



Is there a significant transmural gradient in repolarization time in the intact heart?

Repolarization Gradients in the Intact Heart

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In 1880, Burdon-Sanderson and Page recorded the ECG of the frog simultaneously with monophasic action potentials from the base and the apex of the left ventricle (LV).¹ Part of the ventricular muscle was injured with a hot wire, and monophasic action potentials were recorded as the potential difference between the injured region and an uninjured area. The ECG was recorded with a capillary electrometer, a slow, but reliable instrument. They noted that repolarization occurred earlier at the base than at the apex.¹ Warming the base resulted in a shortening of the basal action potential, leading to a deeper, more negative, and longer T wave in the ECG. Comparable findings were reported by Bayliss and Starling² and by Mines.³ Noble and Cohen⁴ have reviewed the early literature on the T wave.

Response by Patel et al p 96

Thus, around the turn of the 19th century, the concept that the T wave is caused by apicobasal gradients in repolarization was well established. However, nowadays, the notion that transmural differences in repolarization form the basis for the genesis of the T wave has been gaining a wide acceptance. In modern textbooks, there are diagrams depicting action potentials at the endocardium and the epicardium, where repolarization occurs earlier at the epicardium.^{5,6} To quote Mirvis and Goldberger⁷: "... action potential durations are longest near the endocardium and shortest near the epicardium, which produces a transmural gradient in recovery periods. Differ-

ences in action potential durations are greater than differences in activation times, so recovery is completed near the epicardium before it is completed near the endocardium." Because of this, according to Garibyan and Lilly⁸: "... in the normal heart, the forces of depolarization and repolarization are usually oriented in the *same* direction on the ECG recording." Thus, as is evident from the textbooks,⁵⁻⁸ there appears to be a consensus that transmural gradients in activation and repolarization are opposite. This concept is primarily based on the work of Antzelevitch and colleagues^{9,10} on the isolated, arterially perfused canine wedge preparation. There are, however, many data from whole animal hearts, as well as from human hearts, that show absence of a significant repolarization gradient across the wall of the LV. The data are either measurements of refractory periods¹¹⁻¹⁴ or measurements of activation-recovery intervals (ARIs)¹⁵⁻¹⁸ in intact canine hearts. Only in a study of El-Sherif et al¹⁹ a small prolongation of ARIs in midmural regions was found in young dogs, albeit only at long cycle lengths. In the human heart, no transmural gradients in ARIs²⁰ or repolarization times²¹ (ie, the sum of activation time and ARI) were found and an analysis of the data from Franz et al²² showed that epicardial repolarization occurred later than endocardial repolarization.²³ In the study of Chauhan et al,²⁴ repolarization time in the antero-septal right ventricular endocardium in cardiomyopathy patients without arrhythmias was on average 288 ms, and left ventricular epicardial repolarization time adjacent to the septum was 287 ms.

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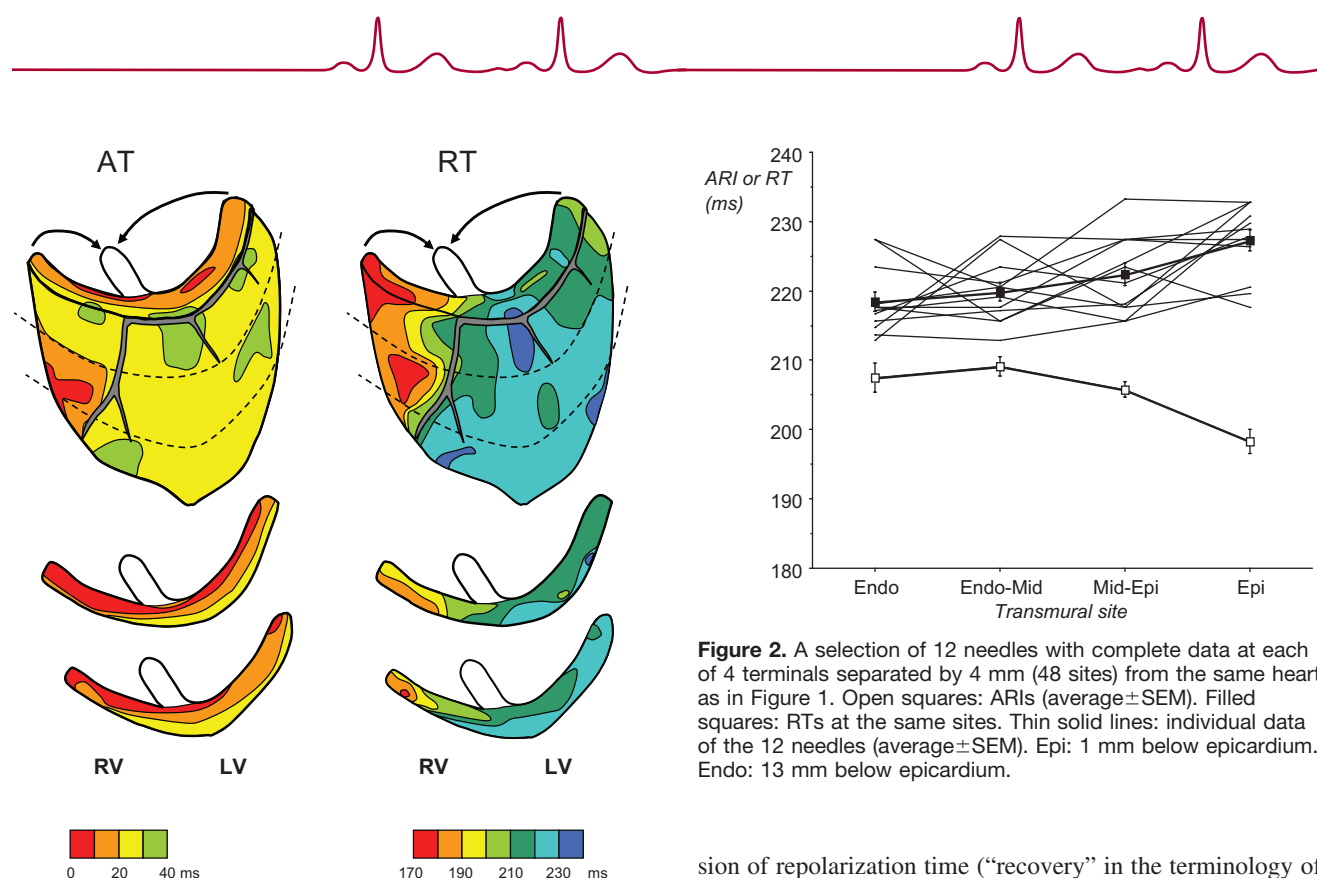


