Vulnerability to Atrial Fibrillation under Stretch Can Be Explained by Stretch-Activated Channels

NHL Kuijpers[1], RJ Rijken[1], HMM ten Eikelder[1], PAJ Hilbers[1]

[1]Department of Biomedical Engineering, Eindhoven University of Technology, The Netherlands

Abstract

Experimental studies show an increased vulnerability to atrial fibrillation (AF) in acutely dilated atria. By application of a stretch-activated channel (SAC) blocker, vulnerability to AF decreases significantly, indicating a role for SACs in the initiation of AF. Using a computer model of cardiac electromechanics, we investigate the hypothesis that increased vulnerability to AF may be attributed to SACs.

In our model, the human atria are represented by a triangular mesh obtained from MRI data. Electrophysiology is modeled by thirteen ionic membrane currents, including the stretch-activated current I_{sac} and intracellular calcium handling. Mechanical behavior is modeled by a series elastic, a contractile, and a parallel elastic element. The contractile force is related to the intracellular concentration of free calcium as well as to the sarcomere length. To mimic acute dilatation, overall stretch is applied to the atria. Due to contraction of some areas, stretch increases in other areas, leading to a variation in I_{sac} conductance.

In the presence of I_{sac}, the membrane potential depolarizes, which causes inactivation of the sodium channels and results in conduction slowing or block. Inducibility of AF increases under stretch, which is explained by an increased dispersion in atrial effective refractory period (AERP), conduction slowing and local conduction block. Our observations explain the large differences in intra-atrial conduction measured in experiments and provide insight in the vulnerability to AF in dilated atria.

1. Introduction

Atrial fibrillation (AF) is characterized by rapid and irregular electrical activity, which results in irregular contraction of the atria [1]. Experimental studies indicate an increased vulnerability to AF in acutely dilated atria [2, 3, 4, 5]. Stretch-induced changes in electrophysiology are explained by the stretch-activated channel (SAC) hypothesis [6, 7]. In the present simulation study we investigate the effect of the stretch-activated current (I_{sac}) on impulse propagation through the atria. Atrial dilatation was simulated by the application of overall stretch. After repetitive stimulation with stimulation interval 0.6 s, we observed conduction slowing, an increased atrial effective refractory period (AERP), and conduction block with increasing stretch. With 10% stretch, conduction slowing and local conduction block lead to a reentrant depolarization wave after 3 s. The path of the reentrant wave changed over time and the arrhythmia stopped after 14 s. Our results are in agreement with experimental observations and explain the vulnerability to AF in acutely dilated atria.

2. Methods

To investigate the effect of stretch on atrial electrophysiology, we apply our discrete bidomain model, the Cellular Bidomain Model [8, 9]. The model describes active membrane behavior as well as intracellular coupling and interstitial currents, and has been extended to describe cardiac mechanics [10]. The human atria are modeled by a triangular mesh composed of 7446 triangles created from MRI data [11, 12].

2.1. Atrial electrophysiology

In the Cellular Bidomain Model, a distinction is made between the intracellular domain and the interstitium. The triangular mesh is refined by subdividing each of the triangles in nine smaller triangles. The electrophysiological state of each node in the refined mesh is defined by the intracellular potential (V_{int}), the extracellular potential (V_{ext}), and the state of the cell membrane, which is expressed in gating variables and ion concentrations. The membrane potential (V_{mem}) is defined by

$$V_{mem} = V_{int} - V_{ext}. \quad (1)$$

Intracellular and extracellular currents between adjacent segments are related to intracellular and extracellular conductivities (g_{int} and g_{ext}). In the present study, we assume equal g_{int} and g_{ext} in all directions, i.e., the atrial tissue is assumed to be isotropic (Table 1).

Exchange of current between the intracellular and extracellular domains occurs as transmembrane current (I_{trans}),

Table 1. Model parameters.

