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U waves in ventricular hypertrophy: possible demonstration of mechano-electrical feedback

MAURICE H CHOO, DEREK G GIBSON

From the Cardiac Department, Brompton Hospital, London

SUMMARY The relation between ventricular function and electrocardiographic evidence of hypertrophy (by voltage criteria, "strain", and U wave inversion) was examined by means of M mode echocardiography and apex cardiography in 73 patients with diseases associated with left ventricular hypertrophy and 10 normal volunteers. In patients with disease, left ventricular cavity dimension and fractional shortening were unrelated to electrocardiographic findings, but left ventricular posterior wall thickness was greater in those with strain or U wave inversion. Without U wave inversion, hypertrophy and strain were weakly related to diastolic abnormalities, but the addition of U wave inversion was strongly associated with a reduced rate of early diastolic posterior wall thinning, prolonged isovolumic relaxation time, delayed mitral valve opening after minimum cavity dimension, and a pronounced increase in transverse dimension during the isovolumic period suggesting incoordinate relaxation.

It is concluded that, whereas a negative U wave frequently occurs in association with the pattern of left ventricular hypertrophy or strain, it alone is strongly related to abnormalities of isovolumic relaxation. The close relation between incoordinate relaxation and U wave inversion, events which occur virtually simultaneously during the isovolumic period, suggests a mechanical influence on U wave genesis.

U wave abnormalities rarely occur alone.[1] More prominent and better understood changes in the QRS complex and ST–T segment frequently overshadow associated U wave alterations, which as a result are often neglected. This would not be of consequence unless an added U wave abnormality provided further diagnostic information. U wave inversion, the best recognised U wave abnormality, is believed almost always to signify heart disease; its commonest associations are hypertension, coronary artery disease, and aortic or mitral valve disease, all of which have well recognised and clinically important effects on ventricular diastole.[2] Excluding coronary artery disease, left ventricular hypertrophy characterises this group of patients in some of whom we have previously described the significance of a superimposed "strain" pattern.[3] Another reason for examining the U wave in more detail is that it is the only part of the ventricular electrocardiographic complex that is recorded predominantly or exclusively in diastole, and thus may be expected to relate more closely to mechanical events in diastole.[4] The present study of such patients was aimed at investigating the relation between diastolic events on the one hand and the electrocardiographic changes of hypertrophy, strain, and U wave inversion on the other. Further, it was hoped that any correlation might contribute towards refining current perceptions about the genesis of the U wave which remain unclear.

Requests for reprints to Dr Maurice H Choo, Department of Medicine, National University Hospital, Lower Kent Ridge Road, Singapore 0511.

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Patients and methods

STUDY GROUPS

Eighty three subjects were divided into four groups according to electrocardiographic diagnoses (Table 1). These were 10 normal volunteers with normal electrocardiograms and 73 patients with heart disease of whom 15 had left ventricular hypertrophy on voltage criteria alone, 20 had left ventricular hypertrophy with strain, and 38 had U wave

Table 1 *Electrocardiographic diagnoses*

Group	*Number of patients*
Normal (N)	10
Left ventricular hypertrophy (H)	15
Left ventricular hypertrophy + strain (S)	20
Left ventricular hypertrophy + strain + U wave inversion (U)	38

inversion with left ventricular hypertrophy or strain. All had sinus rhythm with normal intraventricular conduction.

As U wave interpretation is difficult and unreliable at heart rates below 50 beats/min or above 100 beats/min,[5 6] patients with such rates were excluded from the study. When the heart rate is 50–100 beats/min normal U waves may be identified in several leads as a positive deflection smaller than and following the T wave. The U wave is normally negative in aVR. The interval between the apices or nadirs of a T and U wave complex is, as a rule, 150 ms or more, and this relation is used to distinguish U waves from bifid T waves.[7] Further, the onset of the U wave usually coincides with the second heart sound which also marks the completion of the T wave.

