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Editorial

The patient U wave

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See also article by Ritsema van Eck et al. [7] (pages 256–262) in this issue.

1. Historical aspects

After having described the electrocardiogram in 1895 [1], Einthoven extended our notion of the ECG by mentioning the U wave in a later paper in the Lancet in 1912 [2]. Sandwiched between a paper on paratyphoid fever following meat poisoning and a paper on a ruptured kidney, Einthoven's seminal paper ended in two brief sentences: "The method of electrocardiography is still a young plant. We may reasonably expect that it will continue to bear good fruit" [2]. Einthoven died in 1927 after having earned the Noble Prize in 1924, and he could not foresee that, almost one century later, we still do not fully understand the relationship between cardiac repolarization and the T wave in the ECG, let alone the significance of the U wave...

Einthoven described the U wave as being of "considerable height" in pathological cases, but as present also in normal hearts, albeit of small amplitude. Lewis had estimated that the U wave was present in 75% of all ECGs and Einthoven agreed that it was present in more than 50% of all persons [2]. The source of the U wave remained obscure at that time, but Einthoven made two other important observations. First, he noted that the U wave was "not of equal height in all heart beats. This wave must be regarded as an inconstant one." Second, we quote the following: "The end of the U wave lies after the second (heart) sound, so that there is no doubt that wave U falls wholly or partly in that phase of the cardiac cycle which follows the closing of the semilunar valves. The heart is in diastole after the closing of these valves. But the heart muscle, which does not begin to contract at all points at the same time, does not relax at all points at the same time either".

2. Significance of the U wave

After a long period of dormancy, Kishida et al. [3] reported that a negative U wave, whatever its nature, was specific for the presence of heart (related) disease, such as systemic hypertension, aortic and mitral regurgitation, and (chronic) ischemia. But the debate on the significance of the U wave continued, and there were two hypotheses. Thus, Hoffman and Cranefield [4] argued that the U wave is the reflection of the fact that repolarization of Purkinje fibers outlasts that of working myocardium. Lepeschkin [5] and Surawicz [6], on the other hand, hypothesized that mechanoelectrical feedback with a prolonging effect on late repolarizing ventricular muscle underlies the U wave.

In the present issue of *Cardiovascular Research,* Ritsema van Eck et al. [7] make an effort to 'solve the 100-year-old riddle' as they mention it in the title of their paper. Let us first mention that the paper is a computer simulation study without experimental data, although the model itself is based as much as possible on (human) experimental data. This constitutes a serious limitation of the study, although we wish to underscore the importance of the study at the same time. Just to mention another point, Ritsema van Eck et al. [7] explain in their paper in a relatively simple way that at infinity it is only relevant to know subendocardial and subepicardial action potential durations (or better configurations) and repolarization times (or better configurations)

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to construct the ECG at the body surface. Therefore, at infinity it does not matter what occurs in the midmyocardium. However, the distance between the body surface and the heart is far from infinity, and this unfortunately complicates the picture with the practical consequence that it *does* matter what happens between endocardium and epicardium. Ritsema van Eck et al. [7] add a third hypothesis to the 'Purkinje' hypothesis and the 'mechanoelectrical feedback' hypothesis (see previous paragraph): the 'M cell' hypothesis as an explanation of the U wave.

3. 'Purkinje' hypothesis

Ritsema van Eck et al. [7] present a string model (one-dimensional) and a slice model (two-dimensional). Conduction velocity (see Fig. 3A in Ref. [7]) is scaled such that transmural activation occurs in 22 ms (in accordance with a conduction velocity of 40–60 cm/s) and that conduction along the endocardial surface –a much longer distance– occurs in 28 ms (in accordance with a conduction velocity of 3 m/s, mimicking the Purkinje system). Total activation time of the slice amounts to 46 ms. There is, however, no contribution in the model of the much longer action potential of the Purkinje action potential compared to the action potential of ventricular muscle. The consequence is that this model study cannot refute a contribution of the Purkinje system to the U wave. However, one may argue that U waves can occur (Fig. 5 in Ref. [7]) despite the absence of late Purkinje repolarization.