Figure 1. Three-dimensional diagram of a normal canine heart. The left and right ventricular free walls have been detached at their posterior margins from the septum and folded open (arrows). The lower 2 panels are virtual slices cut along the dotted lines in the top panels. ATs and RTs are depicted in isochrones at the basal level (top), at the level midway between base and apex (middle) and at the apical level (bottom). Activation proceeded from endocardium to epicardium. In the left ventricle the epicardium repolarized in general later than the endocardium (T Opthof, R Coronel, FJG Wilms-Schopman, AN Plotnikov, IN Shlapakova, P Danilo Jr, MR Rosen, MJ Janse, unpublished results).

As stated above repolarization time is the sum of activation time and action potential duration (or ARI). With activation proceeding from endocardium to epicardium, even in the presence of shorter epicardial action potentials compared with endocardial action potentials, repolarization time may still be longer in the epicardium. A good case in this point is a study of Antzelevitch and associates,²⁵ who recorded activation times and intramural monophasic action potentials in the dog's LV in vivo. Activation times from endocardium to epicardium ranged from 15 to 19 ms, depending on the type of anesthesia used, and gradients in action potential duration ranged from 20 to 30 ms, with epicardial action potentials being shorter than endocardial action potentials. Thus, at the long cycle length of 1500 ms, the repolarization time at the epicardium could at most have been 5 to 11 ms earlier than at the endocardium. Incidentally, no midmural regions with long action potentials were detected. It is remarkable that the authors nevertheless speak of transmural heterogeneity of repolarization in the title of the article.²⁵ It has previously been pointed out by Burgess²⁶ that the disper-

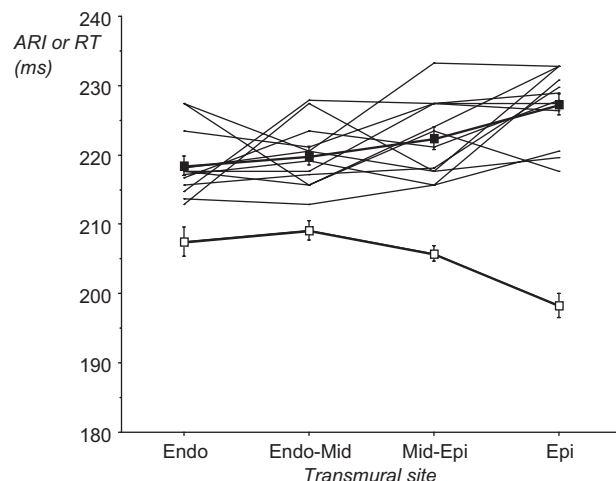


Figure 2. A selection of 12 needles with complete data at each of 4 terminals separated by 4 mm (48 sites) from the same heart as in Figure 1. Open squares: ARIs (average \pm SEM). Filled squares: RTs at the same sites. Thin solid lines: individual data of the 12 needles (average \pm SEM). Epi: 1 mm below epicardium. Endo: 13 mm below epicardium.

