Three Things You Should Know When Considering the Atria

Location, Location, Location

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Atrial fibrillation (AF) is an arrhythmia of varied phenotypes, yet we continue to classify it under one heading. In an attempt to demystify it, the AF phenotype has been subdivided not by mechanism but by duration; that is, we acknowledge that AF comes in three not-so-simple varieties: paroxysmal, persistent, and permanent.1,2 Our knowledge of the mechanism underlying the progression from the paroxysmal to persistent form and then onto the permanent form is still limited, but it recently has been expanded with the study by Wijffels et al,3 which showed that AF begets AF. Now we are comfortable with the idea that rapid pacing per se can alter atrial cell/ionic electrophysiology as well as wall/cellular morphology (remodeling), which subsequently causes changes in atrial refractoriness. Here the basic assumption is that changes in atrial action potential duration and refractoriness track each other (but this is not always the case; for example, see Reference 4). Importantly, an increase in heterogeneity of refractoriness plays a significant role in both animal and human forms of AF.5–7 This increased heterogeneity could result from either a different response of regions of atrial cells to mediators of remodeling or from different initial or starting conditions of myocytes of different atrial locations.

It has long been appreciated that normal, nonremodeled atrial cell transmembrane voltage profiles vary considerably and depend on the anatomical location of cells of interest. Some scattered reports have suggested that some K+ currents may differ in density depending on the location of a cell in the atrial chamber. These studies have focused mainly on the regional ionic current heterogeneity of right atrial (RA) cells.8–10 The study by Li et al11 in this issue of Circulation Research compares the atrial cell and ionic properties of cells from one RA location (pectinate muscle) with those from one left atrial (LA) location (freewall). The results are remarkable not only in what was found but also in what was not found. In particular, Li et al11 show that whereas there is a significant increase in cell size in LA versus RA cells, there are no differences in the densities of $I_{Kr}$, $I_{Kr,d}$, $I_{Ks}$, and $I_{Cal}$ in the cells from the two groups. This suggests that with the reported 13% increase in LA cell size, there must be a concomitant increase in the number of functional channels, such that the densities of several ionic currents in RA and LA cells are similar. In contrast, in published data from the same laboratory,10 larger RA cells (by 15%) from the crista terminalis have increased $I_{Cal}$ density compared with the smaller RA cells from differing locations. Thus, it might be that our long-standing assumption of using ion channel density for comparisons may not always be appropriate for atrial cells.

Importantly, Li et al11 now report that the critical difference between RA and LA cells is the peak current density of the rapidly activating delayed rectifier $I_{Kr}$. This finding is the result of a systematic and careful comparison of the ionic current makeup of RA and LA cells from normal nonremodeled atria. The authors conclude that the larger $I_{Kr}$ density in LA cells contributes importantly to the shorter action potential duration (APD) in LA cells. Clearly it might not be the sole factor for the transmembrane voltage differences between RA and LA cells, because other ionic currents (such as those generated by transporters or ionic pumps or those activated by endogenous ligands) were not included in this study.

Li et al11 also suggest that $I_{Kr}$ differences underlie the greater class III effect of dofetilide in LA versus RA cells. Interestingly, and as expected from previous in vivo studies, a maximal concentration of dofetilide when applied to RA and LA cells produced a greater percent change in APD of LA cells, resulting in action potentials of RA and LA of similar durations (less heterogeneity of repolarization). This greater effect of dofetilide in LA cells may be just the result of the initial conditions of the LA cell (that is, the short APD). It would have been of interest to test the effects of dofetilide in RA and LA cells of the same initial APD using an action potential clamp approach. A direct comparison of dofetilide-sensitive currents during the repolarization phase would have resulted in a definitive answer as to whether differing $I_{Kr}$ densities in these subsets of LA and RA cells underlie the enhanced dofetilide effect in LA cells and whether this effect continues to be significant at atrial pacing rates, such as those seen during AF. In this way, the time at plateau voltages would be equivalent in the two cell types, thus obviating the effect plateau duration has on the amplitude of $I_{Kr}$ transients in atrial cells.12 Interestingly, studies in

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this last report emphasize that within the study population of LA cells, the density of the peak $I_{Kr}$ transient, critical for repolarization in canine atrial cells, can vary as much as 0.9 pA/pF (range, 0.2 to 1.1 pA/pF).\textsuperscript{12}

Li et al.\textsuperscript{11} complete their study of RA and LA differences by comparing Western blots of ether-a-go-go–related gene (ERG) protein in tissues of several RA and LA regions. They report a greater amount of total ERG protein in LA tissues; it seems that a significant difference existed only when freewall tissues were compared. Whereas these data are consistent with a role of ERG proteins in the manifestation of functional atrial $I_{Kr}$ currents in dog, it is not clear whether regional $I_{Kr}$ differences might also be related to the presence (or absence) of auxiliary K\textsuperscript{+} channel subunits. Recent data have suggested that both minK and MiRP1 coassemble with ERG proteins to produce functional channels.\textsuperscript{13–15} Finally, in adult nonremodeled canine atria, it seems that a single ERG protein (165 kDa) exists in both LA and RA tissues and that multiple forms of this protein, indicating differentially glycosylated proteins, evident in both rat and mouse atria\textsuperscript{16} were not described by Li et al.\textsuperscript{11}

Do the initial starting conditions of cells of the normal, nonremodeled LA region reported by Li et al\textsuperscript{11} (that is, an increased $I_{Kr}$) predispose the atria to initiate AF or do they provide a suitable substrate for perpetuating AF? It is difficult to know now, because we are not certain how these initial conditions in LA cells will respond to high rates of pacing and stretch or other stresses that predispose the atria to AF. It might be that the “location, location, location” that matters to a normal atria in normal sinus rhythm no longer matters.

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**References**


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