The reasoning of advocates of other hypotheses than the 'Purkinje' hypothesis is usually that the mass of the Purkinje system is too small to contribute to the surface ECG [8], as with the sinus node and the atrioventricular node. Also, it is of interest that amphibians do show U waves despite the absence of a Purkinje network [5], as mentioned by the authors themselves [7].

4. 'Mechanoelectrical feedback' hypothesis

The 'mechanoelectrical feedback' hypothesis cannot be refuted by the present study, because there was no impact or feedback of contractility involved in the model for understandable reasons. As with the 'Purkinje' hypothesis, one may at least say that U waves can be simulated (Fig. 5 in Ref. [7]) without mechanoelectrical feedback.

5. 'M cell' hypothesis

A novel aspect of the present study is the formulation of an alternative, third hypothesis for the U wave. Fig. 5 [7] shows that there were no examples of an isoelectrical segment between the end of the T wave and the onset of the U wave. On the basis of this, the authors have concluded (see Abstract [7]): "T and U form a continuum. Together they are the resultant of one and the same process of repolarization of the ventricular myocardium. This has implications for the measurement of QT duration and for safety testing of drug-induced QT prolongation." This may require future clarification. There are examples of short QT syndromes in which there is an isoelectric segment between the end of the T wave and the onset of the U wave. If the U wave indeed is the result of late repolarization of normal ventricle, this implies that a short QT syndrome still constitutes a long QT syndrome. In addition, most patients with a normal QT interval would have a long QT syndrome if the U wave is included in the measurement.

There are, however, other interesting assumptions in the study of Ritsema van Eck et al. [7] that deserve a critical appraisal. Fig. 1 [7] assumes that the action potential duration of the subendocardial layer is 350 ms. The next 10 midmyocardial layers have increasing action potential durations varying from 372 ms in the second layer to a zenith of 378 ms in the 5th layer and decreasing to 352 ms in the 11th layer. Finally, the subepicardial layer has an action potential duration of 342 ms. The authors state that these numbers have been chosen in agreement with what has been reported in a study on the human wedge preparation [9]. However, in the latter study the epicardial action potential duration (at 90% of the amplitude) was reported to be 351 ms at the epicardium and only 330 ms at the endocardium (with 439 ms for the M region). The endocardial–epicardial gradient in action potential duration in the model [7] is therefore opposite to the gradient as observed in the human wedge preparation [9]. Even in the case that the assumptions in the model are correct, the difference between 350 ms for the endocardial action potential duration (Fig. 1 in Ref. [7]) and 342 ms for the epicardial action potential duration is not sufficient to compensate for the activation time from endocardium to epicardium of 22 ms (Fig. 3A in Ref. [7]) and thus leads to later epicardial repolarization rather than earlier epicardial repolarization compared to the endocardium. This is also exemplified by Fig. 2 [7] and is in line with other reports on repolarization time in the human heart [10–12].

Apart from these considerations on the endocardial–epicardial gradient in action potential duration in the human heart, it is important to emphasize that in the intact human heart a zenith either in activation recovery interval (as an index for action potential duration) in the midmyocardium [13] or in repolarization time [14] has not been demonstrated, although the authors show such a zenith in repolarization time in the model in Fig. 3B [7]. It would therefore have been of interest to see whether U waves as shown in Fig. 5 [7] can also be demonstrated in the absence of a midmyocardial zenith in repolarization time. One cannot exclude that a U wave can result from later repolarization in the posterior wall of the left ventricle compared to the anterior wall (see also Fig. 3B in Ref. [7]).

We certainly appreciate the study by Ritsema van Eck et al. [7], but we do not think that there is 'a solution for a 100-year riddle' as the title of the paper promises. On the contrary, none of the two previous hypotheses [3–6] has been refuted, but a third one has been added. The ball, therefore, stays in the court of the patient U wave. We expect it to bear good fruit there if we are allowed to paraphrase Einthoven [2].

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