sion of repolarization time ("recovery" in the terminology of the author) along endocardium and epicardium by far outlasts the transmural dispersion (see Figure 6 in ref. 26). The controversy between the significance of transmural dispersion in repolarization time seems, at first glance, to result from differences in models, ie, the intact heart versus the LV wedge preparation. It is therefore of interest that there are also articles from Zipes and associates in which the presence of a midmyocardial zenith in action potential duration could not be confirmed, neither in a wedge from the LV free wall,²⁷ nor in a wedge from the interventricular septum.²⁸ Recently, absence of a midmural zenith in action potential duration was demonstrated in wedge preparations of the LV free wall of patients with cardiomyopathy.²⁹

Figure 1 is a diagrammatic, 3-dimensional representation of activation times (dV/dt_{\min} of local QRS complex) and repolarization times (dV/dt_{\max} of local T wave)³⁰ of a normal canine heart during atrial pacing at 130 b/min. Measurements were made at 159 sites (19 right ventricle [RV] epicardial, 17 RV transmural, 47 LV epicardial, 76 LV transmural). Intramural needle electrodes had 4 terminals each, separated by 4 mm in the LV and 2 electrode terminals separated by 4 mm in the RV (see for more methodological details refs. 18,31). The ventricles are depicted as if they are folded open (arrows). The lower 2 panels are virtual slices cut along the dotted lines in the top panels. As expected, activation proceeded from endocardium to epicardium. Earliest repolarization is seen at the RV, latest repolarization at the basal LV. Figure 2 is a selection of 12 transmural needles from the LV free wall with a complete set of 4 measurements each at 1, 5, 9, and 13 mm below the epicardium. The open squares and fat line show the averaged $ARI \pm SEM$ at these 4 planes parallel to the epicar-

