infusion, which is well compatible with our findings of pronounced mechanical dispersion in LQTS patients. Our study focused on prolongation of contraction and systole in LQTS patients. Given a fixed heart rate, prolonged duration of systole necessarily results in reduced duration of diastole.

The length of diastole is indeed important for coronary blood flow as commented by Belardinelli and in the work of Mayet’s group. Importantly, duration of diastole shortens relatively more at higher heart rates than duration of systole. This fact may be of particular importance in LQT1 patients. At higher heart rates, defect If channels in LQT1 patients lead to a reduced shortening of the QT interval, i.e. systole, and as a consequence diastole duration may be significantly reduced. As discussed by Dr Belardinelli et al., bradycardia was considered to protect LQT3 patients from developing overt diastolic dysfunction. However, considering that bradycardia can be a trigger of arrhythmias in LQT3 patients, preventing diastolic dysfunction by inducing bradycardia may be ambiguous. In LQT1 and LQT2 patients, β-blocker therapy is the treatment of choice and is shown to be protective against arrhythmic events, mainly due to inhibition of catecholaminergic stimuli. In the context of diastolic duration, β-blocker treatment lowers heart rate and prolongs diastole. The favourable effect of β-blockers in LQT1 and LQT2 patients may therefore consist of both protection from arrhythmias in addition to prolongation of diastole that facilitates diastolic filling.

Finally, we totally agree with Belardinelli et al. and De Ferrari and Schwartz that traditional cardiac electrical disorders should be studied beyond electricity, since electrical and mechanical function are closely related.

References

Resting heart rate and excessive heart rate increase during pre-exercise mental stress: which one predicts mortality?

In the study of Juven et al., the excessive heart rate (HR) increase during the preparation of an exercise test was indicated as a novel predictor of sudden cardiac death. The authors attributed this increase of HR to the mild mental stress caused during the pre-exercise preparation phase and suggested that a localized release of norepinephrine or a faster vagal withdrawal during this mild mental stress could be potentially related to this phenomenon. However, it is difficult to explain why subjects of the tertile with the lower HR increase were surprisingly found to have significantly higher HR at rest. As Juven et al. have previously described, the crude risk of sudden death increases linearly with the level of resting HR, a fact that does not agree with the present findings. Furthermore, an impaired autonomic balance should also affect the decrease of HR during the recovery period (post-exercise HR recovery).

It would be of great interest to examine whether subjects with excessive increase in HR also have a slower decrease of HR during the recovery period, since HR recovery is a well-documented prognostic factor. Although HR recovery predicts all-cause mortality and not sudden cardiac death, the common pathophysiological link makes this comparison intriguing. Finally, the magnitude of the mental stress before a diagnostic test might possibly be exaggerated by the ‘first-time’ effect. It would be useful if we knew which of these subjects had undergone an exercise stress test before and how this factor influenced their performance.

References

Christos A. Fourlas
Exercise Stress Test Laboratory
Ateneu Euroclinic
22 EL Venizelou Street, Nea Ionia
TK 14231, Athens
Greece
Tel: +30 210 272 4099
Fax: +30 210 272 4006
Email: chrisfourlas@yahoo.gr

doi:10.1093/eurheartj/ehp447
Online publish-ahead-of-print 22 October 2009

Resting heart rate and excessive heart rate increase during pre-exercise mental stress: which one predicts mortality? Reply

We thank Dr Fourlas for his interest on our article. The main result is that the heart rate increase during a mild mental stress in preparation for exercise is a strong predictor of sudden death. Specifically, individuals with the largest heart rate increase during mild mental stress and the smallest increase in heart rate during an exercise test are at higher risk. Dr Fourlas expressed concerns about the several potential mechanisms that we listed in the discussion. We share his opinion, and obviously, there is not one simple physiological explanation for the results that we observed in this long-term epidemiological study. We observed only a very modest correlation between heart rate increase during stress and during exercise. The heart rate increase during exercise is negatively associated with sudden death risk, whereas heart rate increase during mental stress is positively associated with sudden death. This suggests that at least two different physiological mechanisms are involved.

We are pleased to be able to provide data concerning the association between heart rate during recovery and risk for sudden death, which have been obtained in the same cohort and published previously. Heart rates at 1, 2, 3, and 4 min after cessation of exercise were all associated with overall mortality and particularly with sudden death, but not with non-sudden coronary death. When subjects with a heart rate recovery at 1 min higher than 40 b.p.m. were taken as reference (higher quintile), subjects with a low heart rate recovery, <25 b.p.m. (lower quintile), had a 2.1-fold risk of sudden death, a 0.9-fold risk of non-sudden coronary death, and a 1.3-fold risk of overall death. As suggested by Dr Fourlas, we still have to compare together the heart rate increase during mental stress and heart rate decrease during recovery. In summary, beside resting heart rate, heart rate changes during specific stimulations such as mental stress, exercise, and recovery provide additional predictive value for sudden death risk and clearly challenge the current physiological explanations.

Reference

Xavier Jouven
Hôpital Européen Georges Pompidou
20 rue Leblanc
Paris 75015
France
Email: xavier.jouven@egp.ap-hop-paris.fr

doi:10.1093/eurheartj/ehp448
Online publish-ahead-of-print 22 October 2009