Declining Into Failure
The Age-Dependent Loss of the L-Type Calcium Channel Within the Sinoatrial Node

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Background—The spontaneous activity of pacemaker cells in the sinoatrial (SA) node controls heart rate under normal physiological conditions. Clinical studies have shown the incidence of SA node dysfunction increases with age and occurs with peak prevalence in the elderly population. The present study investigated whether aging affected the expression of Ca\(_{\text{1.2}}\) channels and whether these changes could affect pacemaker activity, in turn leading to age-related SA node degeneration.

Methods and Results—The SA node region was isolated from the right atrium of guinea pigs between birth and 38 months of age. Immunofluorescence studies showed Ca\(_{\text{1.2}}\) protein was present as punctate labeling around the outer membrane of atrial cells but was absent from the center of the SA node. The area lacking Ca\(_{\text{1.2}}\)-labeled protein progressively increased from 2.06 ± 0.1 (mean ± SEM) mm\(^2\) at 1 month to 18.72 ± 2.2 mm\(^2\) at 38 months (\(P<0.001\)). Western blot provided verification that Ca\(_{\text{1.2}}\) protein expression within the SA node declined during aging. Functional measurements showed an increased sensitivity to the L-type calcium blocker nifedipine; SA node preparations stopped beating in 100 \(\mu\)mol/L nifedipine at 1 day old, compared with 30 \(\mu\)mol/L at 1 month and 10 \(\mu\)mol/L at 38 months of age. Furthermore, the amplitude of extracellular potentials declined within the center and periphery of the SA node during aging.

Conclusions—The present data show Ca\(_{\text{1.2}}\) channel protein decreases concurrently with reduced spontaneous activity of the SA node with increased age, which provides further evidence of mechanisms underlying the age-related deterioration of the cardiac pacemaker. (Circulation. 2007;115:1183-1190.)

Key Words: calcium ■ ion channels ■ pacemakers ■ sinoatrial node ■ aging ■ proteins ■ electrophysiology

Dysfunction of the sinoatrial (SA) node progressively increases with age regardless of gender, with the highest incidence occurring within the elderly population (≥65 years old), who by 2040 will account for 30% of the Western population. Clinical observations of sinus dysfunction range from rhythm disturbance to bradycardia, sinus pauses, sinus arrest, and arrhythmias, which without medical intervention can result in sudden death. Sinus node dysfunction may account for >50% of pacemaker implants in the United States.

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The apparent causes of sinus node dysfunction considered across the entire age range can be intrinsic or extrinsic in origin. Extrinsic factors known to induce dysfunction include hypoxia, digitalis, and antiarrhythmic agents such as \(\beta\)-blockers and calcium antagonists. Intrinsic factors include congenital abnormalities, myocarditis, dystrophies, and cardiomyopathies, often associated with structural remodeling and fibrosis of the SA node. Healthy aging, however, is associated with an intrinsic decline in pacemaker function in the absence of such structural remodeling, which implicates a progressive change in the cellular properties of the constituent cells of the SA node.

A number of ion channels, including the high-voltage activated L-type Ca\(^{2+}\) current and low-voltage activated T-type Ca\(^{2+}\) current, contribute to the pacemaker activity of the SA node. However, it was the L-type calcium current rather than the T-type current that was determined to be responsible for the upstroke of the action potential and, thus, depolarization of the SA node. L-type Ca\(^{2+}\) currents are conducted via Ca\(_{\text{1.2}}\) channels, which consist of a pore-forming \(\alpha_1\)-subunit in association with \(\beta\)- and \(\alpha_{2\delta}\)-subunits. The \(\alpha_1\)-subunit contains the voltage sensor, the selectivity filter, and binding sites for all known calcium channel blockers and possesses a molecular weight of ≈200 kDa. L-type calcium channels are sensitive to dihydropyridines,
such as nifedipine, which selectively block the α₁-subunit of the Caᵥ1.2 channel.

Spontaneously beating cells from the SA node have been characterized in terms of their pharmacological responses to nifedipine. Peripheral SA cells only exhibit moderate negative chronotropism in the presence of nifedipine, compared with central nodal cells where spontaneous activity was abolished. Therefore, the L-type Ca²⁺ current has been demonstrated to play an obligatory role in pacemaking within the center of the SA node.