CRITERIA

The following criteria were adopted (see Fig. 1): (1) left ventricular hypertrophy was diagnosed when at least one of the following criteria, modified after Romhilt and Estes,[8] was met (*a*) SV1 + RV5/6 > 35, (*b*) RV5/6 > 26, (*c*) R1 + S3 > 25, (*d*) RaVL > 11, (*e*) SaVR > 14 (units are mm); (2) a strain pattern was identified as ST segment depression (> 1·0 mm) and T wave flattening or inversion in the lateral or inferior leads[3]; (3) U wave inversion was considered to be present if a discrete negative deflection was consistently seen within the T–P segment in leads in which the U wave is normally positive. Negativity was judged with reference to the ensuing PR segment.[1 9] Since the normal U wave is negative in lead aVR, an upright U wave there denotes U wave inversion.

CLINICAL DIAGNOSES

Table 2 shows the study population categorised by clinical diagnoses. Patients with hypertrophic cardiomyopathy were included on the grounds that in such cases left ventricular hypertrophy is always present, subaortic stenosis often occurs, and U wave inversion is a known association.[2]

ELECTROCARDIOGRAPHY

Within seven days of echocardiography standard 12 lead electrocardiograms were recorded by means of a Hewlett-Packard (model 1511B) single channel or a Cambridge (model 3058/2) Series C three channel recorder with patients in the supine position and during quiet respiration. In addition to measurements made to see whether the criteria for left ventricular hypertrophy were met, the following were determined: (*a*) QQ (or RR) interval and heart rate (*b*) QT interval taken from the initial QRS deflection to the end of the T wave (from this, the QTc was derived using the formula, $QTc = QT\sqrt{RR}$); and (*c*) QaU interval measured from the initial QRS deflection to the apex or nadir of the U wave. No measurements were made on extrasystoles and postextrasystoles. For each interval the average of two measurements was calculated. The electrocardiogram was interpreted and measured before digitised information from echocardiography was analysed. Heart rates from the electrocardiogram were compared with those from the echocardiogram.

ECHOCARDIOGRAPHY

M mode echocardiograms were recorded with Cambridge Instruments equipment or an Advanced Technology Laboratories (ATL) Mark 300 machine with a 2·25 or 3·0 MHz transducer. The patients were studied in the left semilateral position, and simultaneous electrocardiograms and phono-

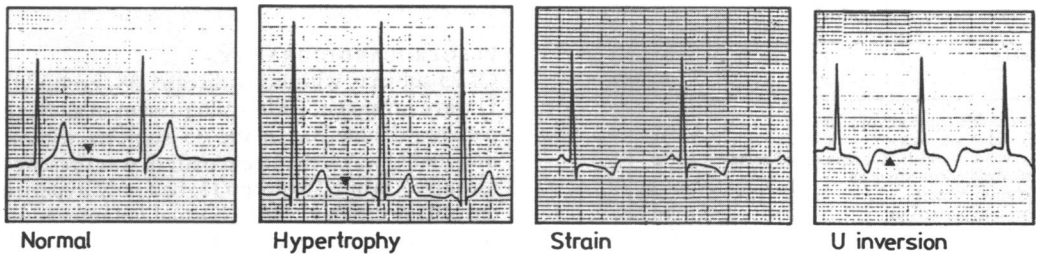

Fig. 1 *Single leads (lateral precordial) from electrocardiograms showing normality, hypertrophy on voltage criteria, strain pattern, and strain pattern with U wave inversion. Arrowheads point to the first U wave in each example; no U waves are present in the example of strain alone. Rapid QRS deflections that do not register sufficiently boldly for reproduction purposes have been darkened.*

