The results reported in this issue of *Heart Rhythm* by Porter et al1 suggest that AV nodal reentrant tachycardia (AVNRT) is more common in women than men and that aging makes AV reciprocating tachycardia less likely and AVNRT and focal atrial tachycardia (AT) more likely. These observations imply differences in the basic electrophysiology of the AV node, the atrium, and the accessory pathways that are determined by age and gender. Changes in ion channel function and/or regulation (e.g., by the autonomic nervous system), in connexin distribution, and in tissue architecture all could be involved.

Aging importantly changes basic cardiac electrophysologic properties. Resting potential, action potential amplitude, and phase 0 upstroke velocity are not altered in atrial cardiomyocytes of elderly dogs, but the plateau is more negative and the action potential duration is longer.2 L-type Ca²⁺ currents are reduced in right atrial cells from elderly dogs, although maximally stimulated current in the presence of isoproterenol is unchanged.3 Much less is known about K⁺ currents, although the transient outward current system seems to be increased in elderly dogs.3 Innervation of the cardiac conduction system decreases with advancing age,4 as does the ability of adrenergic stimulation to antagonize cholinergic effects.5 A consistently reported change in elderly atria is an increase in fibrous tissue, which is associated with an increased ability to maintain atrial fibrillation.2,6,7 Myofiber width increases with aging, and intermyocyte fat cell infiltration occurs.8 Studies of connexin43 changes have provided conflicting results, with one showing reduced connexin expression in lateral cell membranes8 and another increased lateral expression.6 Transverse conduction is selectively reduced,6,8 and “zigzag” conduction patterns that can lead to microreentry are favored.8,9 There is an interesting interaction between age and haploinsufficiency of the gene encoding the cardiac Na⁺ channel SCN5A, leading to progressive conduction impairment with age in patients bearing a mutation that promotes the occurrence of Lenègre’s disease.10

Thus, we have established enough about age-related changes in basic cardiac electrophysiology to know two things with certainty: (1) aging has major effects on cardiac electrical function; and (2) our present knowledge is very limited. In order to understand the type of findings reported by Porter et al, we need to know much more about aging-related changes in the basic determinants of cardiac arrhythmias. Key issues such as age-related changes in atrial myocyte Ca²⁺ handling (regarding the substrate for triggered activity) alterations in the Iₛ pacemaker current and the expression of underlying HCN ion channel subunits (regarding enhanced automaticity); changes in AV node molecular electrophysiology (including structure, ion channel and connexin distribution, and functional properties in various components of the AV nodal system); changes in the regulation of ion channel function by the autonomic nervous system and transduction pathways such as those involving G proteins and various neurohormones; and alterations in the determinants of accessory pathway function need to be determined. This is a potentially fertile area for future exploration, given the clinical importance of supraventricular arrhythmias and the aging of the population.

The female predilection to delayed ventricular repolarization and drug-induced long QT syndromes is well recognized and has led to an impressive body of work studying sex hormone and gender-related differences in regional cardiac repolarization and ion channel properties (for review, see Pham and Rosen11). Much less is known about gender differences in atrial and AV nodal electrophysiology. AH, HV, and PR intervals are longer in men than women, as is the AV nodal effective refractory period (AVNERP) and Wenckebach cycle length.12 It is possible that shorter AVNERPs allow AVNRT to be more easily sustained in women. However, AVNERP is only one of the determinants of AVNRT, and dual AV nodal physiology does not appear to be more common in women.12 Clearly, much more needs to be learned about gender differences in basic electrophysiology if the female predominance of AVNRT is to be understood.

Perhaps one of the most valuable outcomes of the study...
by Porter et al is that it highlights how ignorant we are of age- and gender-related basic electrophysiologic determinants of supraventricular arrhythmia mechanisms. This ignorance is not due to a lack of methodological capability; many investigative groups now have the skills to study sophisticated aspects of cellular Ca\textsuperscript{2+} handling, ion channel and connexin distribution, impulse propagation in complex structures such as the AV node, and atrial and AV nodal structural properties. Hopefully, this provocative study will stimulate further activity in these directions.

References