Research Reports in Clinical Cardiology

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REVIEW

Giant U waves: an important clinical clue

This article was published in the following Dove Press journal:
Research Reports in Clinical Cardiology
8 April 2011
Number of times this article has been viewed

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Abstract: Electrocardiographic U waves are a common clinical finding, and yet are poorly understood by many physicians. They can be seen in many clinical conditions, most importantly hypokalemia and ischemic heart disease. Over the years, many theories have been put forth to explain their origin. While still not completely understood, it now appears that mechano-electrical interactions are responsible for normal U waves. Pathologic U waves may be seen in ischemic heart disease where they sometimes point to acute ischemic events. The large U waves of hypokalemia are most likely not true U waves but rather the terminal deflection in a bifid T wave.

Keywords: U waves, hypokalemia, myocardial ischemia, electrocardiogram

Introduction

The origin and significance of U waves on the electrocardiogram (ECG) remain mysterious to many physicians. They have been associated with multiple clinical conditions including hypokalemia and ischemic heart disease, and can provide important clinical information. We present a case highlighting the significance of prominent U waves in a patient with multiple comorbidities.

Clinical scenario

A 78 year old female with prior coronary artery bypass grafting presented with complaints of severe diarrhea. Her past medical history included hypertension, type 2 diabetes mellitus, atrial fibrillation treated with radio frequency ablation, stroke, and heart failure. She denied any chest pain, shortness of breath, or palpitations upon admission. Physical examination was notable for an S4 gallop and the absence of signs of heart failure. The vital signs were normal. Laboratory tests on admission were within normal limits except for a serum potassium of 3.2 mEq/dL. Her initial ECG showed sinus rhythm with normal axis and "giant" positive U waves in leads V1–V4 (Figure 1). Though she had no cardiac symptoms she developed a low level troponin I elevation which peaked at 0.08 mcg/L. She was subsequently diagnosed with pseudomembranous colitis which was treated with metronidazole. A follow-up ECG on the third hospital day showed deep T wave inversions across the precordium that were suggestive of ischemia (Figure 2). She continued to have no cardiac symptoms. Coronary angiography was performed one week later and revealed occlusion of the native right coronary artery and its vein bypass graft.

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submit your manuscript | www.dovepress.com
Dovepress
DOI: 10.2147/RRCC.S18459

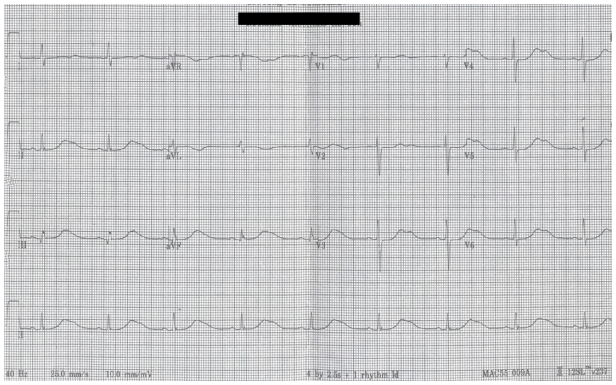

Figure 1 Initial ECG at presentation to the emergency department. Prominent positive U waves are seen in the anterolateral leads (V3–V6).

Discussion

U waves were first described by Willem Einthoven in the beginning of the twentieth century.[1] A "physiologic" U wave is a small, usually positive, deflection following the T wave that occurs in the setting of normal serum potassium and an absence of cardiac pathology. It can be found in up to 90% of ECGs with heart rates <65 beats/min but is observed less often at higher heart rates.[2] Normal U wave amplitude rarely exceeds 0.2 mV,[2,3] although there are reports of amplitudes exceeding 1.0 mV in normal individuals.[4] The largest U waves are usually in the precordial leads; normal U wave height is less than one-quarter that of the T wave.[2] Amplitude can vary strikingly under sympathomimetic stimulation.[5] The genesis of U waves is still not entirely clear, despite their having been described in the literature for decades. However, much recent progress has been made.

