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When U Say “U waves,” What Do U Mean?

Sami Viskin, MD, David Zeltser, MD, and Charles Antzelevitch, M.D.¹

From the Department of Cardiology, Sourasky-Tel Aviv Medical Center, Sackler-School of Medicine, Tel Aviv University, Israel and the

¹Masonic Medical Research Laboratory, Utica, New-York. U.S.A.

In this issue of *PACE*, Nakagawa et. al.¹ describe how changes in heart rate affect the morphology of the U waves in the electrocardiogram of two patient groups: 1) in patients with idiopathic ventricular tachycardia originating from the right ventricular outflow tract (RVOT-VT) and 2) in healthy controls. The results appear to be straightforward: As the heart *accelerates* the amplitude of the U wave *increases* in RVOT patients but *decreases* in healthy controls. Somehow paradoxically, the same patients with RVOT-VT also show “post-extrasystolic U wave augmentation,” that is, in RVOT patients the U wave amplitude increases not only during heart rate acceleration but also after the heart rate *deceleration* that follows extrasystoles. To record this intriguing phenomenon the authors used a 4-fold amplitude magnification of the electrocardiographic recordings (the paper speed was left at the nominal 25 mm/sec but the amplitude of electrocardiographic recordings was set at 0.25mV/10mm). Thus, the readers should not expect to see U wave changes, as obvious as the ones presented by Nakagawa,¹ in their standard electrocardiograms.

The U wave is not only the last electrical event of the cardiac cycle discernible with the electrocardiogram; it is also the smallest. This dimension disadvantage has contributed to the fact that while the electrical mechanisms underlying the larger QRS complexes and T waves have been properly explained,^{2–4} controversy still surrounds the explanation for the U waves.^{4,5} In point of fact, physicians still have difficulties deciding where the T wave ends and the U wave begins.⁶ Willem Einthoven is credited with first describing the U wave a century ago.⁷ Actually, Einthoven did not *describe* the U wave, he *showed* in it in an electrocardiographic trace.² Consequently, even before we attempt to understand the physiologic mechanism underlying its formation, we encounter difficulties with its mere definition. Some name “U-wave” the second repolarization wave or “the wave that follows the T-wave.” Doing justice to the figure actually shown by Einthoven, however, we would define the U wave as “the wave that begins after the T wave terminates, i.e., after the T wave returns to the baseline (or close to it).”⁵ The distinction between these two definitions stopped being trivial when it became clear that in pathologic conditions, like the long QT syndromes (LQTS), T waves with two distinctive components become evident.^{8,9} Considering that the T wave is the electrocardiographic representation of the repolarization of the ventricles and that these double T waves or “T wave humps” denote the marked dispersion of repolarization seen in the LQTS⁴ it is probably better to use terms like T1 and T2 (instead of “T” and “U”) to describe two contiguous repolarization waves, while reserving the term “U wave” for the last wave (rather than the second one) that begins after the ventricular repolarization, including all the T components, terminated.

The normal U wave is best seen at rest in the precordial leads and is more commonly seen during sinus bradycardia.⁵ Studies evaluating the response of the QT interval to tachycardia

(produced by exercise or atrial pacing) in healthy individuals have often ignored the U waves.^{10–12} Nevertheless, exercise-induced augmentation of the U wave amplitude may occur in 15%¹³ of patients without apparent heart disease and is more commonly observed in patients with coronary heart disease.^{13,14} From all the interesting theories that have been proposed to explain the cellular mechanism underlying the formation of the U wave,⁴ the observations reported by Nakagawa in this issue of PACE are most consistent with the mechano-electrical theory (advanced by Lepeschkin half a century ago)¹⁵ suggesting that the U wave represents *delayed afterdepolarizations* of cardiac cells that arise following stretch of the ventricular myocardium.

