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Electrophysiologic Characteristics of Cells Spanning the Left Ventricular Wall of Human Heart: Evidence for Presence of M Cells

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Objectives. **The present work was designed to provide an initial characterization of M cells in the normal human heart.**

Background. **Recent studies have uncovered a unique population of cells in the midmyocardial region of the canine ventricle. These cells, named M cells, were found to possess electrophysiologic features and a pharmacologic responsiveness different from those of other myocardial cells. Although well characterized in the dog, their presence or absence in the human heart is unknown.**

Methods. **Standard microelectrode techniques were used to map slices of ventricular free wall obtained from normal human hearts (n = 4). Preparations were paced at cycle lengths ranging from 1 to 10 s.**

Results. **We identified three cell subtypes: endocardial, subepicardial (M cells) and epicardial cells. The principal features differentiating M cells from the other cell subtypes were their longer action potential duration, more accentuated action potential duration rate relations and greater maximal rate of increase in action potential upstroke (Vmax). Our findings suggest that M cells represent ~30% of the cellular mass of the left ventricular wall. Concordance between changes in their repolarization and changes in QTU interval provide support for the role of M cells in the generation of the electrocardiographic (ECG) U wave.**

Conclusions. **This study provides evidence for the existence of M cells in the human heart that contribute to heterogeneity of repolarization within the ventricular wall. Our findings provide strong support for the hypothesis that M cells contribute importantly to the manifestation of the U wave on the ECG.**

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Until recently, repolarization of ventricular myocardium was thought to be relatively homogeneous. Recent studies (1) involving canine hearts have shown that ventricular epicardial, deep subepicardial (M cells) and endocardial cells differ in their electrophysiologic characteristics as well as in their response to pharmacologic agents. The action potentials of epicardial and M cells are characterized by a prominent phase 1 repolarization due to a large transient outward current (2). This gives them a typical spike-and-dome morphology, usually not observed in endocardial cells. M cells were shown to differ from surface epicardial and endocardial cells in that they display a greater maximal rate of rise of the action potential upstroke (Vmax) as well as a more accentuated rate dependence of action potential duration. Their characteristics are similar to those of Purkinje cells, except for the absence of phase 4 depolarization. M cells are also more sensitive than epicardial and endocardial cells to pharmacologic agents that induce early and delayed afterdepolarizations and triggered activity (3,4).

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The extent to which similar electrical heterogeneity exists in the human heart is not known. The present study was designed to assess the characteristics of cells spanning the ventricular free wall of the normal human heart.

Methods

Preparations. Preparations were obtained from patients with cystic fibrosis (n = 3) undergoing heart–lung transplantation or from a normal donor (n = 1) whose hearts could not be used for transplantation. Patient characteristics and treatments are shown in Table 1. Patients (two female, two male; age range 14 to 46 years) received no cardioactive drugs, including catecholamines, and exhibited normal electrocardiographic (ECG) findings.

Cardioplegia was not performed, and the hearts were quickly excised and immediately immersed in oxygenated cold Tyrode's solution with the following composition (in mmol/liter): NaCl 131, NaH_2PO_4 1.8, $MgCl_2$ 0.5, $CaCl_2$ 2.7, KCl 4, glucose 5.5, mannitol 1.1, HEPES (*N*-[hydroxyethyl]piperazine-*N'*-[2-ethanesulfonic acid]) 5. The pH was adjusted to 7.35 with Tris([hydroxymethyl]aminomethane). The hearts were transported to the laboratory in <5 min. The experimental preparations consisted of transmural slices isolated from the left ventricular free wall according to the method described by Sicouri and Antzelevitch (1) (i.e., by razor blade shaving [Dermatome Power Handle no. 3293, with cutting head no. 3295, Davol Simon]) made perpendicular (transmural) to

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Table 1. Clinical Characteristics Before Heart Transplantation

Pt No./ Gender	Age (yr)	Disease	Structural Heart Disease	HR (beats/min)	PR Interval (ms)	QRS Interval (ms)	QT/QTc Interval (ms)	U Wave	Treatment Before Operation
1/F	25	Cystic fibrosis	None	64	134	86	436/443	Absent	Fluindione (20 mg/day)
2/M	46	Fracture of the skull	None	NA	NA	NA	NA	Absent	Absence of treatment
3/F	14	Cystic fibrosis	None	60	100	80	390/390	Absent	Absence of treatment
4/M	22	Cystic fibrosis	None	122	80	75	300/428	Absent	Tocopherol (200 mg/day)

