The authors suggested that the surface record of repolarization of the intraventricular conducting system or Purkinje fibre T-wave is represented by the U wave. This conclusion was based on the electrophysiological properties of the Purkinje system as studied by microelectrode techniques. In an experimental canine model, Watanabe conducted a comparison of the AP of Purkinje and ventricular muscle fibres under conditions accentuating the U wave[18]. Trans-membrane potentials of Purkinje fibres and ventricular muscle were simultaneously recorded from canine tissue preparations, and various factors causing prominent U waves such as bradycardia, low potassium concentrations, hypothermia and quinidine were studied. The duration of phase 3 was markedly increased, while the slope of phase 3 was significantly decreased by all of these factors. The difference between Purkinje fibre and ventricular AP duration increased significantly. These comparisons revealed a good temporal correlation between phase 3 repolarization in Purkinje fibres and the electrocardiographic U wave.

Arguments against the His-Purkinje hypothesis include the fact that the involved tissue mass is too small to be recorded on the surface ECG[19]. Moreover, the interval between the end of the T-wave and apex of the U wave is constant at different heart rates, whereas Purkinje fibre AP duration is heart rate dependent[20]. Furthermore, in patients with right bundle branch block the timing of the U wave correlates better with the presence of right myocardial hypertrophy than with timing of intraventricular conduction[21]. Furthermore, amphibia can have a U wave but no Purkinje fibres[22]. Additionally, the morphology of the U wave does not fit the repolarization pattern of Purkinje fibres. The ascending limb of the T-wave is longer than its descending limb, which is similar to the repolarization pattern of ventricular and Purkinje fibres, whereas the U wave rises faster than it decays[10].

A longer duration of the T-wave to the apex of the U wave in patients with a left bundle branch block favours the Purkinje hypothesis for the generation of the U wave, as Watanabe argued[18]. The U wave most likely represents a delayed or inhomogeneous repolarization process in the ventricles. The AP duration of the Purkinje fibres is longer than that of the ventricular fibres and therefore the U wave follows the T-wave and has the same polarity. The authors found a significantly prolonged Q–T and Q–aU interval (time interval of Q wave until apex of U wave) in patients with a left bundle branch block in comparison to patients with a right bundle branch block despite no difference in the ECG RR interval. The delayed Purkinje activation led to a delayed appearance of the U wave.

However, the delayed appearance of the U wave in relation to timing of ventricular repolarization did not prove the mechanism of U wave genesis due to Purkinje fibre activation because the finding could be explained either by delayed repolarization of the

undergo cancellation[23]. Autenrieth *et al.* had no evidence of silent repolarization in dogs as all monophasic AP recorded from the surface of the left ventricle terminated during the T-wave[24]. The T-wave has the same polarity as the QRS complex, although at the cellular level depolarization and repolarization represent changes of opposite polarity. Franz *et al.* demonstrated a transmural gradient of repolarization, with earlier repolarization occurring at the epicardium, and they showed that the duration of the AP correlated with the duration of the QT interval in surface ECG recordings without evidence of a post-AP electrical activity responsible for the generation of the U wave[25].

Hypothesis 2: delayed repolarization of mid-myocardial layers

The ventricular myocardium is not as homogeneous as previously thought, as it is comprised of electrically and functionally distinct cell types. Cardiomyocytes differ with respect to currents that contribute to the early repolarization phase (phase 1). AP of epicardial and M cells display a prominent transient outward K^+ current (I_{to})-mediated phase 1, which is largely absent in endocardial cells. The principal feature of M cells is their ability to prolong AP duration during heart rate reduction much more than epicardial or endocardial cardiomyocytes.

Where present, M cells are more abundant in terms of tissue mass than Purkinje fibres, and their delayed repolarization could be sufficient to give rise to the U wave, particularly the pathological U wave appearing in LQTS or drug-induced QT prolongations[26]. In contrast, experimental findings suggest that M cells may give rise to a second component of the T-wave, often confused as an accentuated or inverted U wave[27,28]. Antzelevitch and co-workers suggested the use of the terms T1 and T2 to describe the two contiguous repolarization waves, or bifurcated T-wave, which is distinct from the U wave[28–30].

The fact that the T-wave and U wave are separate deflections was also shown in patients with acute myocardial ischaemia, where the monophasic transformed ventricular complex is independent of the shape and timing of the U wave[10].