The cardiac action potential originates from the center of the SA node at the leading pacemaker site and propagates to the periphery (the border of the SA node with the surrounding atrial muscle), then across the remaining heart tissue, assisted by the presence of specialized cellular junctions. Myocardial tissue possesses desmosomes that are responsible for the intercellular adhesion of the cardiac myocytes, consisting of desmoplakin and desmin protein, and electrical junctions or “gap junctions” that predominantly consist of connexin43 (Cx43) protein, which facilitates propagation of the action potential through the heart. The location of the center of the SA node can be identified either by mapping of action potentials across the SA node or by the absence of Cx43 protein via anti-Cx43 antibodies. Studies of humans and rodents (including the hamster, rabbit, rat, and guinea pig) have failed to detect Cx43 protein within the center of the SA node, and consequently, it was concluded that Cx43 protein was absent from the center of the SA node. Our previous studies of the guinea pig found that Cx43 protein expression in the center of the SA node was absent, and during aging, the area without Cx43 protein increased to encompass the center and periphery of the SA node in the elderly animals. The resultant electrical disconnection of the SA node in the elderly animal will contribute to the increasing incidence of SA node dysfunction in the elderly; however, other electrophysiological changes may also contribute to the developing dysfunction.

Our hypothesis is that expression of the Caᵥ1.2 channel may decline with age, resulting in a depression of excitability of the tissue and failure of the pacemaker ability of the SA node, due to a suppression of the upstroke of the SA node action potential. Additionally, subsequent changes in intracellular calcium handling are likely to occur: A reduction in calcium influx is likely to lead to reduced intracellular calcium and content of the sarcoplasmic reticulum, which may have important implications for pacemaking and the ability of the heart to respond to β-adrenergic stimulation. Hence, we have investigated expression of the Caᵥ1.2 channel within the SA node and the susceptibility of pacemaking to L-type calcium channel blockade with age to determine whether changes in \( I_{Ca} \) are implicated in the age-related degeneration of the SA node.

**Methods**

For detailed materials and methods, please see the online-only Data Supplement.

**Sample Acquisition**

Healthy tricolor guinea pigs were studied at <1 day of age, at 1 month of age (young), at 18 months of age (adults), at 26 months of age (old), and at 38 months of age (senescent).

**Extracellular Electrode Recording**

The SA node preparation was maintained in Krebs Ringer solution at 37°C. Extracellular modified bipolar electrodes were used to measure the intrinsic heart rate and monitor changes when subjected to incremental doses of nifedipine from 0.3 to 100 μmol/L.

**Immunofluorescence**

Frozen SA node sections were labeled with antibodies to Caᵥ1.2 and Cx43 protein according to protocols described previously.

**Analysis of Protein Expression**

Tissue samples (50 μg total protein per lane) were separated by electrophoresis under reducing conditions by 10% SDS-PAGE, followed by transfer to nitrocellulose membrane, and subsequently probed by antibodies as described previously.

**Statistical Analysis**

Data are expressed as mean±SEM, and statistical differences were assessed by ANOVA with subsequent pairwise ad hoc analysis made with a Holm-Sidak comparative test. Differences and correlations were taken as significant if \( P<0.05 \), and \( n \) corresponds to the number of animals.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Expression of Caᵥ1.2 Protein**

Immunofluorescent-labeled Caᵥ1.2 protein was detected by confocal imaging of guinea pig right atrial tissue sections at high magnification. Regions where Caᵥ1.2 protein was expressed as a punctate pattern around the outer membrane of myocytes were classified as positive Caᵥ1.2, and those regions where labeling could not be detected were concluded to be lacking Caᵥ1.2 protein (Figure 1A).

**Expression of Caᵥ1.2 Protein Within the SA Node Declines With Age**

Sections across the right atrium taken at 0.5-mm intervals, perpendicular to the crista terminalis, were labeled with anti-CNC1 to permit 2D assessment of Caᵥ1.2 protein distribution with age (\( n=5 \) right atria per age group). Confocal images of immunofluorescent-labeled tissue sections were converted into representational schematics in which the region lacking Caᵥ1.2 protein was highlighted in blue (Figure 1B). To indicate the location of the SA node by the absence of Cx43 protein, adjacent sections were labeled with anti-Cx43 (highlighted in red). To illustrate this further, the right atrium of a 1-month-old animal was examined, and the schematic images of adjacent sections are shown at 0.5-mm intervals: the region lacking Caᵥ1.2-labeled protein (left, Figure 1C) and the region lacking Cx43-labeled protein (right, Figure 1C). This procedure was repeated for each atrium examined in every age group. Those regions lacking labeled Caᵥ1.2 protein and Cx43 protein were taken from sections and mapped to the photograph of the intact right atrium. These areas lacking Caᵥ1.2- and Cx43-labeled protein were outlined, and examples are shown for a 1-month-old animal in Figure 1D and for a 26-month-old animal in Figure 1E. Figures 1D and 1E illustrate that the length of the area lacking Caᵥ1.2-labeled protein increased from 2.0 mm in the 1-month-old animal to 7.0 mm in the 26-month-old animal,
and in addition, the area lacking Cav1.2-labeled protein was seated within the area lacking Cx43-labeled protein.