F = female; HR = heart rate; M = male; NA = not available; Pt = patient; QTc = heart-rate corrected QT interval.

the surface of the ventricular free wall. Briefly, the left ventricle was cut from the mitral valve to the apex, and 1-mm-thick transmural slices were made at different locations on the cut surface. This two-step procedure was repeated several times to obtain slices from most of the ventricular wall. For each heart, three to four slices from different locations were studied (total of 14). The slices of ventricular free wall were then cut to obtain final preparations 10 to 12 mm long (from epicardium to endocardium), 8 mm wide and ~1 mm thick (Fig. 1).

The preparations were placed in a tissue bath and allowed to equilibrate for at least 2 h while superfused with oxygenated (95% O_2:5% CO_2) Tyrode's solution (37 ± 0.5°C, pH 7.35) containing (in mmol/liter) NaCl 131, KCl 4, NaH_2PO_4 1.8, $NaHCO_3$ 18, $CaCl_2$ 2.7, $MgCl_2$ 0.5, D-glucose 5.5, mannitol 1.1.

After equilibration, the preparations were mounted in a lucite chamber perfused with Tyrode's solution warmed to 37°C and equilibrated with 95% O_2/5% CO_2. Solutions were pumped through the chamber at a rate of 12 ml/min, providing at least three changes in chamber content per minute. During this equilibration period, the tissues were stimulated at a pacing cycle length of 1,000 ms, using square wave pulses 1 to 2 ms in duration and twice the diastolic threshold in intensity delivered through Teflon-coated bipolar silver wires. Tissues were impaled with 3 mol/liter KCl–filled glass capillary microelectrodes (tip diameter <1 μm, resistance 10 to 25 MΩ). The electrodes were coupled by a 3 mol/liter KCl interface to an Ag/AgCl electrode that led to an amplifier with a high input impedance and input capacity neutralization (Biologic VF-102). Output was displayed on a digital storage oscilloscope (Gould 1604) coupled to a plotter by a 488 IEEE interface (Gould Colorwriter 6300) to a strip chart recorder (Gould 8188) and a modified digital audio processor (Sony PCM-501ES) coupled to a video-tape recorder (JVC HR-D755S). The tissue chamber was connected to ground through a 3 mol/liter KCl Ag/AgCl junction. The maximal rate of rise of phase 0 (Vmax) was differentiated electronically and the system calibrated as described by Rosen et al. (5).

During the experimental protocol, the action potentials were recorded at different pacing cycle lengths. Their maximal