Theories on the genesis of U waves

Purkinje fiber hypothesis

Based on animal experiments, Watanabe linked U waves to the repolarization of the Purkinje fibers, which have a prolonged action potential.[6] However, this hypothesis has been questioned, as the total mass of the Purkinje fibers is likely insufficient to generate the electrical force required to produce U waves. In addition, U waves have been observed in amphibian hearts, which do not have Purkinje fibers.[7]

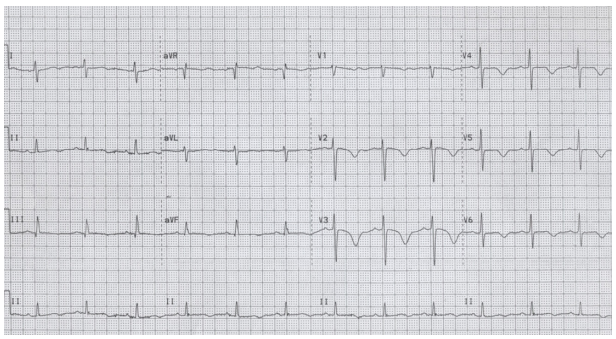

Figure 2 ECG on hospital day three. Prominent U waves have been replaced by deep T wave inversions in the precordial leads.

"Syndrome of the papillary muscle" hypothesis

Bufalari et al postulated that a functional derangement (ischemia or "strain") of the papillary muscles resulted in U waves whose morphology reflected the electrical vectors involved.[8] "Left papillary muscle syndrome", said to occur in hypertension, aortic valve disease, and anterior myocardial infarction, was associated with the vectors directed anteriorly and to the right, producing negative U waves in leads I, aVL, V5, and V6. "Right papillary muscle syndrome", said to occur with right ventricular enlargement and congenital heart disease, was associated with negative U waves in leads III, aVF, and the right precordial leads. "Biventricular papillary muscle syndrome" was said to be characterized by negative U waves in leads I, II, aVL, and the precordial leads.

Mechanoelectrical hypothesis

This older hypothesis, which has recently regained support, maintains that the U wave is caused by delayed afterdepolarization of the ventricular wall occurring during ventricular filling (electrical diastole).[2,3,7,9,10] Choo and Gibson, studying a group of patients with left ventricular hypertrophy, observed that U wave abnormalities (inversion) were strongly associated with abnormalities of isovolumic relaxation. Using M-mode echocardiography these investigators recorded "incoordinate" relaxation of the left ventricle during this phase of diastole.[7] Such incoordinate relaxation creates localized areas of increased stretch, thereby opening stretch activated channels. The resulting inward current produces positive electrocardiographic waves in electrical diastole. Previous work by Lab had suggested that mechanical inhomogeneities between different areas of the left ventricle could indeed generate delayed afterpotentials following the T wave.[11,12] Given that the U wave has no known "excitation-contraction function", these investigators suggested that mechanical events of the left ventricle are responsible for the production of the U wave. They further suggested that the U wave vector is determined by the summation of the differences in the electrical potential of mechanically inhomogeneous areas within the left ventricle.[12]

M cell hypothesis

M cells are a subpopulation of myocardial cells between endocardium and epicardium which have unique

electrophysiological and pharmacological features. Located in the mid-myocardium, they exhibit electrophysiologic properties intermediate between those of muscle and Purkinje cells. In particular, they demonstrate marked prolongation of the action potential as heart rate decreases. For this reason, it has been postulated that they may be involved in the formation of U waves. Antzelevitch et al, using a canine model, demonstrated that U waves might actually be a component of the T wave.[13] They studied left ventricular action potential duration via transmembrane recordings in combination with surface ECG. Epicardial cells were the earliest to repolarize and M cells were the last. Voltage gradients on either side of the M cells (epicardium-M and endocardium-M gradients) were noted to be responsible for the morphology of the T waves on the surface ECG. The interaction between these opposing repolarizing currents determined the height and width of the T wave as well as its morphology. They further noted that the ascending or descending limb of the T wave may be interrupted because of the summation of these gradients, resulting in a bifurcated or notched appearance. Variation in current flow across the wall due to shifting voltage gradients between epicardium and M cells, and endocardium and M cells, especially in the setting of a prolonged QT interval, resulted in the appearance of U waves (Figures 4 and 5).[13–15]

Current thinking

Schimpf et al revisited the mechanoelectrical hypothesis of U wave formation.[3] Five subjects with short QT syndrome were compared with controls. Short QT patients had markedly shorter action potential duration than controls but similar timing of mechanical events as measured by Doppler echocardiography. In both groups the U wave coincided with aortic valve closure and the beginning of isovolumic relaxation. In short in QT subjects this meant that the U wave was unrelated to ventricular repolarization, being separated from the early occurring T wave by >100 milliseconds. This suggests that stretch-induced delayed afterdepolarizations occurring during ventricular relaxation are the likely cause of U waves under normal physiologic conditions. Under certain pathophysiologic conditions, prolongation of the M cell response, particularly in the setting of bradycardia, leads to amplification of the second component of the T wave which may be confused with a true U wave.[16]