Parameter	Definition	Value
g_{int}	Intracellular conductivity	6.25 mS/cm
g_{ext}	Extracellular conductivity	6.25 mS/cm
C_{mem}	Membrane capacitance	1.0 μF/cm^2
χ	Surface-to-volume ratio	2000/cm
G_{sac}	Maximum I_{sac} conductance	0.5 nS/pF
E_{sac}	Reversal potential for I_{sac}	0 mV
K_{sac}	Parameter for I_{sac}	100
α_{sac}	Parameter for I_{sac}	3

which depends on ionic current (I_{ion}) and capacitive current according to

$$I_{trans} = \chi(C_{mem}\frac{dV_{mem}}{dt} + I_{ion}), \quad (2)$$

where χ is the ratio of membrane area to tissue volume and C_{mem} represents membrane capacitance. Currents are expressed per unit of tissue volume in μA/cm^3. Assuming $C_{mem} = 1$ μF/cm^2, ionic current is expressed in pA/pF and depends on V_{mem}, gating variables, and ion concentrations. To model I_{ion}, we extend the Courtemanche-Ramirez-Nattel model [13] with the stretch-activated current I_{sac}. The total ionic current is given by

$$\begin{aligned} I_{ion} &= I_{Na} + I_{K1} + I_{to} + I_{Kur} + I_{Kr} + I_{Ks} + I_{Ca,L} \\ &\quad + I_{p,Ca} + I_{NaK} + I_{NaCa} + I_{b,Na} + I_{b,Ca} + I_{sac}, \quad (3) \end{aligned}$$

where I_{Na} is fast inward Na^+ current, I_{K1} is inward rectifier K^+ current, I_{to} is transient outward K^+ current, I_{Kur} is ultrarapid delayed rectifier K^+ current, I_{Kr} is rapid delayed rectifier K^+ current, I_{Ks} is slow delayed rectifier K^+ current, $I_{Ca,L}$ is L-type Ca^{2+} current, $I_{p,Ca}$ is Ca^{2+} pump current, I_{NaK} is Na^+-K^+ pump current, I_{NaCa} is Na^+/Ca^{2+} exchanger current, and $I_{b,Na}$ and $I_{b,Ca}$ are background Na^+ and Ca^{2+} currents [13].

I_{sac} is modeled as a nonselective cation current with a linear current-voltage relation. The current size depends on the membrane potential V_{mem} and stretch ratio λ by

$$I_{sac} = \frac{G_{sac}(V_{mem} - E_{sac})}{1 + K_{sac}\exp(-\alpha_{sac}(\lambda - 1))}, \quad (4)$$

where G_{sac} is the maximum membrane conductance, E_{sac} is the reversal potential, K_{sac} is a parameter to define the amount of current when $\lambda = 1.0$, and α_{sac} is a parameter to describe the sensitivity to stretch. Parameters K_{sac} and α_{sac} are from Zabel *et al.* [14] (Table 1). The influence of I_{sac} on intracellular Na^+, K^+ and Ca^{2+} concentrations is modeled as described in Ref. [10].

In Figure 1 the effect of stretch on the propagating action potential is shown. For increasing λ, the action potential duration (APD) increases, while I_{Na} decreases. The

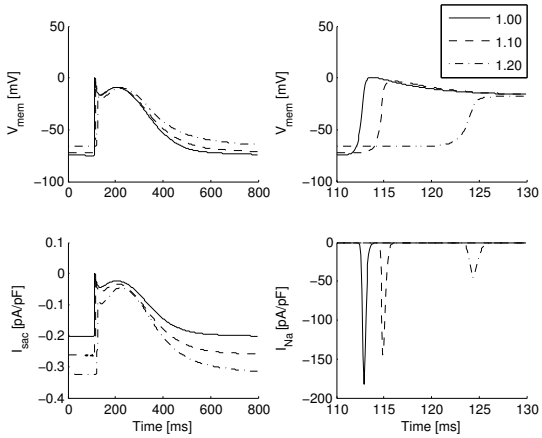

Figure 1. Effect of stretch on the action potential (AP) and impulse propagation. Left: membrane potential (V_{mem}) and stretch-activated current (I_{sac}). Right: V_{mem} and fast Na^+ current (I_{Na}) during AP upstroke. A stimulus current was applied at 100 ms. Data are plotted for stretch ratios 1.00, 1.10 and 1.20 for a segment located 0.5 cm from the stimulation site.