cardiograms were recorded at a paper speed of 100 mm/s. Simultaneous apex cardiograms were also recorded in 27 of the patients with heart disease. Records of the left ventricular cavity were taken at the level of the tips of the mitral leaflets showing cusp separation. Here both cusps were visible at the onset of diastolic separation and early diastole, but not during the remainder of diastolic filling. Aortic valve closure (A_2) was taken as the onset of the first high frequency vibration of the second heart sound. A_2 was not recognised in many patients with aortic stenosis. The O point of the apex cardiogram was identified in the usual way as a sharp early diastolic nadir. Echocardiograms were digitised by means of a Summagraphics digitiser and a Prime 750 computer system. Two or, if available, three optimally recorded cardiac cycles were digitised so that mean values could be calculated. The following measurements were obtained: (1) maximum (Dd) and minimum (Ds) left ventricular dimension, and fractional shortening (%) calculated as 100(Dd−Ds)/Dd; (2) thickness of left ventricular posterior wall (PWd) at the onset of the QRS; (3) peak value of normalised rate of dimension (D) increase, calculated as 1/D.dD/dt (NPRDI), during early diastole; (4) normalised peak rate of posterior wall thinning (NPRWT) during early diastole calculated in the same way; (5) the following time intervals (*a*) cycle length, from which the echocardiographic heart rate was derived, (*b*) A_2 to mitral valve opening (A_2–MVO) which is the period of isovolumic relaxation, (*c*) left ventricular minimum dimension to mitral valve opening (MD–MVO), (*d*) O point to the time of peak rate of left ventricular dimension increase (O–PRDI), (*e*) interval from the onset of the QRS to the time of minimum dimension (QMD), (*f*) interval from the onset of the QRS to mitral valve opening (QMVO), (*g*) interval from the onset of the QRS to the O point (QO), (*h*) interval from onset of the QRS to the time of peak rate of dimension increase (QPRDI); and (6) the percentage of dimension increase occurring during the interval from minimum dimension to mitral valve opening (%DI,MD–MVO).

Table 2 *Clinical diagnoses*

Diagnoses	*Number of patients*
Hypertrophic cardiomyopathy	20
Aortic valve stenosis	21
Aortic valve stenosis, coarctation of aorta	2
Supravalvar aortic stenosis	3
Coarctation of aorta	4
Systemic hypertension	10
Aortic valve stenosis and regurgitation	3
Aortic regurgitation	5
Mitral regurgitation	3
Idiopathic left ventricular hypertrophy	2
Normal volunteers	10
Total	83

Table 3 *Electrocardiographic findings and time intervals (ms)*

	U	*S*	*H*	*N*
Number of subjects	38	20	15	10
Voltage, SV1 + RV5/6 (mm)	42 (14)	38 (13)	41 (49)	26 (6)
QQ	844 (52)	868 (95)	911 (120)	920 (152)
QT	429 (47)	425 (38)	423 (33)	427 (31)
QTc	395 (72)	396 (50)	404 (52)	425 (59)
QA_2	435 (77)	442 (54)	424 (34)	440 (21)
QMD	432 (76)	442 (62)	423 (54)	463 (31)
QMVO	534 (78)	516 (61)	486 (58)	502 (24)
QaU	524 (52)	528 (49)	518 (50)	522 (34)
QO*	533 (57)	541 (26)	521 (34)	NA
QPRDI	479 (55)	530 (45)	531 (22)	NA

*Data from 27 subjects with apex cardiograms.
Groups U, S, H, and N as in Table 1.
NA, not available. Mean values are given with standard deviation in parentheses. QA_2, interval from onset of QRS to aortic second sound; QMD, interval from onset of QRS to time of minimum dimension; QMVO, interval from onset of QRS to mitral valve opening; QaU, interval from initial QRS deflection to apex or nadir of U wave; QO, interval from onset of QRS to O point; QPRDI, interval from onset of QRS to time of peak rate of dimension increase.

STATISTICAL METHODS

Five electrocardiographic, five combined electrocardiographic and echocardiographic, and nine echocardiographic variables (Tables 3 and 4) were selected for statistical analysis. Data are expressed as mean (1 SD). For each variable, detection of significant differences among the four defined study groups was performed by a one way analysis of variance (ANOVA). Where appropriate, mean values of individual pairs were compared by Student's *t* (unpaired) test. A p value of < 0.05 was regarded as significant.

Results

To avoid lengthy repetition, the study groups are identified by the initials U (U wave inversion), S (strain), H (hypertrophy), and N (normals) as described in Table 1.