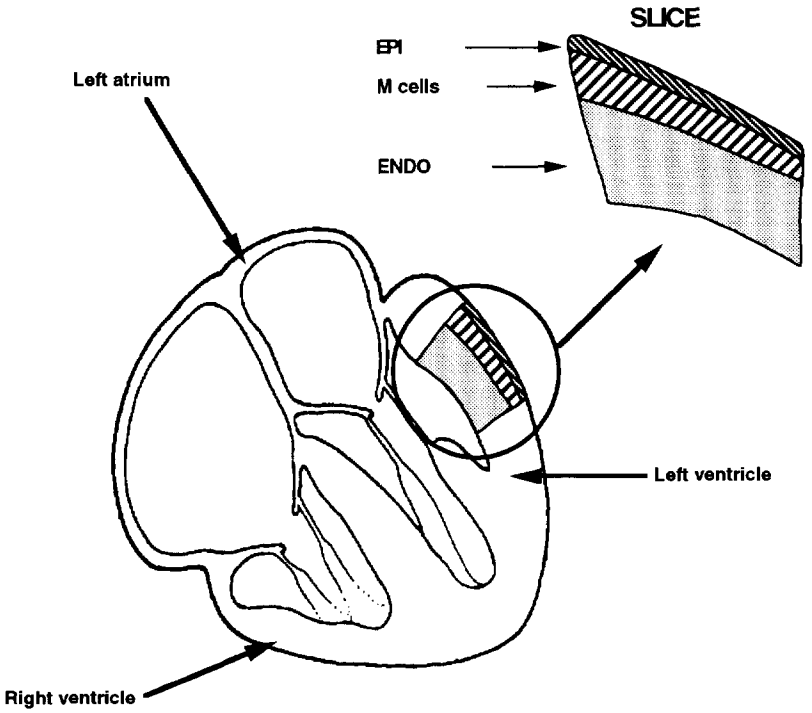

Figure 1. Preparation of slices of ventricular free wall. Incision of the left ventricle was performed with scissors from the base to the apex. Slices of ventricular free wall were made with a dermatome applied to one edge of the incision. Slices were then carefully cut with scissors to adjust the size of the preparations to those of the experimental chamber. This preparation is represented at **top right**, with the different regions from which the cellular subtypes were recorded. As indicated, epicardial (EPI) cells are located in a thin layer; endocardial (ENDO) cells represent the major area; and M cells are recorded in an area located between epicardial and endocardial cells, 4 to 5 mm thick.

diastolic potential was measured as well as action potential duration at 30% (APD_{30}), 60% (APD_{60}) and 90% (APD_{90}) of full repolarization at a pacing cycle length varying from 1,000 to 10,000 ms.

Statistical analysis. Data are expressed as mean value ± SEM. Statistical analysis was performed using the Student *t* test for paired data or nested analysis of variance coupled with the Scheffé procedure.

Results

Action potential configuration and location of cellular subtypes. To localize and characterize the different subpopulations of ventricular cells, we mapped the transmural preparations by recording action potentials along their length. Three major characteristics were used to differentiate the cell subtypes: 1) configuration of the action potential (particularly the presence or the absence of a spike-and-dome or prominent phase 1); 2) Vmax; and 3) the rate dependence of action potential duration.

Figure 2 shows typical action potentials recorded from epicardial, subepicardial (M cells) and endocardial cells in the same preparation. All cells are normally polarized, and no difference in resting potential is apparent. Action potentials recorded from epicardial and M cells display a distinct early repolarization phase (phase 1) that is not observed in endocardial cells. We did not observe a prominent spike-and-dome configuration as reported in the dog. M cells displayed a larger Vmax and an action potential duration longer than that of epicardial and endocardial cells. The action potential configuration of the endocardial cell resembled that of the canine endocardial cell, displaying little to no phase 1 and a phase 0 amplitude greater than that observed in epicardial cells. Epicardial behavior was observed only in a thin layer of tissue at the surface of the ventricle, comprising ~10% of the mass of the preparations. M cell characteristics were observed within 1 mm and up to 4 to 5 mm from the epicardial surface. The transition in action potential duration between epicardial and M cells was quite sharp, suggesting that the electrical coupling between these two cellular subtypes was poor. This could be linked to the finding that epicardial layers are oriented perpendicularly to subepicardial layers (M cells region) (Fig. 3). By contrast, the transition between M cells and endocardial cells was much more gradual, and there was a transition zone where the action potential duration was progressively becoming shorter. We observed that typical M cells (as shown by Fig. 2) comprise ~30% of the surface of the preparations studied. This estimation does not include the transition zone between M cells and endocardium. Because our preparations were obtained from different parts of the left ventricular free wall, it could be extrapolated that typical M cells represent ~30% of its total mass.

Table 2 summarizes the action potential characteristics of the three cell types observed in four normal human hearts. APD_{60} and APD_{90} were significantly longer in M cells than in epicardial and endocardial cells at a pacing cycle length of 1,000 ms. There was no difference in rest potential, but Vmax was significantly greater in M cells.