Staining of tissue sections with aniline blue and fuchsin red to observe collagen and myocyte content, respectively, revealed no changes in collagen or myocyte content or distribution from the 18- to the 38-month-old animal. With advancing age, no signs of fibrosis or myocyte loss were observed (see online Data Supplement). The changes observed from the adult to the oldest animals studied therefore reflect changes in protein expression by the constituent cells.

The area lacking labeled Cav1.2 protein increased with age from 2.0 ± 0.1 mm² at 1 month to 6.2 ± 0.4 mm² at 18 months, 9.5 ± 0.9 mm² at 26 months, and 18.7 ± 2.2 mm² at 38 months (n=5; ANOVA, P < 0.001; Figure 1F). Linear regression to the total data set indicated a significant and proportional correlation between the area lacking Cav1.2 protein and age (linear regression: y (mm²) = 0.4355x + 0.0805, where x is the age in months; R² = 0.91). Overall, the area lacking Cav1.2 protein increased 9-fold during aging. The area lacking Cav1.2 protein was seated within an area also lacking Cx43 protein, known to be a marker of the SA node. This area lacking Cx43 increased from 3.5 ± 0.6 mm² in the 1-month-old animal to 47.6 ± 2.0 mm² in the 38-month-old animal (n=5; ANOVA, P < 0.0001; linear regression: y (mm²) = 1.2007x + 1.9099; R² = 0.998).

A significantly correlated linear relationship exists between the increasing area lacking protein for both Cav1.2 and Cx43 versus progressive age. Further analysis of the linear regressions, however, determined a significant difference in the slope of the 2 regressions (P < 0.002), which indicates that the rate of Cav1.2 protein loss from tissue with age was less than that of Cx43 protein. This shows a scenario in which advancing electrical disconnection of the tissue precedes a loss of an additional ion channel (CaV1.2) critical for main-
Western Blot Analysis of Cav1.2 Protein Expression

To confirm our findings, paired samples of right atrial muscle and SA node from each animal were analyzed for Cav1.2 protein expression by Western blot (Figure 2). Specificity of the anti-CNC1 antibody was confirmed, as preadsorption with the supplied control peptide resulted in no band (Figure 2A). Illustrative membranes of desmin (53 kDa) and Cav1.2 (200 kDa) proteins across the examined age range. For every animal from each age group, Cav1.2 protein expression in the SA node region was expressed as a percentage of the paired atrial muscle sample. Data shown mean±SEM. Cav1.2 protein expression fell in the SA node with increased age. Specificity of Cav1.2 protein expression was confirmed by the absence of the 200-kDa band in the presence of the supplied control antigen. For every animal from each age group, Cav1.2 protein expression within the SA node region was expressed as a percentage of the paired atrial muscle sample. Data shown mean±SEM. Cav1.2 protein expression was confirmed by the absence of the 200-kDa band in the presence of the supplied control antigen.

Intrinsic Heart Rate Shows Increasing Sensitivity to Nifedipine With Age

The intrinsic heart rate, the spontaneous rate at which action potentials manifest in the autonomically denervated SA node, was measured on the endocardial surface at the leading pacemaker site (LPS) of the preparations, then each preparation was subjected to incremental doses of nifedipine to block ICa,L (Figure 3). The rate of generated spontaneous action potentials in the absence of nifedipine significantly decreased with age from 249±13 bpm at 1 day to 177±5 bpm at 1 month and 152±5 bpm at 38 months of age (n=5; ANOVA, P<0.01). The 1-day-old animal showed the lowest sensitivity to nifedipine compared with the other ages studied; spontaneous activity of SA nodes from 38-month-old animals was halted by nifedipine 10 μmol/L, a 10-fold lower concentration than required to cause cessation of the SA node in 1-day-old animals. Overall, the SA node preparations from the 38-month-old animals stopped beating spontaneously at the lowest concentration of nifedipine compared with the other ages studied.