reduced I_{Na} is explained by inactivation of sodium channels as a consequence of the increased V_{mem} during diastole [10]. As can be observed in Figure 1, the smaller I_{Na} current size leads to a lower maximum upstroke velocity and a reduced impulse propagation.

2.2. Atrial mechanics

The mechanical behavior of a single segment is modeled by a series elastic, a contractile, and a parallel elastic element [10]. Active force generated by the contractile element is described by *Model 4* of Rice *et al.* [15] and is related to intracellular Ca^{2+} concentration and sarcomere length (see Ref. [10] for details).

To simulate atrial dilatation, it is assumed that the same amount of force is applied to each segment. During the simulation, the amount of force applied to the atria is adjusted, such that the overall stretch ratio remains constant (isometric simulation). Contraction of early activated regions may thus lead to increased stretch ratios in late activated regions. To incorporate bundles, thickness of the tissue is varied as shown in Figure 2. Since thicker tissue is harder to deform, variation in thickness will lead to differences in local stretch and, hence, influences I_{sac}.

3. Results

Simulations were performed with overall stretch varied between 0% and 20%. The atrial tissue was stimulated near the pulmonary veins with a stimulation interval of 0.6 s. With increasing stretch, conduction veloc-

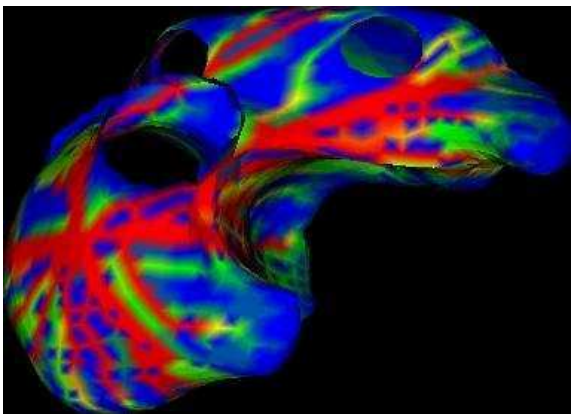

Figure 2. Thickness variation in atrial geometry. Red is thick tissue, green is tissue of medium thickness, and blue is thin tissue.

ity decreased, while the refractory period increased. In Figure 3, depolarization of the atria is shown after the fourth stimulation without stretch, with 10% stretch, and with 12% stretch. While conduction was normal without stretch, conduction slowing and local conduction block was observed with 10% stretch. With 12% stretch, conduction was normal after the first, third and fifth stimulation, while conduction was blocked after the second and fourth stimulation due to the increased refractory period. Conduction was completely blocked with 20% stretch (not shown). Due to conduction slowing and local conduction block with 10% stretch, a reentrant depolarization wave developed after 3 s. The path of the depolarization wave changed over time and the arrhythmia stopped after 14 s.

4. Discussion and conclusions

Atrial dilatation is simulated by application of overall stretch to the atria. Contraction of early activated areas leads to increased stretch in late activated areas and influences impulse propagation, action potential duration (APD), and atrial effective refractory period (AERP). Dispersion in APD and AERP is further enhanced by variations in atrial thickness.