Clinical significance of U waves

Hypokalemia

Hypokalemia is associated with flattening of the T waves and the appearance of prominent U waves.[17,18] U wave amplitude >0.5 mm in lead II or >1.0 mm in V3 has been included in electrocardiographic criteria of hypokalemia.[4] This pathological "U wave" is actually part of the T wave and results from slowing of phase three of the action potential with resultant electrical interaction between the three myocardial layers.[10,19] This abnormality of electrical repolarization gives rise to small opposing voltage gradients that crossover producing a low amplitude, bifid T wave. Under these conditions, full repolarization of the epicardium marks the peak of the first component of T wave, whereas repolarization of both endocardium and M cells contribute to the second component of the T wave. The apparent "T-U" complex seen during hypokalemia is in fact a T wave whose ascending or descending limb is interrupted due to this interplay of opposing voltage gradients between epicardial, endocardial, and M cells.

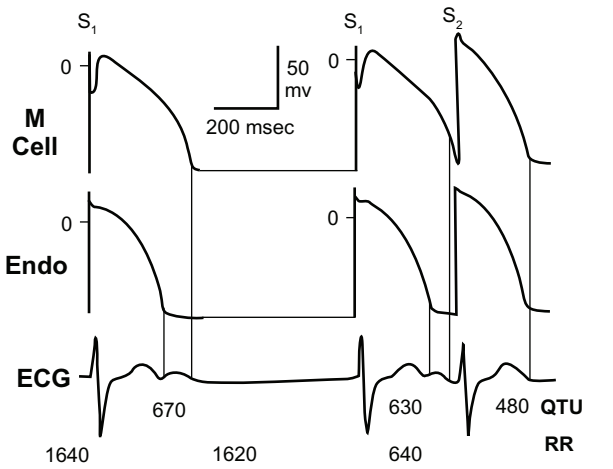

Figure 3 M cell as the basis for the U wave.
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Notes: Combined clinical electrocardiographic (ECG) trace with transmembrane recordings from canine ventricular tissues to demonstrate concordance between rate-dependent changes in the duration of the M cell action potential and in the manifestation of the U wave. Upper trace, action potentials recorded from the endocardial (Endo) and M cell region of a transmural strip of canine left ventricular free wall. The first two responses are basic beats elicited at an S1–S2 interval of 2,000 milliseconds. The third response was evoked by a stimulus introduced S1–S2 interval of 300 milliseconds. Lower trace shows marked bradycardia due to sinoatrial block and a long QTU interval. A prominent U wave is apparent after the long RR intervals (1,640 and 1,620 milliseconds) but not after the much shorter RR of 640 milliseconds.

Coronary artery disease

Reinig et al[20] studied the prognostic significance of U waves in a large series of consecutive ECGs. Medical records were searched for documentation of cardiovascular disease. They divided patients into three groups: negative T-U concordance (both T and U waves negative), type 1 T-U discordance (negative T waves and positive U waves), and type 2 T-U discordance (positive T waves and negative U waves).

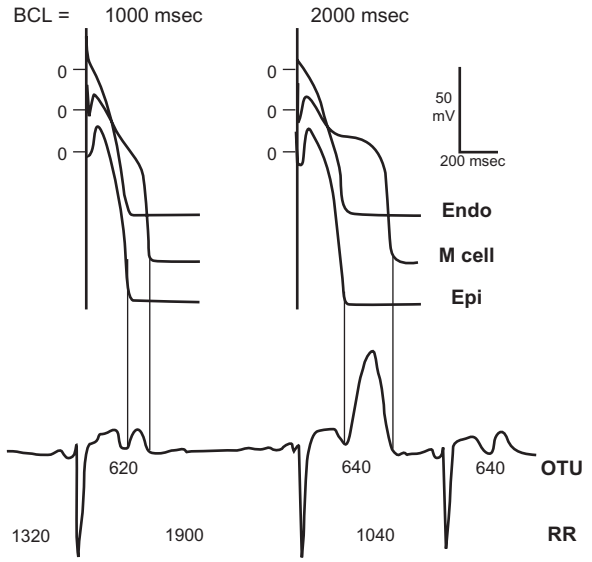

Figure 4 M cells and the "giant" U wave.
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Notes: Upper trace, transmembrane activity recorded simultaneously from endocardial (Endo), deep subepicardial (M cell), and epicardial (Epi) tissues obtained by successive dermatome shavings made parallel to the epicardial surface (canine left ventricular free wall). The M cell action potential, free of the electrotonic influence of epicardium and endocardium, shows a dramatic prolongation of the action potential as the basic cycle length (BCL) is increased from 1,000 to 2,000 milliseconds. Lower trace, Holter recording from a patient showing dramatic rate-dependent changes in the QTU interval, with a "giant U wave" apparent after a pause of 1,900 milliseconds. The rate-dependent changes in the action potential duration of the M cell correlate well with the manifestation of the U wave in the ECG.