This increased sensitivity to nifedipine indicates that these oldest SA node preparations contained the fewest Cav1.2 channels across the age range and were highly sensitive to further loss of functional channels. Clinically, such a blockade of these channels might occur when calcium antagonists are used to treat high blood pressure or arrhythmias. The presented results suggest that in the elderly, even low doses of such drugs could induce SA node dysfunction.

Extracellular Potentials Decrease in Amplitude With Age

The peak negative deflection of extracellular potentials recorded by surface-positioned bipolar electrodes has been shown to correlate with the upstroke of the action potential in the underlying tissue. A small, slow depolarization is associated with a small deflection, and the reverse is true for large...
rapid depolarizations.\textsuperscript{12} Peak extracellular potentials were recorded at 4 sites across the SA node preparations: the earliest site of SA node depolarization or LPS; the central region of the SA node (recorded at /\textasciitilde 2 mm from the LPS), peripheral region (\textasciitilde 2 mm from the crista terminalis), and atrial muscle (for each site within an age group, \( n = 5 \); ANOVA per age group, \( P < 0.01 \)). #Not significant \( (P > 0.05) \). F, Age produced a significant decline in amplitude of the recorded deflections in central and peripheral regions of the SA node \( (n = 5; \text{ANOVA, } P < 0.001) \).

The 1-day-old SA node preparations exhibited significant differences in peak amplitude between all sites examined (Figure 4A). For the 1- and 18-month-old SA node preparations, significant differences in amplitude were determined between all sites, with the exception of LPS to center (Figures 4B and 4C). At the ages of 26 and 38 months, no differences were exhibited in the amplitude between the sites of the LPS, center, and periphery of the SA node preparations; however, significant differences among these sites existed when they were compared with the atrial muscle site (Figures 4D and 4E).

For further analysis, data were summarized for the individual sites by increasing age. A significant decline in the amplitude of the recorded extracellular potential was revealed at the central and peripheral regions of the SA node during progressive aging (Figure 4F; \( n = 5, \text{ANOVA, } P < 0.001 \)). The other examined sites, the LPS and atrial muscle, did not exhibit significant changes in potential amplitude with increasing age.

**Discussion**

Four conclusions can be drawn from the present study: (1) from 1 month of age onward, Ca\textsubscript{1.2} protein cannot be
detected at the center of the SA node, and (2) this area lacking labeled Ca$_{1.2}$ protein progressively increases in size during aging. Functionally, (3) sensitivity of the SA node to nifedipine increases during aging, and (4) the amplitude of the extracellular potential, which correlates to the upstroke of the action potential (principally determined by $I_{Ca,L}$), decreases with age at the center and periphery of the SA node. Overall, the present data provide strong evidence that expression of the Ca$_{1.2}$ channel, and, consequently, $I_{Ca,L}$, significantly declines with age within the SA node, resulting in suppressed excitability, which contributes in turn to failure of the SA node in the elderly.

We have previously reported that the guinea pig SA node contains an area lacking Cx43 protein that continues to progressively increase in size as the animal ages, which leads to slowed conduction of the action potential within the area deficient in Cx43 protein.$^{24}$ The present study furthers this observation, showing that Ca$_{1.2}$ protein was not detectable in an area within the SA node of 1-month-old animals and that this area lacking Ca$_{1.2}$ protein (2.0±0.1 mm$^2$) significantly increased in a linear manner that correlated with age, to 18.7±2.2 mm$^2$ at 38 months (Figures 1B through 1E). This area lacking Ca$_{1.2}$ protein always lies within the expanding area lacking Cx43 protein. However, the loss of Ca$_{1.2}$ protein occurs at a rate slower than the loss of the Cx43 protein (Figure 1E). Analysis by Western blot confirmed these observations (Figure 2).