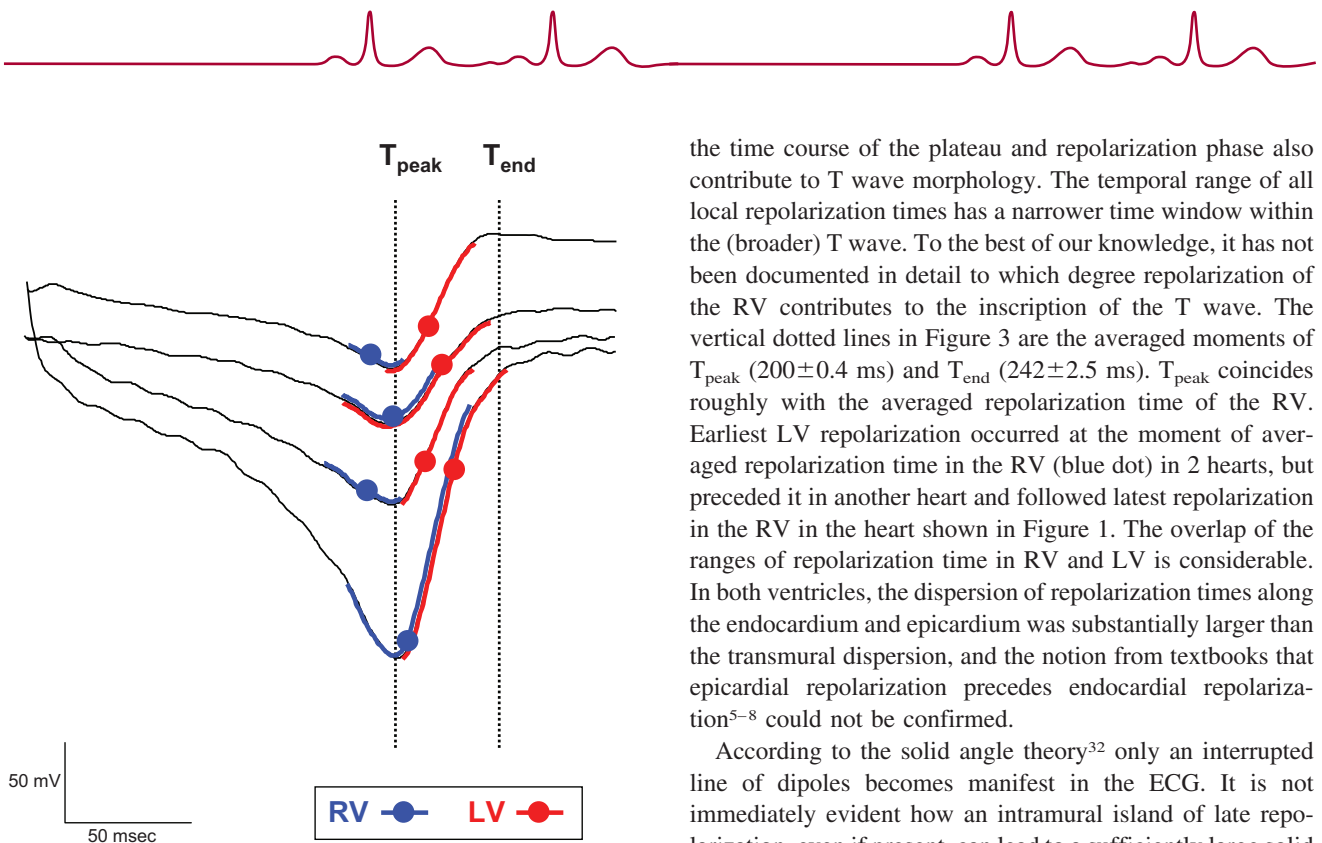


Figure 3. Magnified T waves from ECG lead II from 4 normal dogs. Earliest and latest repolarization times in the right ventricle (blue) and left ventricle (red). Circles indicate the averaged repolarization times for the RV and the LV. The averaged values for T_{peak} and T_{end} for these 4 hearts are indicated by the vertical dotted lines (modified from Figure 2 in Ref. 31 with permission from Elsevier Limited, Oxford, UK).

dium and transmurally separated from each other by 4 mm. The decrease in ARI from endocardium to epicardium was highly significant (ANOVA, $P < 0.0005$). Despite this, the decrease in ARIs was not enough to compensate for the increase in activation times from subendocardium toward subepicardium. The filled squares and fat solid line show repolarization times (average \pm SEM) for the same sites. Again the (small) changes were highly significant (ANOVA, $P < 0.001$), albeit that the gradient was opposite to that of the ARIs. Along these 12 needles with complete data the decrease in ARIs from subendocardium to subepicardium was 9.2 ± 3.1 ms, whereas the increase in repolarization times was 8.7 ± 1.9 ms. The thin lines show the data of the 12 individual needles. In 11 of these 12 needles repolarization time at the subepicardium was longer than ($n=8$) or equal to ($n=3$) that at any of the other 3 deeper located sites. In only 1 of the 12 needles we observed a midmural zenith in repolarization time, but it was only 6 ms longer than at the subepicardium. In summary, the epicardium repolarized later than the endocardium.

Figure 3 shows the results of 4 experiments in which local activation times, ARIs and repolarization times were measured at up to 98 epicardial sites and up to 120 midmural and endocardial sites per open-chest dog. The repolarization data are superimposed on T waves from lead II of the ECG. The T wave starts earlier than the earliest repolarization time in all 4 hearts. This is no surprise, because regional differences in

the time course of the plateau and repolarization phase also contribute to T wave morphology. The temporal range of all local repolarization times has a narrower time window within the (broader) T wave. To the best of our knowledge, it has not been documented in detail to which degree repolarization of the RV contributes to the inscription of the T wave. The vertical dotted lines in Figure 3 are the averaged moments of T_{peak} (200 ± 0.4 ms) and T_{end} (242 ± 2.5 ms). T_{peak} coincides roughly with the averaged repolarization time of the RV. Earliest LV repolarization occurred at the moment of averaged repolarization time in the RV (blue dot) in 2 hearts, but preceded it in another heart and followed latest repolarization in the RV in the heart shown in Figure 1. The overlap of the ranges of repolarization time in RV and LV is considerable. In both ventricles, the dispersion of repolarization times along the endocardium and epicardium was substantially larger than the transmural dispersion, and the notion from textbooks that epicardial repolarization precedes endocardial repolarization⁵⁻⁸ could not be confirmed.

According to the solid angle theory³² only an interrupted line of dipoles becomes manifest in the ECG. It is not immediately evident how an intramural island of late repolarization, even if present, can lead to a sufficiently large solid angle and would contribute to the T wave. Apicobasal and left-right gradients in repolarization clearly do produce interrupted lines of dipoles.

Concordant and Discordant T Waves

To quote Cowan et al³³: “The concordance of QRS and T waves led to the classical hypothesis that activation and repolarization must proceed in opposite directions. Such an inverse relation might result from a transmural endocardial-epicardial gradient, from gradients across the epicardial surface, or from both.” Wilson et al³⁴ had stated already that nonuniformity of the recovery process existed not only between epicardium and endocardium but also between apex and base, between LV and RV and between the anterior and posterior ventricular walls. Cowan et al³³ recorded activation sequences together with monophasic action potentials from the epicardial surface in patients with upright and with inverted T waves in left ventricular ECG leads. In patients with upright T waves, activation and repolarization proceeded in opposite directions. In patients with negative T waves, caused by aortic stenosis, there was no relation between activation sequence and action potential duration.