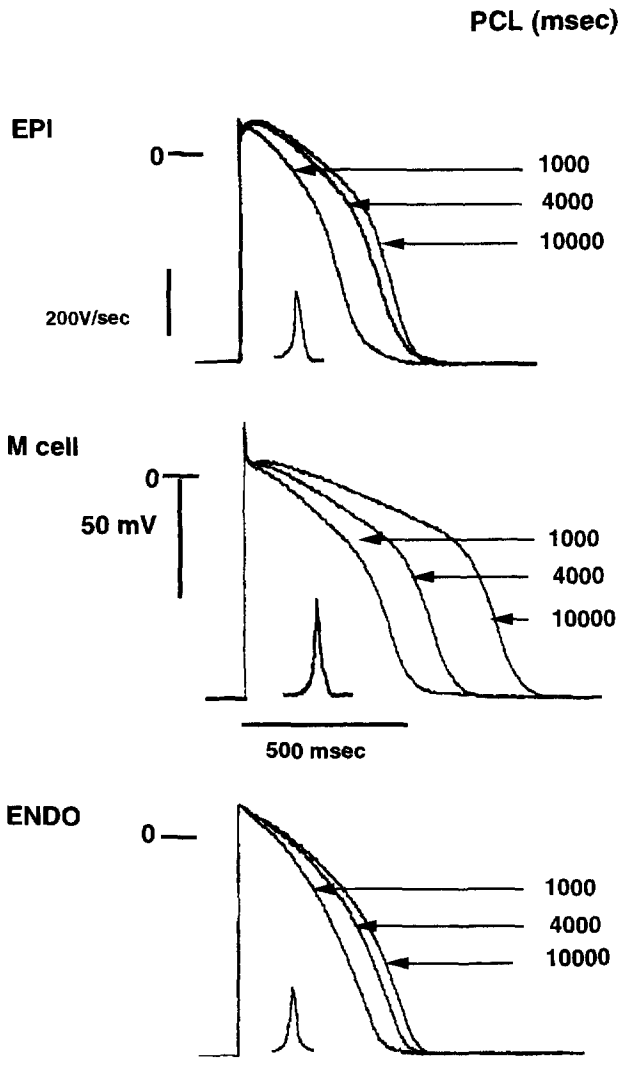

Figure 2. Action potentials recorded under steady state conditions at pacing cycle lengths (PCL) of 1,000, 4,000 and 10,000 ms from epicardial (EPI), deep subepicardial (M cell) and endocardial (ENDO) regions of transmural preparations isolated from a human left ventricle.

Rate dependence of action potential duration. A major characteristic differentiating M cells from the other cell types is the more accentuated rate dependence of their action potential duration. To study this feature, we paced the preparations at pacing cycle lengths ranging from 1 to 10 s. Figure 4 shows the effects of the pacing cycle length on APD_{90} of epicardial, M and endocardial cells. At a pacing cycle length of 1 s, the APD_{90} of epicardial and endocardial cells is similar to and ~100 ms shorter than that of the M cells. At progressively longer pacing cycle lengths, the APD_{90} of the three cell types increases, but the slope of the APD_{90} cycle length relation is clearly much steeper for M cells than that for endocardial and epicardial cells. In the absence of drugs, no repolarization abnormalities were encountered in any of the cell subtypes.

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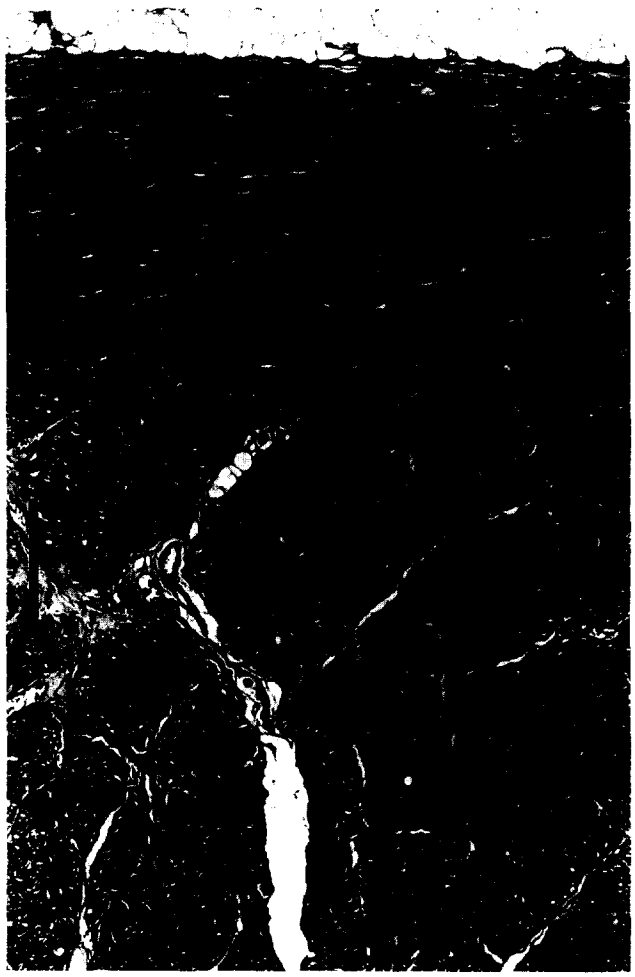


Figure 3. Histologic slice of human left ventricular free wall showing fibers in epicardium (EPI) oriented perpendicularly to those in the M cell region (M). **Vertical bar** = 1 mm.