Hypothesis 3: mechano-electric coupling

The concept of mechano-electrical coupling as a cause for, or contributor to, the U wave was suggested by Lepeschkin in 1957[31]. As the end of the T-wave coincides with the second heart sound, the mechano-electrical hypothesis suggests that after-potentials, caused by stretching of the circular muscle layers of the left ventricle, give rise to the U wave[2,7]. The existence of mechano-sensitive ion channels that transduce changes in the cardiomyocytes' mechanical environment into electrical signals has been amply documented[32–34]. Conclusive proof for the mechano-electrical

I_{K1} as modulator of the U wave

Postema and coworkers recently presented the hypothesis that the U wave is modulated by either a decrease of I_{K1} or an increase of I_{K1} with corresponding changes in the amplitude of the U wave[6]. The authors performed high resolution ECG sampling (fiducial segment averaging) focusing on the low frequency U wave signal at the end of the T-wave in patients with SQTS (SQTS-1, SQTS-3). They found that the deflection in the precordial leads V2—V3 that is referred to as the U wave seems to start 105 ms after the end of the T-wave and has its peak about 100 ms later. However, in the extremity leads II–III a positive deflection could be already observed immediately after the end of the T-wave. Following the definition that all variations of the potential after the T-wave are part of the U wave, the authors concluded that the T and U waves are parts of a single long repolarization process. The different appearances of the U wave in various leads were attributable to the varying projections on different lead vector axes. There were no differences in the effect on the amplitude of the U wave comparing

I_{Ks} (slow component of the delayed rectifier K^+ current) or I_{Kr} (rapid component of the delayed rectifier K^+ current) gain of function mutations. However, I_{K1} which regulates membrane potential differences in the late phase 3 and phase 4 of the cardiac AP may explain the genesis of the U wave. The U wave seems to be modulated by increase or decrease of I_{K1}. The authors demonstrated an influence of I_{K1} loss of function in six patients with an Anderson–Tawil syndrome (LQTS-7), in comparison to I_{K1} gain of function mutations in two patients with SQTS (SQTS-3). The resultant changes in the ECG show a modest attenuation of the T-wave and a decreased or increased amplitude of the U wave (Fig. 38.4).

The discovery of extended U waves in high resolution ECG, and their modulation by I_{K1}, is not incompatible with the theory that mechano-electrical coupling is a causal contributor to the U wave. If and how both hypotheses may be reconciled will be determined in future.

Conclusions and outlook

One hundred years after the initial description of the U wave, the mechanistic origin of this last wave in the ECG is still a matter of debate. Findings from SQTS patients have focused new attention on the theories for the origin of the U wave, due to the clear separation between the T and U waves in this cohort. Furthermore, evidence has been presented to show that intrinsic differences in the late phase of the AP are modulated by I_{K1}, which affects U wave morphology. A better understanding of the links between surface potentials and mechano-electrical coupling at the cellular level may

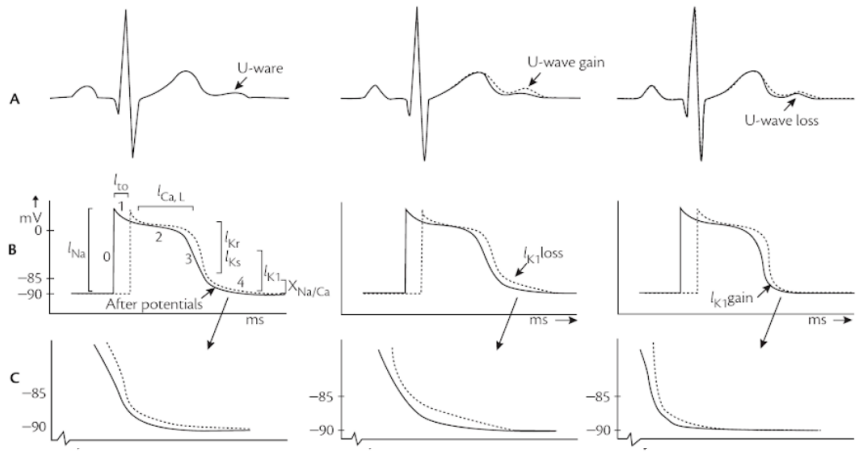

Fig. 38.4 I_{K1} and the U wave. Simplified presentation of the ECG (**A**) and the action potential with key ionic currents (**B** and **C**). The effects of either loss or gain of function of I_{K1} are illustrated in the terminal phase of the action potential (dotted lines) and the ECG. Loss of I_{K1} function (here LQTS-7) gives rise to an increase in action potential duration and U wave amplitude; gain of I_{K1} function (here SQTS-3) had the opposite effect. [Reproduced, with permission, from Postema PG, Ritsema van Eck HJ, Opthof T, *et al.* (2009) I_{K1} modulates the U-wave: insights in a 100-year-old enigma. *Heart Rhythm* **6**:393–400.]

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