In normal dogs, there is discordance between QRS and T waves in most ECG leads.^{18,35} Interestingly, the pseudo ECG of the wedge preparation shows concordance between QRS and T waves,³⁶ underscoring once more that the repolarization order is different in the LV wedge preparation compared with the whole heart. In man QRS and T wave are concordant in most ECG leads. To date it is unknown whether this results from different electric vectors during repolarization in the heart itself, which would limit the significance of data

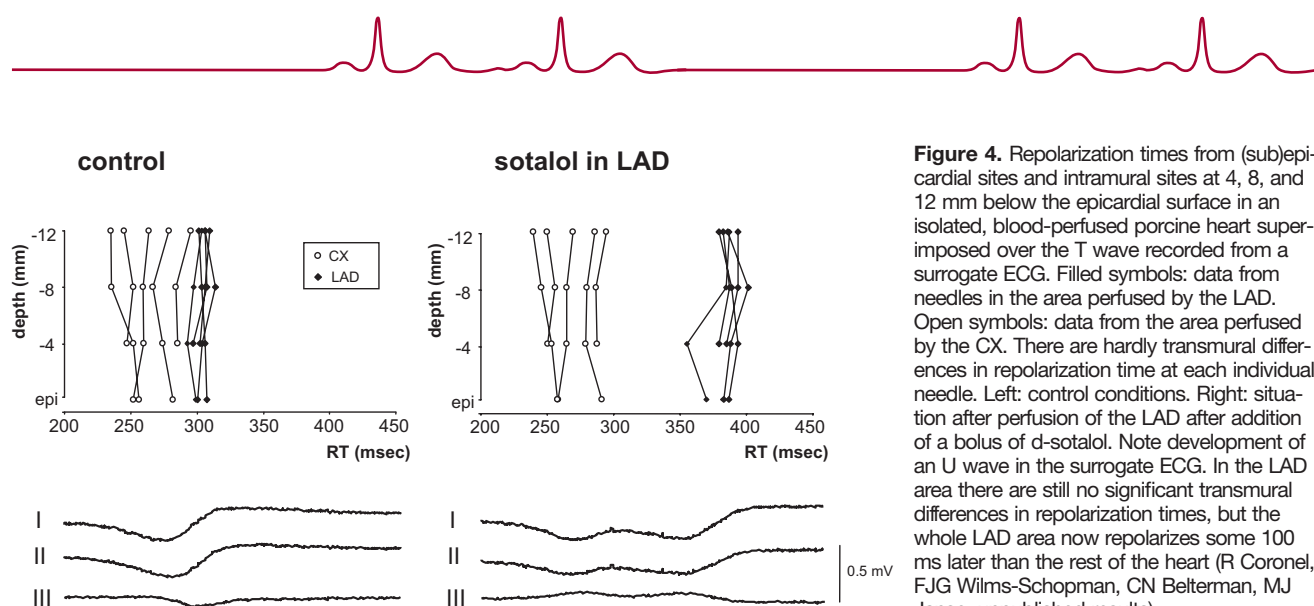


Figure 4. Repolarization times from (sub)epicardial sites and intramural sites at 4, 8, and 12 mm below the epicardial surface in an isolated, blood-perfused porcine heart superimposed over the T wave recorded from a surrogate ECG. Filled symbols: data from needles in the area perfused by the LAD. Open symbols: data from the area perfused by the CX. There are hardly transmural differences in repolarization time at each individual needle. Left: control conditions. Right: situation after perfusion of the LAD after addition of a bolus of d-sotalol. Note development of an U wave in the surrogate ECG. In the LAD area there are still no significant transmural differences in repolarization times, but the whole LAD area now repolarizes some 100 ms later than the rest of the heart (R Coronel, FJG Wilms-Schopman, CN Belterman, MJ Janse, unpublished results).

obtained in the dog for understanding of repolarization in man, or from another position of the heart in the chest, related to our vertical posture.

An important, largely overlooked and hardly cited, article addressing the question whether a transmural gradient in repolarization is responsible for concordance between QRS and T waves is the one by Higuchi and Nakaya.³⁷ They recorded monophasic action potentials from the endocardial and epicardial surfaces in 7 dogs. In normal conditions, the local epicardial T wave was negative (as in the canine ECG). When the epicardial surface was warmed, T waves became less negative and finally became positive. Isoelectric T waves appeared when the endocardial action potential was 22 to 42 ms longer than the epicardial action potential, leading to 14 to 31 ms earlier repolarization at the epicardium than at the endocardium. This implies that in an intact heart earlier epicardial repolarization by 14 to 31 ms, which would create a positive T wave in a wedge preparation, is apparently counterbalanced by alternative electric forces. Only with further warming of the epicardium in the experiments of Higuchi and Nakaya,³⁷ T waves became positive, but this only happened when endocardial action potentials were 40 to 60 ms longer than epicardial action potentials. This is a much larger gradient in action potential duration than the 20 to 30 ms difference reported by Weissenburger et al²⁵ in the intact canine heart.