Table 2. Action Potential Variables of Epicardial, M Region and Endocardial Cells Recorded From Human Heart Left Ventricle

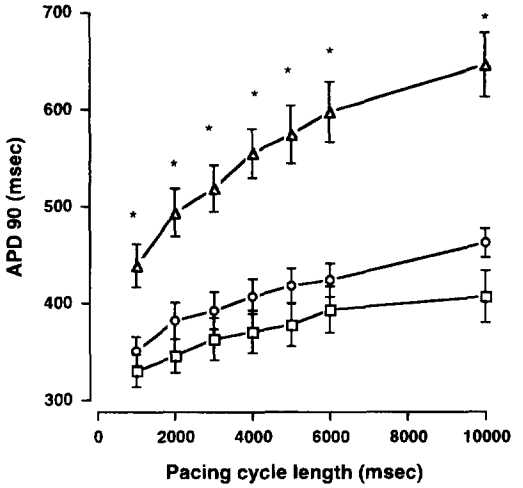
	EPI (n = 14)	M Region (n = 14)	ENDO (n = 14)
PCL 1,000 ms			
APD_{90} (ms)	351 ± 14	439 ± 22*	330 ± 16
APD_{60} (ms)	290 ± 14	365 ± 20†	270 ± 17
Vmax (V/s)	228 ± 11	326 ± 16‡	234 ± 28
MDP (mV)	−86 ± 1	−86 ± 4	−87 ± 1
Phase 0 ampl. (mV)	104 ± 2	105 ± 3	105 ± 2
PCL 10,000 ms			
APD_{90} (ms)	456 ± 15	645 ± 33*	407 ± 26
APD_{60} (ms)	399 ± 15	574 ± 30§	366 ± 29
Vmax (V/s)	210 ± 10	320 ± 14‡	251 ± 20
MDP (mV)	−88 ± 1	−87 ± 1	−88 ± 1
Phase 0 ampl. (mV)	105 ± 2	108 ± 3	109 ± 3

*$p < 0.001$, †$p < 0.002$, ‡$p < 0.01$, §$p < 0.0001$ versus epicardium (EPI) or endocardium (ENDO). Significance was determined by paired Student *t* test. Data presented are mean value ± SEM, four experiments in normal hearts. APD_{60}, APD_{90} = action potential duration at 60% and 90% of repolarization respectively; MDP = maximal diastolic potential; M region = deep subepicardial cells; PCL = pacing cycle length; Phase 0 ampl. = amplitude of phase 0 of the action potential; n = number of slices; Vmax = maximal upstroke velocity of phase 0 of the action potential.

Effects of epinephrine and low potassium. The electrophysiologic features of the human M cells are similar to those of Purkinje cells (higher Vmax and longer action potential duration [6]). One prominent difference is that we did not observe a phase 4 depolarization in M cells. As phase 4 depolarization and automaticity in Purkinje fibers are known to be enhanced by low external potassium concentration and adrenergic stimulation, we examined the response of our preparations to epinephrine (10^{-6} mol/liter) in a 2 mmol/liter potassium-containing Tyrode's solution. Neither automatic activity nor phase 4 depolarization were ever observed in M cells (14 of 14 preparations), suggesting that there were no Purkinje cells.

Possible role of M cells in genesis of U wave. Although it is generally accepted that the T wave is the result of a repolarization gradient within ventricular myocardium, the origin of the U wave remains controversial. Because M cells represent ~30% of the ventricular cellular mass and display longer action potentials than other myocardial cells at moderate to slow pacing rates (comparable to those of Purkinje cells), they are likely to contribute to the generation of the U wave. The appearance of a U wave in the ECG is usually a sensitive function of heart rate or of the preceding diastolic interval, as is the repolarization of the M cell action potential. The example shown in Figure 5 illustrates the virtual disappearance of the U wave after premature activation of the ventricle as well as the disappearance of a difference in the repolarization times of M cells and other myocardial cells after a premature beat. An untreated 85-year-old woman with normal electrolyte levels was admitted to hospital for severe bradycardia (30 beats/min) secondary to sinoatrial block. Her ECG shows a prominent U wave that disappears after a premature junc-

Figure 4. Effects of pacing cycle length on action potential duration at 90% repolarization (APD_{90}) in epicardial cells (**circles**), M cells (**triangles**) and endocardial cells (**squares**) of the human left ventricle. Significance was determined by analysis of variance coupled with the Scheffé test. *$p < 0.001$ versus epicardium or endocardium.



