We thank Dr. Opthof and Dr. Coronel for the interest in our recently published work [1] and appreciate their comments. We aimed at developing a novel intact heart model of LQT3 for a better understanding of the mechanisms by which functional electrical instability at the level of the whole heart leads to torsade de pointes (TdP). The potassium concentration was repeatedly lowered to design an experimental setup that reproduced conditions and circumstances that are clinically known to be associated with an increased propensity to the development of TdP [2]. The low potassium concentration of 1.5 mM results in a markedly reduced repolarization reserve, which, in combination with bradycardia and a QT-prolonging agent, reproducibly causes TdP. Under baseline conditions (without inhibiting sodium channel inactivation or blocking IKr) TdP do not occur. With higher potassium concentrations, e.g. 2.0 mM [3] up to 3.0 mM (data not published), TdP do also occur in some hearts (fewer hearts, less episodes as compared to the low concentration of 1.5 mM).

Dispersion in repolarization is caused by the combined differences in activation times between the RV (pacing site) and the LV, and by the local MAP. We agree that the term ‘dissempersion of repolarization of MAP90’ would be more correct than just “dispersion of repolarization”. However, several groups [4,5], including Dr. Coronel’s group [6], use the two terms as synonyms. In previous studies, we observed only insignificant changes in local activation time even in the presence of amiodarone [7]. Thus, it is unlikely that the main message of our study is due to changes in activation pattern.

Veratridine led to a marked increase in transmural dispersion of MAP90 mainly due to excessive prolongation of left endocardial MAP90 in contrast to epicardial recorded action potentials. This indicates that action potential differences across the ventricular myocardium may be of particular importance for the increased arrhythmia susceptibility. Transmural action potential heterogeneity may support reentrant mechanisms responsible for the perpetuation of TdP, after being initiated by early afterdepolarizations. Dr. Opthof and Dr. Coronel make the valid point that a clear distinction between endocardial cells and subendocardial “M cells” is not possible with our setup. Therefore, the combined use of simultaneous microelectrode and contact MAP electrode catheter recordings would be of additional value. Anyhow, it is apparent in cases of mixed cell population that the MAP duration reflects the average duration of the underlying cell population. If this is or is not a so-called M cell population remains an open issue. However, an “insignificant” role of M cells in the human heart is far from being proven [8,9] with regard to the conditions under which the recordings of the quoted study [10] were obtained. The discussion on the existence of M cells and their contribution to arrhythmogenesis in experimental intact heart models as well as the human heart awaits further investigations, and the extent to which transmural heterogeneity exists within the human heart remains to be definitely determined.

References