Conduction slowing and block in our model is explained by a decreased membrane excitability caused by the stretch-activated current I_{sac}. In an experimental study, Eijsbouts *et al.* [5] reported a decreased conduction velocity and local conduction block when the right atrium of a rabbit was acutely dilated. Satoh and Zipes [2] measured an increased AERP both in the thin atrial free wall and in the crista terminalis under stretch. The AERP of the thin free wall was increased more than the AERP in the thicker crista terminalis, which they explain by the assumption that the thin free wall is more stretched compared to the thicker bundles [2]. These experimental observations are in agreement with our simulation results and explain the vulnerability to AF under acute stretch. Bode *et al.* [3] report that SAC blocker gadolinium reduces the stretch-induced vulnerability to AF, confirming that I_{sac} plays a significant role in the vulnerability to AF in acutely dilated atria.

In conclusion, conduction slowing and block is related to the amount of stretch and is enhanced by contraction of early activated areas and inhomogeneity in the atrial wall. Variation in thickness increases the dispersion in refractory period and is proarrhythmic. Our observations are in agreement with experimental results and provide an explanation for the increased inducibility of atrial fibrillation observed in acutely dilated atria.

Acknowledgements

The authors would like to thank Peter van Dam and Adriaan van Oosterom for providing the triangular mesh of the human atria.

References

[1] Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002;415:219–226.

[2] Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. J Cardiovasc Electrophysiol 1996;7:833–842.

[3] Bode F, Katchman A, Woosley RL, Franz MR. Gadolinium decreases stretch-induced vulnerability to atrial fibrillation. Circulation 2000;101:2200–2205.

[4] Ravelli F. Mechano-electric feedback and atrial fibrillation. Progr Biophys Mol Biol 2003;82:137–149.

[5] Eijsbouts SCM, Majidi M, Van Zandvoort M, Allessie MA. Effects of acute atrial dilation on heterogeneity in conduction in the isolated rabbit heart. J Cardiovasc Electrophysiol 2003;14:269–278.

[6] Hu H, Sachs F. Stretch-activated ion channels in the heart. J Mol Cell Cardiol 1997;29:1511–1523.

[7] Kohl P, Sachs F. Mechanoelectric feedback in cardiac cells. Phil Trans R Soc Lond 2001;359:1173–1185.

[8] Kuijpers NHL, Keldermann RH, Arts T, Hilbers PAJ. Computer simulations of successful defibrillation in decoupled and non-uniform cardiac tissue. Europace 2005;7:S166–S177.

[9] Kuijpers NHL, Keldermann RH, Ten Eikelder HMM, Arts T, Hilbers PAJ. The role of the hyperpolarization-activated inward current I_{f} in arrhythmogenesis: a computer model study. IEEE Trans Biomed Eng 2006;53:1499–1511.

[10] Kuijpers NHL, Ten Eikelder HMM, Bovendeerd PHM, Verheule S, Arts T, Hilbers PAJ. Mechanoelectric feedback leads to conduction slowing and block in acutely dilated atria: a modeling study of cardiac electromechanics. Am J Physiol Heart Circ Physiol 2007;292:H2832–H2853.

