At the end of the 19th century Einthoven described the configuration of the human ECG [1] and in later papers he elaborated on the magnitude and direction of its components [2]. From an intellectual point of view it is in fact unacceptable that we still do not know exactly how the T wave emerges. More precisely, we may understand how (dispersion in) repolarization within the ventricles transforms into the T wave in the ECG, but we have to live with the fact that we cannot translate the T wave into dispersion in repolarization. Biophysicists recognize this as the inverse problem [3] and it might be that it will never be solved, because multiple cardiac repolarization orders may translate into one and the same T wave. This may be based on the fact that 90% of all signals during repolarization are canceled [4]. There is wide recognition that dispersion in repolarization is proarrhythmogenic. Studies which aim at elucidation of the relation between local repolarization differences and the T wave are important in our understanding of arrhythmias.

We have read with interest the paper by Peter Milberg and colleagues in the February 2005 issue of Cardiovascular Research [5]. The authors have mimicked LQT3, based on mutations in the gene encoding the fast inward Na+ current, in a rabbit model by administration of veratridine, which interferes with inactivation of these channels leading to inward current during the plateau phase of the action potential. Under normal conditions these channels are closed during the plateau phase. It logically follows that this leads to prolongation of the action potential as shown in Fig. 1 and Table 1 [5] and we may assume that the QT intervals were prolonged as well. Arrhythmias occurred in the presence of fixed concentrations of veratridine during a transition from the normal extracellular K+ concentration of 5.9 mM to 1.5 mM. This raises several questions. First, did any arrhythmias occur without lowering the K+ concentration? Second, what were the additional changes in (dispersion of) action potential duration following the change in K+ concentration? Third, was lowering to such an extreme K+ concentration (incompatible with life) not sufficient to provoke the arrhythmias without the presence of veratridine?

In addition, however, we were puzzled by an important issue. The authors report to have measured dispersion in repolarization, but in fact have measured dispersion in action potential duration. This is not the same. Repolarization time is obtained by summing local activation time and local action potential duration. Dispersion in moments of repolarization is arrhythmogenic, dispersion in action potential duration not necessarily. The shortest action potentials are recorded from sites that are activated late, thereby reducing dispersion in repolarization moments as has been shown along the human ventricular endocardium and epicardium [6]. When dispersion in action potential duration is as large as the time needed for activation of the heart, it is theoretically possible that dispersion in moments of repolarization is zero. In that case there is no T wave in the ECG or in local electrograms. We admit that this problem is less serious in a smaller heart with brief activation times and narrow QRS complexes, but nevertheless dispersion in action potential duration may seriously overestimate the relevant amount of dispersion in repolarization.

Finally, the authors elaborate on the role of M cells in these rabbit ventricles. More specifically they wonder whether the high sensitivity of the left ventricular sub-endocardium to veratridine leading to very long action potentials is caused by the response of M cells directly...
beneath the subendocardium. In our opinion the results of Milberg and colleagues [5] in these rabbit ventricles should be appreciated without any assumption on M cells, amongst others due to the absence of intramural recordings. Because a rabbit model of LQT3 aims at increasing our understanding of a rare disease in the human ventricle, it should also be noted that a role of M cells in the human ventricle is far from settled and in fact seems insignificant [7,8].

References