Dispersion of Repolarization and Arrhythmogenesis

Increased dispersion of repolarization is widely considered as being arrhythmogenic. One possible mechanism has been thought to be reexcitation of fibers with short action potentials by adjacent fibers with longer action potentials. However, as Moe wrote: “my friend and colleague Carlos Mendez . . . convinced me that electrotonic interaction across closely coupled junctions between tissues having intrinsically different action potential durations would prolong the briefer, and abbreviate the longer action

potential at the junctional site; in other words the potentially excitatory current flow during repolarization would be attenuated.” “I was thus forced to abandon an attractive hypothesis.”³⁸ A similar mechanism, called phase 2 reentry, was proposed for cardiac preparations, where in some fibers, but not in all, the action potential plateau (dome) was suppressed. Local reexcitation occurred when the action potential dome propagated from sites where it was maintained to sites where it was abolished.³⁹ In the isolated, arterially perfused wedge preparation Shimizu and Antzelevitch created transmural dispersion in repolarization by the addition of a variety of drugs, such as the combination of chromanol and isoproterenol⁴⁰ or d-sotalol.⁴¹ In these examples, transmural dispersion of repolarization was caused by a long action potential duration in the midmural layer of M cells, and a relatively short action potential duration in endocardial and epicardial layers. Both spontaneous and induced Torsade de Pointes occurred in these circumstances. The arrhythmogenic mechanisms were thought to be both triggered activity caused by early after depolarizations in the M cells, and transmural reentry.

Figure 4 shows results from an experiment we performed on an isolated, Langendorff perfused porcine heart. The heart was perfused with a mixture of blood and Tyrode’s solution as described previously⁴² and the left anterior descending artery (LAD) was cannulated and connected to the perfusion system. The LAD-cannula could be selectively perfused. The heart was submerged in a container with perfusion solution, from which a surrogate ECG could be recorded from 3 electrodes attached to the wall of the container, positioned relative to the heart in a manner to produce standard lead configurations. The heart was paced from the atrium at a cycle length of 500 ms. Ten transmural needle electrodes were inserted in the left ventricular wall, 5 into the LAD area and the other 5 into the area perfused by the circumflex artery (CX). Each needle contained 4 electrode terminals, separated by 4 mm. The lines connect data from the same needle (filled symbols: LAD needles; open symbols: CX needles inserted in the posterior RV and the lateral and apical LV). The figure

shows repolarization times (RT) from each needle electrode and the corresponding T waves of the surrogate ECG recorded simultaneously. The left panel displays the control condition. It shows that the transmural differences in repolarization time derived from terminals in each needle are smaller than the differences between the needles, and that the duration of the T wave corresponds to the overall differences between the needles, as reported previously.³¹ The shortest repolarization time occurs at the endocardial posterior base of the RV and the longest repolarization time at the anterior LV. After infusion of a bolus of d-sotalol into the LAD, leading to a peak concentration of about 0.2 mmol/L, a large U wave developed in the surrogate ECG (right panel). Given the fact that under these experimental conditions there is repolarization of 2 areas, distinct in time and in location, one may question whether it would not be more correct to describe the signal as 2 components of one T wave rather than as a U wave. Transmural gradients in repolarization time did not increase, in contrast to the findings of Shimizu and Antzelevitch,⁴¹ and the repolarization profiles remained essentially the same, except for the significant delay of repolarization in the myocardium perfused by the LAD. The activation sequence did not differ between the 2 conditions and did not contribute to the changes in repolarization time. No spontaneous arrhythmias occurred, despite the large repolarization gradient in the order of 100 ms between LAD and CX area. This underscores that dispersion in repolarization, in the absence of other factors such as (partial) electric uncoupling, slow conduction, short refractoriness or the occurrence of shortly coupled premature beats, is not sufficient to induce arrhythmias, even when dispersion in repolarization is substantial.

Quantitative Aspects of Dispersion in Repolarization: Activation Versus Action Potential Duration

Dispersion in repolarization time concerns absolute differences in timing but also distances over which such dispersion occurs. Why action potentials are longer at the endocardium than at the epicardium of the LV is not known in detail. Presumably there is both an intrinsic and a functional cause. Although the electrotonic interaction between 2 single myocytes yields intermediate action potential durations after making sufficient electric contact, the situation is different in a whole heart. Late activated tissue, also repolarizing late, may not only repolarize by current flowing through the membrane to the extracellular space, but possibly also by axial current flowing through gap junctions toward tissue upstream which is already fully repolarized (see for discussion refs. 21 and 23). The result is that action potentials in a whole heart can be substantially shorter than even the shortest intrinsic action potential of all isolated myocytes that make up the intact heart. Not only the intrinsic features of the