ELECTROCARDIOGRAPHY

Of 73 subjects with heart disease, 38 (group U) had U wave inversion, with strain present in all but three patients (Table 3). In the 35 subjects without an inverted U wave, the strain pattern was present in 20 (group S), while 15 (group H) had only hypertrophy on voltage criteria. All 10 normal volunteers (group N) had no electrocardiographic abnormality. Voltage (SV1 + RV5/6, in mm) was not significantly different among groups U, S, and H, but was greater than normal in group U ($p < 0.001$), group S ($p < 0.01$), and group H ($p < 0.001$). The QQ interval in

Table 4 *Echocardiographic findings*

Finding	*U*	*S*	*H*	*N*
LV diastolic dimension (mm)	45 (12)	48 (8)	50 (12)	48 (3)
LV posterior wall thickness (mm)	14 (4)	14 (3)	12 (4)	10 (1)
LV fractional shortening (%)	31 (10)	30 (8)	35 (8)	36 (4)
NPRDI (cm/s)	2·3 (1·0)	2·4 (0·8)	2·9 (1·1)	3·1 (0·8)
NPRWT (cm/s)	2·8 (1·1)	3·6 (1·5)	3·9 (1·7)	5·4 (1·7)
A_2–MVO (ms)*	95 (33)	76 (26)	69 (31)	62 (14)
MD–MVO (ms)	101 (31)	74 (31)	63 (41)	39 (22)
%DI,MD–MVO	28 (13)	19 (12)	14 (7)	7 (5)
O–PRDI (ms)†	−54 (41)	−11 (48)	10 (40)	NA

*Does not include data from 14 subjects without a detectable A_2.
†Data from 27 subjects with apex cardiograms.
NA, not available. Mean values are given with standard deviation in parentheses. LV, left ventricular; NPRDI, normalised peak rate of dimension increase; NPRWT, normalised peak rate of posterior wall thinning; A_2–MVO, A_2 to mitral valve opening; MD–MVO, left ventricular minimum dimension to mitral valve opening; O–PRDI,O point to time of peak rate of left ventricular dimension increase.

groups U and S was shorter than normal ($p < 0.05$). No differences between the groups were present for the QT, QTc and QaU intervals. The mean (SD) heart rates measured from the electrocardiogram (70 (12) beats/min) and echocardiogram (68 (13) beats/min) were similar.

ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY

There were no significant differences among the four groups (Table 3) for any of the time intervals measured from the onset of the QRS to the aortic second sound (QA_2), to minimum dimension (QMD), to mitral opening (QMVO), and to the O point (QO). The interval from the QRS to the peak rate of dimension increase (QPRDI) was shorter in group U compared with that in group H ($p < 0.05$), but not with that in group S ($p = 0.051$). The mean values for QA_2 and QMD were virtually identical in groups U, S, and H, but QA_2 was approximately 20 ms earlier than QMD in the normals.

ECHOCARDIOGRAPHY

Table 4 summarises the results for the nine echocardiographic measurements. There were no significant differences between groups in left ventricular cavity dimension and fractional shortening. Posterior wall thickness was greater than normal ($p < 0.01$) in group U and group S but not in group H ($p = 0.074$).

Unlike the three basic echocardiographic indices just described, the last six (Table 4) reflect events in early diastole—the period during which the U wave is registered. It was only in these diastolic measurements that differences were observed between groups U and S. Group U is distinguished from group S solely by the presence of U wave inversion in the former. Compared with left ventricular hypertrophy with strain (group S), the presence of U wave inversion (group U) was associated with a reduced normalised peak rate of left ventricular posterior wall thinning ($p < 0.05$), a longer isovolumic relaxation period ($p < 0.05$), a longer interval from minimum left ventricular dimension to mitral valve opening ($p < 0.01$), and greater dimension increase during MD-MVO ($p < 0.05$). Directionally similar but larger differences were present for each of these measurements when group U was compared with group H (NPRWT, $p < 0.05$; A_2–MVO, $p < 0.05$; MD–MVO, $p < 0.001$; %DI,MD–MVO, $p < 0.001$) or group N (NPRWT, $p < 0.001$; A_2–MVO, $p < 0.01$; MD–MVO, $p < 0.001$; %DI,MD–MVO, $p < 0.001$). None of these variables was significantly different in the group with hypertrophy alone (group H) and the group with an added strain pattern (group S). Compared with normal individuals, however, both these groups had reduced peak rate of wall thinning ($p < 0.01$ for group S, $p < 0.05$ for group H) and greater percentage of dimension increase during MD–MVO ($p < 0.01$ for group S, $p < 0.05$ for group H), while MD–MVO itself was significantly prolonged only for group S ($p < 0.01$). The normalised peak rate of left ventricular dimension increase was not different among groups U, S, and H, but was decreased in group U ($p < 0.05$) and group S ($p < 0.05$) compared with normal. Peak rate of left ventricular dimension increase with respect to the O point occurred earlier, becoming more negative, in group U compared with group H ($p < 0.01$) but not with