Patients with negative T-U concordance had a higher rate of coronary artery disease than patients with either type of T-U discordance (88% versus 58%).[20]

Myocardial infarction (MI)

Negative U waves usually appear when a large myocardial territory is involved and can help locate the coronary artery involved.[21–24] Negative U waves may be the only ECG sign of ischemia. Kanemoto et al studied the significance of U wave polarity in V4–V6 in patients with anterior MI 6 to 8 weeks prior to enrollment.[25] Subjects were divided into three groups depending on morphology of the U waves: positive U waves, isoelectric or flat U waves, and negative U waves. Polarity of the U waves correlated significantly with left ventricular function and wall motion, as well as the size of myocardial infarction. Negative U waves were an important sign of extensive myocardial infarction involving the apex, with global ejection fraction of less than 50%. In a similar study involving patients with prior inferior MI, those with negative U waves in V4–V6 were more likely to have multi-vessel coronary artery disease, significant left anterior descending coronary artery disease (>70% stenosis), or poor global ejection fraction.[22]

Exercise-induced U waves

As opposed to U waves which arise following MI, U waves that develop during exercise testing have a somewhat different significance. Exercise-induced U wave alterations are useful as a marker of high-grade coronary narrowing and are highly specific in localizing the coronary artery involved.[26] Negative U waves developing in leads II, III, and aVF suggest right coronary or left circumflex stenosis while negative U waves developing in leads V4–V6 suggest left anterior descending coronary artery stenosis. Conversely, positive U waves in the precordial leads usually represent a mirror-image reflection of negative U waves in an electrically opposite territory, thus suggesting left circumflex or right coronary artery stenosis.

It has also been noted that patients with exercise-induced U waves (positive or negative) have less angina and ischemic changes during balloon coronary occlusion, indicating well developed collateral vessels.[26] Patients with recent anterior wall MI who developed negative U waves on stress testing were noted to have a relatively smaller mass of necrotic myocardium due to the presence of good collateral circulation.[27] Tamura et al noted that patients with exercise-induced U wave changes following acute anterior wall myocardial infarction were less likely to have had ST elevation on the presenting ECG, had better collateral circulation, greater left ventricular ejection fraction, and better regional wall motion.[24] These observations suggest that U waves point not only to the presence of severe coronary narrowing but also more robust collateral circulation. It is thought that well collateralized ischemic myocardium provides the necessary substrate to produce heterogeneous repolarization, and thus apparent U waves, under conditions of physical stress.

Summary

Our case highlights the fact that U waves can have a multifactorial etiology. The presenting ECG showed prominent positive U waves in the anterolateral leads (V3–V6) that were initially thought to be due to hypokalemia. However, she subsequently developed a small troponin elevation followed by deep T wave inversions in the precordial leads. Thus it seems in this case that hypokalemia and ischemia may have acted synergistically to produce large positive U waves in the precordial leads at the time of presentation. Hypokalemia (and bradycardia) delayed the repolarizing currents amplifying the discrepancies between the completion of repolarization in the M cells versus the epicardium and endocardium, and causing large positive voltage gradients in electrical diastole. Ischemia in the right coronary artery territory may also have contributed to the positive U waves in the precordial leads

(mirror image of negative U waves in the inferior leads). Possible mechanisms include mechanoelectrical effects due to discoordinate relaxation, or repolarization abnormalities due to effects of ischemia or infarction.

For the practicing clinician it should be borne in mind that normal U waves are probably the result of mechanoelectrical interactions that generate afterdepolarizations in diastole, thus writing a small positive deflection on the resting ECG. These are "true" U waves and have no special clinical importance. Pathologic U waves can occur in the setting of hypokalemia or ischemic heart disease. In the case of hypokalemia, what we take to be a U wave is actually an interrupted T wave. This occurs because of disparities in repolarization of the myocardial layers. Finally, U waves can occur in the setting of infarction or ischemia. In these situations, it is unclear if the underlying etiology is that of mechanoelectrical interaction or abnormalities of repolarization.

Disclosure

The authors report no conflicts of interest in this work.

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