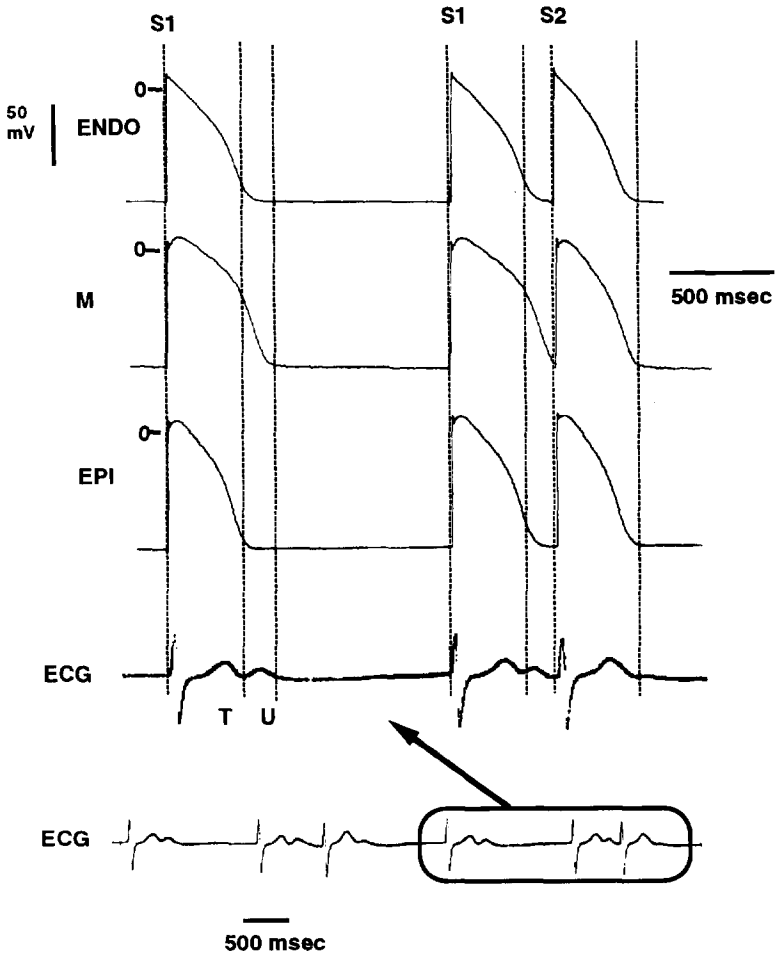


Figure 5. M cells as the basis for the U wave. The electrocardiogram (ECG) in the **lower trace** was recorded from an 85-year old patient (see text). The **end of the trace** where a premature junctional escape beat occurs is magnified and compared with the timing of repolarization of action potentials of epicardial (EPI), M cells (M) and endocardial (ENDO) cells recorded from a transmural strip isolated from a normal human left ventricle. The basic pacing cycle length of the preparation was 2,000 ms, similar to the junctional rhythm. A premature stimulus was applied at a coupling interval of 500 ms, corresponding to the coupling interval of the premature junctional escape. **Vertical dashed lines** at the end of the repolarization of endocardial and M cells show the concordance between the repolarization of the cells and the T and U waves of the ECG.

tional escape beat. Transmembrane action potentials were recorded from the epicardial, subepicardial and endocardial regions of a transmural slice of a normal human left ventricle. The preparation was stimulated at a pacing cycle length of 2,000 ms. At long pacing cycle lengths, M cell action potentials were 130 ms longer than those of the endocardial and epicardial cells. A premature stimulus applied to the preparation at a coupling interval of 500 ms induced an M cell response with a shorter action potential, similar in duration to those of the epicardial and endocardial cells. The concordance between the rate-dependent changes in the duration of the M cell action potential and those of the U wave provide support for the hypothesis that the M cell contributes to the manifestation of the U wave and to long QTU intervals on the ECG.