Seisenberger et al.$^{27}$ using the Ca$_{1.2}$ channel knockout mouse model, elegantly demonstrated the specific effect of the absence of Ca$_{1.2}$ protein from cardiac tissue. The knockout mice die of sudden death regardless of age, owing to the absence of Ca$_{1.2}$ channels necessary for cardiac rhythm generation and muscle contraction.$^{27}$ However, it is not just through genetic manipulations that remodeling of calcium channel expression can be shown to occur and lead to cardiac dysfunction. Anyukhovsky et al.$^{28}$ induced atrial arrhythmias in adult and elderly dogs. The atria of the latter were found to have a shorter action potential duration, slowed conduction, and increased dispersion.$^{28}$ On further analysis, it was ascertained that the right atrial cells (from unidentified locations) of elderly dogs contained 50% less $I_{Ca,L}$ than their adult counterparts.$^{28}$ This finding has a parallel in cases of human atrial fibrillation, in which a shortened action potential duration, decrease in $I_{Ca,L}$ amplitude, and decrease in $I_{Ca,L}$ density have all been noted.$^{29,30}$ We now additionally propose that within the SA node, an age-related decline in expression of the L-type calcium channel causes suppression of action potential formation and propagation, leading to failure of the SA node as a pacemaker. Such changes are likely to increase the probability of atrial fibrillation, leaving questions about whether the changes observed in calcium channel expression in the many elderly patients who suffer from this most common of arrhythmias are a consequence of the arrhythmia or a consequence of an aging effect that has contributed to precipitation of the arrhythmia.

It is widely accepted that aging does not affect in vivo heart rate because of autonomic compensatory mechanisms; however, aging does significantly reduce the intrinsic heart rate.$^{31}$ Previously, we reported that the intrinsic heart rate in our guinea pig model drops from 249±13 bpm at 1 day to 152±5 bpm in the 38-month-old animal.$^{24}$ In the present study, however, we tested the sensitivity of the intrinsic heart rate to the commonly deployed calcium antagonist nifedipine. Nifedipine is known to selectively block Ca$_{1.2}$ channels; therefore, $I_{Ca,L}$ can be blocked with no effect on $I_{Ca,T}$, $I_{Na}$, $I_K$, or $I_f$ in the guinea pig SA node.$^{16}$ Application of incremental doses of nifedipine to the SA node resulted in the slowing of spontaneous activity, followed by the complete termination of beating. At 1 day old, the animal’s SA node exhibited the least sensitivity to nifedipine. The highest sensitivity was observed in SA nodes from the oldest animals (38 months). These data parallel the progressive age-correlated decline in expression of Ca$_{1.2}$ channels from the 1 day old to the oldest animals (38 months of age) and highlight the changing sensitivity of the SA node pacemaker to pharmacological and potentially autonomic influences. Such changes in pharmacological sensitivity highlight that further consideration should be given to adjusting dose according to age, particularly in the case of elderly patients. Previous work has shown that the amplitude of deflection of recordings of extracellular potential correlates closely with the amplitude of the action potential in the underlying tissue.$^{19}$ The present data agree with this previous work: The LPS and central regions of the SA node display small extracellular potentials that correspond with their small, slow action potentials. However, with progressive aging, the central region of the SA node shows an additional decline in the amplitude, as does the periphery region of the SA node until the whole of the SA node displays comparable electrical activity throughout. Yamamoto et al.$^{19}$ showed that blockade of the L-type calcium channel could produce such notable reductions in the amplitude of extracellular potentials. From the data presented, we believe the major contributor to the effect observed in the present data is a dramatic decline in the expression and hence recruitment of the L-type calcium channels in the aged tissue.

The role of calcium in the generation of spontaneous activity within the SA node is controversial but ubiquitously acknowledged as being of significant importance. Maneuvers that increase intracellular calcium and calcium fluxes via Ca$_{1.2}$ lead to increases in spontaneous activity and suppression of calcium fluxes or levels by buffering, or appropriate blockers decrease or halt SA node activity. In the intact structure, such manipulations have a particular fascination because they are also often associated with movements of the LPS within the SA node structure. This “pacemaker shift” presumably reflects the complex heterogeneity of the nodal structure and balance of multiple ionic fluxes and electrotonic interactions that regulate its activity. Previous work has found the expression of the proteins involved in regulation of calcium handling, including Ca$_{1.2}$, to be lower in the center than in the periphery of the SA node in adult rats.$^{32}$ Functionally, in the rabbit SA node, the cells at the center of the SA node have been shown to have smaller, slower calcium transients with each beat than cells from the periphery.$^{33}$ The age-related changes in the expression of Ca$_{1.2}$ reported will lead to significant disruption of the normal heterogeneity of the SA node, which is likely to lead to a reduced ability of the
node to respond to physiological stimuli (such as adrenergic stimuli, responsiveness to which is reduced in the elderly) and to maintain robust function as the leading pacemaker of the heart, a function preserved by the graded heterogeneity of the SA node structure. As the area of tissue lacking Cx43 and Ca,1.2 expands to consume the SA nodal region, heterogeneity declines, electrical depolarization is suppressed, and connectivity and communication across this complex tissue falter. This is what we propose heralds the age-related failure of the SA node as a viable pacemaker for the heart.