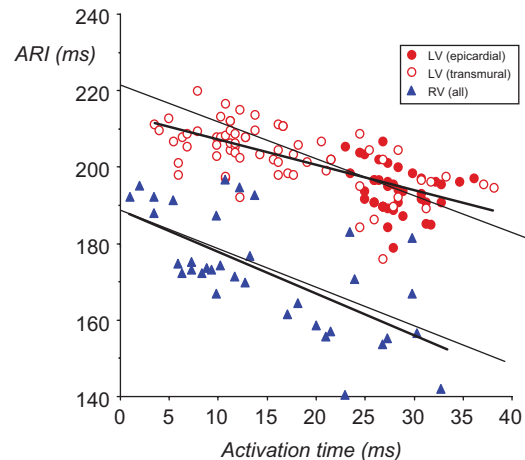


Figure 5. Activation times versus ARIs in RV (blue) and LV (red; filled: epicardial sites, open: intramural sites). Fat lines: regression lines (RV: $Y=189 - 1.10 X$, $n=35$, $r=-0.669$, $P<0.0005$; LV: $Y=214 - 0.66 X$; $n=110$, $r=-0.695$, $P<0.0005$). Thin lines: lines of identity. Lines with slope -1 through the averaged activation times and ARIs for RV and LV. Points on these lines contribute to dispersion in ARIs, but not to dispersion in repolarization time. Data from same heart as in Figure 1 and 2.

myocytes are important for action potential duration but also the direction of propagating wave fronts. Figure 5 shows activation times plotted against ARIs in 110 sites from the LV and in 35 sites from the RV of the same canine heart as in Figure 1. There is a negative correlation between activation times and ARIs in both the RV (blue symbols) and in the LV (red symbols). This relation is similar for the transmural (open red symbols) and epicardial sites in the LV (filled red symbols). The 2 regression lines were almost superimposable (not shown) and therefore only one regression line has been calculated through all LV data points. The slope of the regression line was -0.66 , which means that the decrease in ARIs is not sufficient to compensate for the time activation takes. To appreciate this, a thin line of identity (slope -1.0) has been drawn through the mean activation time (21 ms) and the mean ARI (200 ms) of the LV. All data points (sites) on this line of identity contribute to dispersion in ARIs, but *not* to dispersion in repolarization time. Although the ARIs at early activation are relatively long, they are not long enough to prevent dispersion in repolarization time. At no intermediate range of activation times we observed long ARIs, which might point to M cells. Because the slope of activation time versus ARI was -0.66 , it logically follows that the slope between activation time and repolarization time is $+0.34$ in this heart. When we performed this analysis in a total of 8 hearts (4 from Figure 3 and another 4 described in a previous article,¹⁸ we arrived at mean slopes for 8 hearts of -0.75 ± 0.06 (AT versus ARI) and $+0.25 \pm 0.06$ (AT versus RT), which means that in canine LV, repolarization time is longer in late activated areas than in early activated areas as demonstrated previously by Yuan et al⁴³ in endocardium of pig and man. These AT-ARI slopes decrease dramatically when

Table. Contribution of Different Parts of the Heart to Dispersion in Activation Times and Repolarization Times as a Percentage of Total Dispersion

Source of Dispersion (n=4)	Dispersion in Activation Time (%)	Dispersion in Repolarization Time (%)
Whole heart	100	100
Between LV and RV	4.4±1.7	51.5±10.7
Within RV	24.1±3.1	21.6±6.5
Within LV	71.6±2.4	27.0±5.0
Transmural (endo-epi)	(82.6±2.2)	(13.2±3.1)
Other axes	(17.4±2.2)	(86.8±3.1)

stimulation is performed from other ventricular sites (not shown). This underscores that intrinsic characteristics are important. AT-ARI relationships are less steep in diseased hearts,^{33,44} which therefore will display more dispersion in repolarization time. One other implication of a relatively steep relation between activation times and ARIs is that areas where dispersion in action potential duration is largest⁴⁵ are not necessarily areas where dispersion in repolarization time is also largest.

Quantitative Aspects of Dispersion in Repolarization: Where Is What?

The Table shows the distribution of dispersion in activation times and repolarization time over different parts of the whole heart, based on “explained variance” in ANOVA. For repolarization times about 50% of the dispersion is caused by differences between LV and RV. The remaining 50% resides within the LV (27%) and the RV (22%). However, the differences between hearts are large as can also be appreciated from the differences in overlap between the red and blue traces along the ECGs in Figure 3. When the LV component of dispersion in repolarization time is set at 100%, it appears that only 13% is caused by transmural (endocardial-epicardial) differences and that 87% can be found between base and apex and between the anterior and posterior side of the LV. This amount of transmural dispersion would translate to about 4%, if it were based on the dispersion in repolarization time of the whole heart. This small contribution of the transmural component is remarkable. It might be hypothesized that the transmural component would increase dramatically under other conditions such as during stimulation from an epicardial LV site.⁴⁶ We have tested this. Under such circumstances total dispersion in repolarization time increases dramatically within the LV, but this is fully explained by increased dispersion in repolarization from base to apex and from anterior to posterior, not transmurally (not shown). The Table also shows the contribution of different parts of the heart to dispersion in activation times. The large majority of this dispersion resides within the LV and the contribution of the difference between RV and LV is small. Completely opposite to what is found for repolarization, the dispersion in activation times is primarily caused by differences between

endocardium and epicardium (83%). These numbers once more emphasize that activation is primarily directed from endocardium toward epicardium, whereas repolarization is directed parallel to the epicardial surface.