Discussion

To our knowledge, the present study provides the first demonstration and characterization of M cells in the normal human heart. Our findings indicate that human ventricular myocardium, like that of the dog, is not homogeneous but comprises at least three electrophysiologically distinct cell types.

Our results indicate that M cells exist in deep subepicardial layers of the left ventricular free wall in normal human hearts. As previously described in dogs (1), epicardial cells are found in a thin layer at the epicardial surface of the heart. At moderate to slow stimulation rates, a sharp transition in action potential duration is observed between cells recorded from the epicardial and M regions. In contrast, the transition in action potential configuration between cells recorded from M and endocardial regions was much more gradual.

Action potential characteristics. In the canine model, several features differentiate the action potentials of epicardial and endocardial cells. The epicardial action potential displays a smaller phase 0 overshoot, a much more prominent phase 1 and a phase 2 amplitude greater than that of phase 0. The spike-and-dome configuration in epicardium is due to the presence of a large transient outward current (I_{to}) that is absent or much smaller in endocardium (2,7). Action potential duration and Vmax are similar in canine ventricular epicardium and endocardium. M cells described in the deep subepicardial to midmyocardial layers of the canine ventricular free wall also commonly display a spike-and-dome configuration but are easily distinguished from epicardial cells on the basis of the remarkable prolongation of their action potential duration

at moderate to slow stimulation rates. The other distinguishing feature is the greater Vmax of M cells compared with values recorded from surface epicardial and endocardial cells (1).

In the human ventricle, all cell subtypes display longer action potential durations than in the dog (6,8). As in the dog, M cells in the human heart display a greater Vmax, a longer action potential and a steeper action potential duration rate relation than do epicardial and endocardial cells. However, the spike-and-dome configuration is considerably less pronounced in human epicardial and M cells than in the dog. The reason for this is unknown and apparently not due to the absence of I_{to} because Näbauer et al. (9) have described the presence of a large I_{to} (4-aminopyridine sensitive) in ventricular myocytes isolated from explanted human hearts. It is noteworthy that the action potential described by Beuckelmann et al. (10) for isolated human ventricular myocytes is similar to that recorded in our study. The methodology used by these investigators suggests that their study may have been performed on M cells. The cells were taken from the central one third of the myocardial wall (M region) in patients with terminal heart failure and in patients free of disease.

Rate dependence of action potential duration. The action potential duration and its rate dependence is a major feature differentiating M cells from other cell subtypes present within the ventricular wall. Our data indicate that at a pacing cycle length of 1,000 ms, the action potential duration of M cells is ~100 ms longer than that of epicardial and endocardial cells. As pacing cycle length is increased, the action potential duration of epicardial and endocardial cells increases modestly, whereas that of M cells increases dramatically. The result is a dispersion of repolarization within the ventricular wall at slow rates. The behavior of the three cell subtypes is comparable to that described in the canine heart.

Differences between M cells and Purkinje cells. M cells and Purkinje cells share some common features (higher Vmax and steeper action potential duration rate relation), which could lead to misinterpretation of data recorded from transmural ventricular preparations. M cells, particularly those recorded in the deep subepicardial layers of the heart, are unlikely to be Purkinje fibers for the following reasons. It is well established that subendocardial Purkinje fibers do not penetrate >2 to 3 mm into canine ventricular wall (11,12), and a direct connection of both bundle branches to a complex ramifying system of conducting fibers has only been demonstrated in subendocardial slices of mammalian heart, including human ventricle (13). Furthermore, Oosthoek et al. (14) reported that intramural Purkinje fibers are not found in human ventricle. The normal thickness of the human left ventricular free wall measured ~10 to 12 mm. In our experiments, careful mapping of the preparation showed that M cells were widely distributed and recorded at depths of 1 to 5 mm from the epicardial surface (i.e., 5 to 7 mm from the endocardial surface, a region devoid of Purkinje fibers). Moreover, we never observed automaticity (phase 4 depolarization) in M cells, not even in the presence of catecholamines, such as epinephrine (10^{-6} mol/liter) or low external potassium (2 mmol/liter), or both. These results virtually rule out any possibility that what we describe as M cells may be Purkinje cells.