Afterdepolarizations are depolarizing after-potentials that occur during the later phases of repolarization [*early-afterdepolarizations* (EAD)] or immediately after the completion of the action potential repolarization [*delayed-afterdepolarizations* (DAD)].¹⁶ Both EADs and DADs are created when late depolarizing inward currents overwhelm the repolarizing outward currents. Both EADs and DADs may reach threshold amplitude and thus generate a ventricular extrasystole that triggers ventricular arrhythmias. The most notorious example of EAD mediated triggered activity is the LQTS. In the common forms of the LQTS, outward potassium current through malfunctioning channels is impaired, leading to predominance of electrogenic sodium-calcium exchange current that when combined with reactivated calcium current generates EADs during the late phases (phases 2 and 3) of the action potential. Also, since cells in the deep myocardium (M-cells) are more sensitive to potassium channel blockade than endocardial and epicardial cells, the EADs are formed there more readily. The resulting dispersion of repolarization contributes to the appearance of the bifurcated T wave and creates the substrate for reentry.⁴ The resulting electrocardiogram displays a QT interval that is not only longer than normal but also looks abnormal, often consisting of bifid T waves (T1 and T2). As the EAD gains amplitude, the T2 component becomes taller than T1. When the EAD reaches threshold amplitude, the resulting ventricular extrasystole originates from the terminal part of the QT segment.¹⁷

In contrast, idiopathic RVOT-VT is believed to be caused by DAD-mediated triggered ventricular arrhythmias originating from M-cells in the RVOT.³

It is noteworthy that all the observations made by Nakagawa et. al in RVOT patients in this issue of PACE¹ are consistent with this theory: 1) *Augmentation of the U wave amplitude during sinus tachycardia (in patients with RVOT-VT)* could represent the amplification of DAD amplitude known to accompany rapid pacing.³ 2) Ventricular ectopy encountered in RVOT patients originating *after* the T wave, and coincident with the start of the U wave,¹ could well represent DADs achieving threshold. Endocardial monophasic recordings could provide support for this hypothesis. A problem to be anticipated is that it is generally very difficult to record DADs from the intact heart *in vivo* because DADs that develop in VM are usually of very low amplitude because of the close proximity of the sodium threshold potential to the resting membrane potential in VM.

How then can we reconcile the *bradycardia-dependent* “U wave” augmentation observed by Nakagawa (during post-extrasystolic pauses) in patients with RVOT-VT with the *tachycardia-dependent* U wave augmentation observed in the same patients?¹ Because myocardial stretch is believed to contribute to the development of DADs, greater ventricular filling accompanying a long pause would be expected to augment the amplitude of the U wave. Alternatively, the sudden heart rate slowing could lead to prolongation of the action potential and provoke EADs.¹⁸ It is possible that the post-extrasystolic “U wave” augmentation actually represents an accentuation of T2 secondary to EAD development or post-extrasystolic QT prolongation with encroachment of the T wave on the U wave. Interestingly, half a century ago, Lepeschkin and Surawicz noticed that during sudden pauses the QT interval increases more than the QU

interval, leading to encroachment of the T on the U wave.¹⁹ In fact, post-extrasystolic QT changes similar to those observed here by Nakagawa in patients with RVOT are so well documented in the LQTS, that they are considered diagnostic of that disease. Again, one should remember that Nakagawa used a 4-fold amplitude gain during their electrocardiographic recordings. Thus, the post-extrasystolic accentuation of T2 (apparent U wave) changes described here may be qualitatively similar but quantitatively smaller to those described by Jackman in the LQTS.²⁰ In fact, they are reminiscent of those observed in patients with organic heart disease who are prone to ventricular arrhythmias.²¹ It is noteworthy that Surawicz, when attempting to compile information on the U wave from the literature,⁵ had to concentrate mainly on old articles because no such data could be retrieved from newer publications. The study by Nakagawa and coworkers¹ is a reminder that there is still a great deal to be learned from the last, the smallest (and the often forgotten) repolarization wave.

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