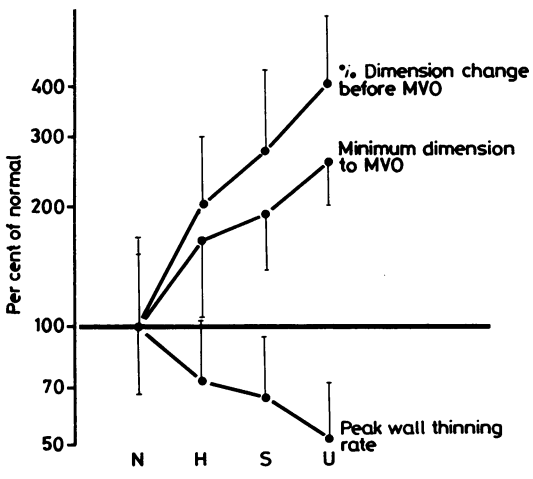

Fig. 2 *Graph comparing the mean values of three diastolic variables in groups with hypertrophy (H), strain (S), or U wave inversion (U) with normal (N). Vertical extensions represent one standard deviation. MVO, mitral valve opening.*

group S ($p = 0.061$) although the difference was almost significant.

In addition to individual comparisons, Table 4 shows that mean values for each of the six diastolic measurements progress in a stepwise manner from N to H to S to U. Fig. 2 illustrates this consistent trend for three of the measurements.

Subset analysis was performed on the largest diagnostically homogeneous group—21 patients with isolated aortic valve stenosis. Of these, 12 had U wave inversion, six had strain, and three had hypertrophy on voltage criteria. Compared with strain alone, U wave inversion was associated with reduced peak rate of wall thinning (2·2 cm/s *vs* 3·2 cm/s, $p < 0.05$) and greater dimension increase during the interval from left ventricular minimum dimension to mitral valve opening (MD–MVO) (32% *vs* 18%, $p < 0.05$); the difference for the MD–MVO interval (103 ms *vs* 78 ms, $p = 0.060$) approached statistical significance. The interval from A_2 to mitral valve opening was not compared because a discrete A_2 could not be identified in many of these patients. Too few apex cardiograms were available to allow meaningful comparisons of the interval from the O point to time of peak rate of left ventricular dimension increase. The subgroup of three patients with hypertrophy alone was too small for analysis.

Discussion

Almost thirty years ago in his clinical study of hypertensive patients Kemp *et al* pointed out that U wave inversion commonly accompanied the pattern of left ventricular strain in the electrocardiogram.[10] Compared with strain alone, additional U wave inversion was associated with a higher incidence of cardiomegaly, cardiac failure, uraemia, cerebrovascular accidents, encephalopathy, and deaths. In worsening disease, serial electrocardiograms may show stepwise evolution of hypertrophy, strain, U wave flattening and, finally, inversion.[6 10] It was proposed then that "an inverted U wave was a late finding in left ventricular strain patterns ... associated with clinical findings of more advanced disease of the left ventricle."

The left ventricular stain pattern does not result from an increase in left ventricular mass since athletes with substantial cardiac hypertrophy do not manifest it. Further, while the strain pattern is only weakly, if at all, related to abnormalities of systolic function, it is closely correlated with diastolic abnormalities.[3] Since ST and T deflections are generally completed before mechanical diastole begins, this correlation must be an indirect one, perhaps due to a direct factor nested within the strain group.