Physiologic and clinical implications. The presence of M cells in the deep subepicardial layers of the human ventricle might be expected to contribute to ECG manifestations (U wave and long QTU interval in particular) (15). Since the beginning of electrocardiography, it has been well appreciated that the QRS complex represents the activation of ventricular myocardial cells (phase 0 of the action potential) and that the T wave represents the currents flowing during the repolarization of the myocardial cells. However, the origin of the U wave has remained unclear.

Einthoven (16), who was the first to describe the U wave, thought that it might be due to repolarization of some myocardial regions (17). It was later suggested that papillary muscles (18) were the sites of late repolarization inducing U waves after the T wave. Because no evidence was found for late repolarization in any region of the myocardium, Hoffman and Cranefield (19) proposed that the U wave could result from repolarization of the Purkinje network. This hypothesis was based on the finding that the duration of the action potential of the free-running Purkinje fibers is longer than that of ventricular myocardium and consistent with the timing of the U wave. Experimental and clinical studies reported by Watanabe (20) and Watanabe and Toda (21) lent support to this hypothesis. However, the total mass of the specialized conducting system is very weak compared with the total mass of the myocardium and is generally thought to be insufficient to produce enough current to generate a discernible voltage deflection on the ECG. This hypothesis became even less convincing when giant U waves were observed clinically (22).

Another hypothesis related the U wave to early afterdepolarizations or even delayed afterdepolarizations occurring in Purkinje fibers or contractile cells (23,24). Support for this hypothesis came from experiments in which early afterdepolarizations were observed on monophasic action potentials in patients with acquired or congenital long QT syndrome (25). However, these early afterdepolarizations occurred only when profound T wave modifications were present in these patients. Early afterdepolarizations are generally not observed in the normal heart, although a distinct U wave is observed in 40% of normal subjects (26).

The role of M cells in generating the U wave was first suggested by Nesterenko and Antzelevitch (27), who showed in a mathematical model based on experiments in dogs, that the U wave amplitude was directly proportional to the size of the M region. They showed that the presence of a distinct U wave, instead of a prolongation of the T wave, is due to a decreased electrical coupling between M cells and the other cell types. This is supported by our results. If M cells, by the hypothesis that they represent 30% of the ventricular mass, were well coupled to the other cell types, a prolongation of their action potential duration could not generate a distinct U wave as would be electronically attenuated by shorter epicardial and endocardial action potentials. In our experiments, the action potential duration at the borders of the M region changes

much faster than can be accounted for with normal intercellular coupling, especially on the epicardial side. This could be due to the finding that epicardial layers are oriented perpendicularly to subepicardial layers (as shown in Fig. 3). In that event it can be hypothesized that the intercellular resistance increases between epicardial and subepicardial layers.

The hypothesis that M cells are at the origin of the U wave is further supported by our results demonstrating similar concordance between the rate dependence of repolarization of human M cells action potentials and the rate dependence of the U wave (Fig. 5). This has also been shown with canine preparations (28). Although the Purkinje system shows similar characteristics, the much greater volume of M cells argues for their predominant role in the generation of the U wave.

The presence of M cells in human ventricular myocardium may also have implications for the development of cardiac arrhythmias. Sicouri and colleagues (3,4,15) recently showed that in the canine heart, M cells develop early afterdepolarizations and triggered activity more readily than other myocardial tissues and cells. It is possible that human M cells, because of their similarity with those of the dog, may also develop early afterdepolarizations and triggered activity more readily. M cells, because of their longer action potential and refractory period, could also produce a midmyocardial "column" of refractoriness, leading to the development of reentrant arrhythmias, including torsade de pointes (28).

Conclusions. Our study provides evidence for the existence of M cells in the deep subepicardial layers of human ventricles. These cells possess electrophysiologic features similar to those of the dog, except for the absence of a prominent spike-and-dome configuration.

The presence of M cells in the ventricular wall could be responsible for the genesis of the U wave frequently seen on the ECG, particularly at slow rates. These cells could also cause T wave abnormalities such as those observed in the long QT syndrome. Furthermore, because of their long action potential, they could be the target for arrhythmogenic mechanisms leading to ventricular arrhythmias.

Much of our knowledge about electrical and mechanical activity of ventricular myocardium has come from studies on endocardial tissues or cells, but these data are too often generalized to ventricular myocardium as a whole. In the human heart, as in that of the dog, there are at least four cell subtypes (Purkinje, endocardial, epicardial and M cells), each with a distinct electrophysiologic profile that should be taken into account.

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