We fail to understand how the relative importance of transmural repolarization gradients can be assessed from an experimental preparation like the wedge preparation that lacks apicobasal, left-right and anteroposterior components. Furthermore, if transmural heterogeneity were to be the major contributor to the T wave, it follows logically that the gradients along the other axes are to be small or nonexistent. This is simply not observed in whole heart preparations.

Conclusions

Dispersion of ventricular repolarization underlies the T wave in the ECG. A broad T wave, including a $T_{peak}-T_{end}$ interval of about 40 ms, is found in the canine left ventricle in the absence of relevant transmural dispersion in repolarization time. In addition, and in contrast with textbook knowledge, we found that in general epicardial repolarization occurs later than endocardial repolarization in the free wall of the LV. In contrast to the results obtained in the wedge preparation, d-sotalol administered to the region of the LV perfused by the LAD, did not increase transmural dispersion in repolarization time, although creating a difference in the order of 100 ms between the LAD area and the rest of the heart. Despite this dispersion, no spontaneous arrhythmias occurred. Finally, we did not observe midmyocardial zeniths in repolarization time, excluding a functional role for M cells.

There have been several debates^{10,47–49} on the spatial aspects of this dispersion during the last decade. We would like to end with a quote of Moe and his associates⁵⁰ back in 1965, when they connected 2 transmembrane potentials from the endocardium and epicardium from a canine left ventricle with a differential amplifier (Figure 13 in ref. 50). After comparing this local differential electrogram with the ECG, they stated: “The resemblance of the differential record to the remote lead QRS-T deflection of the ECG is apparent, although it is not possible to conclude that these epicardial-endocardial APD differences are responsible for the polarity of the T wave.”

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Disclosures

None.

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KEY WORDS: dispersion ■ repolarization time ■ activation ■ ECG

Response to Opthof et al

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The article by Opthof et al claims near absence of transmural dispersion of repolarization. We highlighted in our manuscript that inscription of concordant positive T waves in the precordial leads is principally due to transmural repolarization gradients, though a relatively small regional repolarization gradient may exist. The evidence pointing to a transmural gradient in which epicardium repolarizes before endocardium is overwhelming, having been demonstrated in numerous mammalian species, including man. One such human study by Franz et al concluded that “*These data suggest a transmural gradient of repolarization, with earlier repolarization occurring at epicardium*” (Ref. 22 in Opthof’s article). Ironically, Opthof et al used the same data from Franz et al and compared maximal epicardial repolarization time in 3 patients undergoing open-chest surgery with maximal endocardial repolarization in 7 other patients undergoing cardiac catheterization. They misleadingly state that this “*showed epicardial repolarization occurred later than endocardial repolarization*” (Ref. 23 in Opthof’s article). Similarly, they misinterpreted the *in-vivo* canine study by Higuchi and Nakaya (Ref 37 in Opthof’s article), stating that “*In normal conditions, the local epicardial T wave was negative.*” Higuchi and Nakaya actually indicated that “*The temperature of the epicardial surface was 31°C to 32°C when the chest was opened under room air. Under these conditions the T wave in ECG_{epi} was constantly negative.*” Warming the epicardial surface increased transmural dispersion of repolarization resulting in an upright T wave, consistent with our canine wedge data. The Opthof et al manuscript is replete with such misleading representations. It is also concerning that the lead II ECGs in Opthof’s et al’s article shows deeply negative T waves with pronounced ST segment depression. Are these normal baseline conditions? The discussion of Opthof et al then moves to the absence of M cells. The intricacies and caveats associated with this issue have been previously discussed, but are largely ignored by the authors. A new argument introduced is that one group of investigators failed to show presence of M cells in canine wedge preparations. In contrast to microelectrodes, which record action potentials from single cells, optical mapping recordings represent the summation of signals from numerous cells, obscuring discrete differences in repolarization time. Nevertheless, these authors consistently demonstrated a significant transmural gradient with the clear presence of M cells unmasked by APD-prolonging drugs. Finally, it is important to recognize that because of differences in action potential morphology, transmural voltage gradients sufficient to inscribe a prominent positive T wave can exist even when differences in final repolarization time are very small.