In sinus node dysfunction associated with dystrophies, myopathies, and ischemia, structural changes are well documented and are likely to be an important factor in the creation of sinus dysfunction. The role of structural changes in creating sinus dysfunction in the case of healthy aging is controversial. Some studies have suggested that a loss of cells within the node throughout life together with associated fibrosis could be responsible for dysfunction of the aged SA node. Interpretation of such studies is complicated by the heterogeneous nature of the nodal structure, and few have mapped changes that occur throughout the SA node in detail. Detailed evidence, where available, shows that structural remodeling of the sinus node occurs during development into adulthood, involving increases in collagen content. The size and collagen content of the SA node then remain stable into old age, which suggests that progressive structural remodeling in the elderly does not underlie the increasing incidence of sick sinus syndrome. Other investigators also found no association between collagen and fibroblast content and conduction times of the cardiac action potential across the SA node, nor spontaneous activity of the SA node. We have also found no evidence of structural remodeling and growth of the sinus node from the adult animal to the elderly animal or of evidence of fibrosis (see online Data Supplement). The conclusion of the data from such studies is that age-dependent fibrosis and structural remodeling are not responsible for the progressively increasing incidence of sinus node dysfunction with healthy aging. We conclude that the described changes in the properties of the cells that constitute the SA node lead to age-dependent deterioration in the ability of this vital structure to serve as a stable cardiac pacemaker.

Conclusions

Data shown are consistent with our hypothesis that expression of Ca,1.2 protein within the SA node continues to decline during aging and that this in turn increases the susceptibility of the node to L-type calcium channel blockers such as nifedipine, symptomatic of the loss of Ca,1.2 channels from the SA node. In addition, it is shown that electrical activation of the tissue was reduced across the whole of the SA node, including the central and peripheral regions, in the elderly animal, which implicates a loss of $\text{ICa,L}$ in the age-related degeneration of the SA node. Consequently, the loss of Ca,1.2 channels in conjunction with a depletion of Cx43 protein depresses conductivity and hence increases the potential for dysfunction of the SA node with age and the prevalence of arrhythmogenic activity, as is observed clinically. The results of the present work indicate that methods to restore normal calcium regulation to the SA node and connectivity to the atrial tissue are likely to produce effective treatments for SA node dysfunction. Additionally, this work indicates that care should be taken in prescribing the commonly used calcium antagonists to the elderly, in whom the tolerance of the SA node is reduced and the risk of potentially precipitating SA node dysfunction is increased.

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Disclosures

None.

References

Clinical Perspective

The present study focused on healthy aging and the high incidence of sinoatrial dysfunction in the elderly, hypothesized to be due to progressive changes in the properties of the constituent cells of the sinoatrial (SA) node. L-type Ca\(^{2+}\) currents conducted via Ca\(_{\text{L}}\) channels are responsible for the upstroke of the action potential and, thus, depolarization of the SA node. The present data show that expression of Ca\(_{\text{L}}\) protein within the SA node progressively declines during normal healthy aging, in association with an increasing sensitivity to the L-type calcium channel blocker nifedipine. The amplitude of electrical activation of the tissue was significantly reduced across the whole of the SA node in the elderly animal, thus implicating the loss of \(I_{\text{Ca,L}}\) in the age-related degeneration of SA node function. This loss of Ca\(_{\text{L}}\) channels in conjunction with a previously described depletion of Cx43 protein from the SA node (Cx43 is responsible for connectivity) would be predicted to lead to increasing dysfunction of the SA node with age and an increase in the incidence of arrhythmias, both events that are indeed observed clinically. The results of the present study suggest that therapies aimed at restoration of connectivity and normal calcium regulation to the SA node could provide an effective treatment for progressive age-associated SA node dysfunction. Additionally, the present work indicates that care should be taken in prescribing the commonly used “calcium antagonists” to the elderly, in whom tolerance of the SA node is reduced and the risk of precipitating SA node dysfunction is increased.
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