The present study suggests that this additional factor is closely related to U wave inversion. In the absence of a negative U wave, the strain pattern is only weakly related to diastolic abnormalities. By contrast, addition of U wave inversion was associated with reduced diastolic wall thinning rate, a prolonged isovolumic relaxation period, and delayed mitral valve opening relative to minimum dimension. During this period between minimum dimension and the start of left ventricular filling, significant dimension increase occurred when U wave inversion was present, amounting to almost a third of total dimension increase for diastole. Such an increase in transverse dimension during a period of constant volume indicates correspondingly large reductions in other axes, implying the presence of incoordinate relaxation. Since the U wave, whether upright or inverted, begins at about A_2 or minimum dimension, and reaches a peak or a trough at approximately mitral valve opening, its proximal limb has a consistently close temporal relation with the isovolumic relaxation period. Thus, not only is U wave inversion associated with incoordinate wall movement, but both are virtually simultaneous events during isovolumic relaxation, compatible with a direct relation between the two. If causal, it is likely that mechanical events are primary since the U wave has no known excitation-contraction function. Contraction-excitation feedback, though less conspicuous than excitation-contraction coupling, has been shown to occur.[11] Lab suggested that mechanical inhomogeneities in the intact ventricle after repolarisation is complete generate current flow or afterpotentials following the T wave, and thus form or influence the U wave. Differences in electrical potential between muscle regions with varying degrees of contraction-excitation feedback due to inhomogeneous wall movement may determine the U wave vector.[12] Our finding that incoordinate relaxation is associated with reversal of U wave polarity thus provides strong support for this hypothesis.

To date, the mechanism of even the normal U wave remains controversial.[2] Lepeschkin, in an early review,[13] discussed three possibilities: first, that it results from a longer duration of the action potential in some part of the ventricles, variously thought to be Purkinje fibres,[14] papillary muscles,[15] or the basal wall of the ventricles[16]; second, that it reflects afterpotentials following the action potential; and third, that it is caused by potentials generated by stretching of the ventricular muscle during the phase of rapid filling during early diastole. He argued that the morphology of the U wave was not consistent with the first explanation, and pointed out that amphibians showed U waves despite lacking Purkinje fibres. Subsequent observations suggest that the second

and third theories may in fact be components of a single explanation that attributes the U wave to a "stretch-afterpotential".[7] This concept is provided with a firmer basis by Lab's experimental demonstration of contraction-excitation potentials in the intact ventricle, and is extended by our observations of the link between disordered diastolic mechanics and U wave behaviour.

The exact nature of the entity "stretch" has not been clearly defined. Presumably it must depend on the extent of lengthening, but may also be related to the tension in the muscle affected. It may thus be relevant that the peak rate of dimension increase tends to occur before the O point when the U wave is inverted, and progressively later with lesser electrocardiographic abnormalities. Since ventricular pressures are higher before rather than after the O point, which approximates to the nadir of ventricular diastolic pressure,[17] increase of dimension occurs at higher pressures in those with negative U waves. This may be a further factor leading to the development of abnormal surface potentials after repolarisation in patients with left ventricular hypertrophy and U wave inversion.

The extent of the various diastolic abnormalities in our study population appears to follow consistently the electrocardiographic progression from normal to hypertrophy to strain and to U wave inversion. This parallels the clinical observations of Kemp *et al*[10] and reinforces the concept that U wave inversion represents a more advanced stage of left ventricular disease. More important, a negative U wave may be an electrocardiographic sign of diastolic dysfunction.

In patients with left ventricular hypertrophy, U wave inversion is fairly stable although regression is possible.[18] Stable U wave inversion may also be seen in resting electrocardiograms of patients with coronary artery disease, particularly of the left anterior descending coronary artery.[9] Incoordinate relaxation is also a feature of coronary artery disease.[19] By contrast, transient U wave inversion may appear during infusion of pressors, exercise, and attacks of variant angina.[7 20 21] Therefore it appears that the common factor influencing U wave behaviour may be chronically present or acutely induced. Clearly it is not primarily dependent on changes such as fibrosis or ischaemia. Rather, the underlying mechanism is more likely to be a dynamic one which, for the moment, appears to be best explained by the hypothesis that the U wave is closely related to, if not actually an expression of, the pattern of regional ventricular wall kinetics during isovolumic relaxation. If so, greater attention to techniques of U wave recording and interpretation may provide easily obtained and clinically useful clues to important alterations in diastolic function.

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