[11] Van Dam PM, Van Oosterom A. Atrial excitation assuming

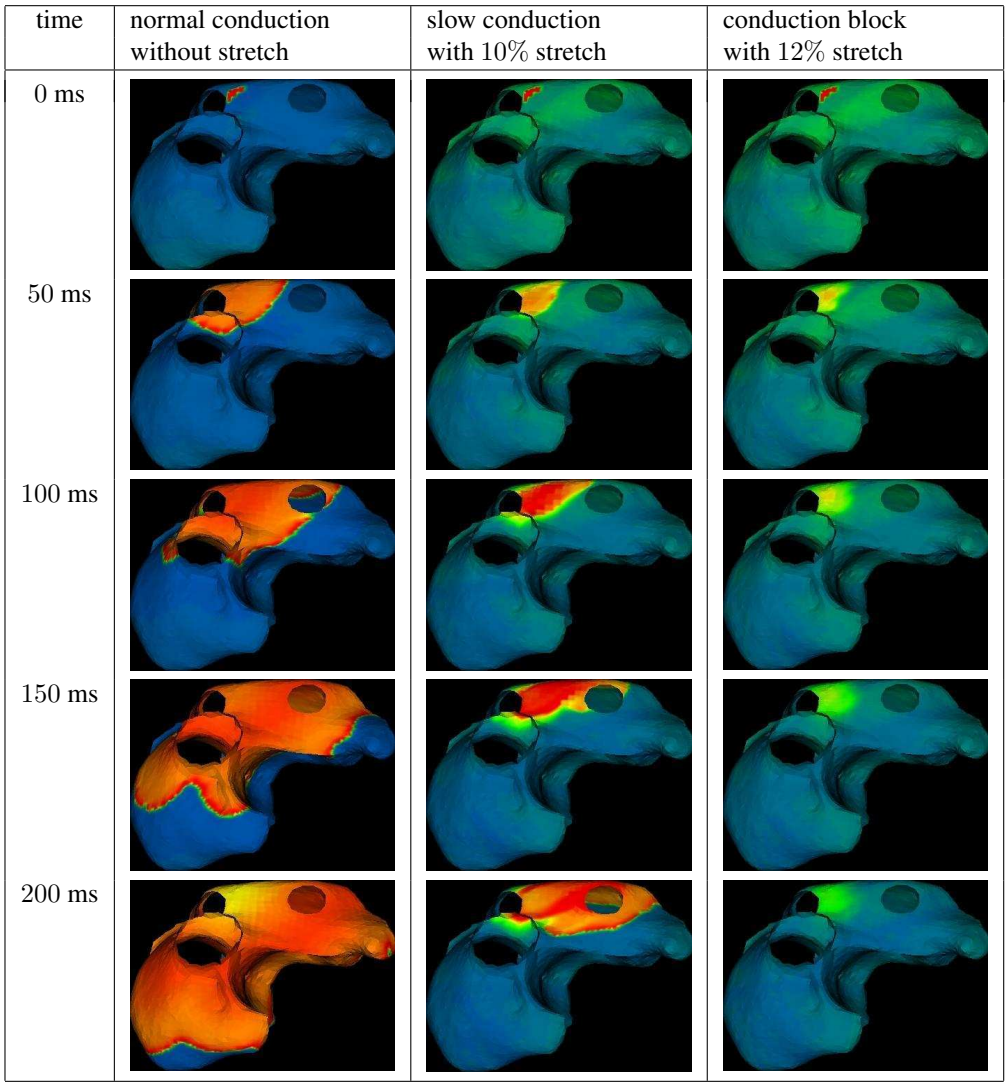

Figure 3. Atrial depolarization after the fourth stimulation near the pulmonary veins. Left: normal conduction when no stretch is applied. Center: slow conduction with 10% stretch. Right: conduction block with 12% stretch. Membrane potential (V_{mem}) is shown after stimulation at 0 ms with intervals of 50 ms. Red is depolarized tissue, green is tissue with increased V_{mem}, and blue is fully recovered tissue.

uniform propagation. J Cardiovasc Electrophysiol 2003;14 (10 Suppl):S166–S171.

[12] Van Dam PM, Van Oosterom A. Volume conductor effects involved in the genesis of the P wave. Europace 2005; 7:S30–S38.

[13] Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. Am J Physiol Heart Circ Physiol 1998;275:H301–H321.

[14] Zabel M, Koller BS, Sachs F, Franz MR. Stretch-induced voltage changes in the isolated beating heart: importance of timing of stretch and implications for stretch-activated ion channels. Cardiovasc Res 1996;32:120–130.

[15] Rice JJ, Winslow RL, Hunter WC. Comparison of putative cooperative mechanisms in cardiac muscle: length dependence and dynamic responses. Am J Physiol Heart Circ Physiol 1999;276:H1734–H1754.

Address for correspondence:

Nico H.L. Kuijpers
Dept. of Biomedical Engineering
Eindhoven University of Technology
Den Dolech 2
P.O. Box 513
5600 MB Eindhoven
The Netherlands
N.H.L.Kuijpers@tue.nl