Role of Hemodialysis in Atrial Fibrillation Onset: Preliminary Results from a Combined Computational and Experimental Analysis

S Severi[1], G Fantini[1], C Corsi[1], A Vincenti[3], S Genovesi[2,3]

[1]University of Bologna, Cesena, Italy
[2]University of Milano-Bicocca, Milano, Italy
[3]S Gerardo Hospital, Monza, Italy

Abstract

In end stage renal disease (ESRD) patients atrial fibrillation (AF) prevalence is extremely high and the hemodialysis (HD) session can trigger paroxysmal AF episodes. We aimed to highlight the role of hemodialysis on the AF onset through a combined experimental and computational study. In l1 ESRD patients the effects of hemodialysis on P wave duration, which reflects the intra-atrial conduction velocity, and on AP characteristics were evaluated. The Courtemanche model of human atrial myocyte was used to simulate the effects of dialysis on AP. The P wave duration slightly but systematically increased after dialysis. Coherently, the model-based analysis indicated a similar reduction in the maximum AP upstroke velocity. The simulated action potential duration) was also reduced at the end of dialysis. These results indicate slowing of atrial conduction and shortening of the refractory period as possible proarrhythmic consequences of the hemodialysis session.

1. Introduction

Atrial fibrillation (AF) is the most common and troublesome arrhythmia in clinical practice and is a significant contributor to cardiovascular morbidity and mortality [1]. It has been demonstrated that in end stage renal disease (ESRD) patients AF prevalence is extremely high [2]. Moreover, the hemodialysis (HD) session can trigger paroxysmal AF episodes. AF onset is determined by two important phenomena: a) extrasystolic firing from atrial ectopic foci, b) structural and electrical atrial remodeling [3]. Supraventricular ectopic beat occurrence increases in the last stage of the HD session and structural remodeling is often present in ESRD patients. There are two electrophysiological aspects of electrical atrial remodeling: a) action potential (AP) shortening and consequent reduction of the atrial cell refractory period, b) slowing of intra-atrial electrical conduction. The ECG P wave duration reflects the atrial conduction velocity, whereas through computational analysis the effects of electrolyte variations on AP morphology and duration can be quantified. Here we present the preliminary results of a combined experimental and computational study aiming to highlight the role of hemodialysis-induced acute electrical remodeling on the AF onset.

2. Methods

In l1 ESRD patients, a P-wave signal-average recording [4] was performed before and after the HD session. The P wave-recording was derived from three bipolar orthogonal leads (X, Y and Z). The QRS was used as the trigger for the signal-averaging process. A sinus P-wave template was selected by the operator and P wave complexes that did not match the template with 99% correlation coefficient were automatically rejected. The P waves were acquired until a noise end point <0.3 uV was achieved. Approximately 150-200 beats were averaged and stored. The filtered and averaged signals for the three leads were combined into the vector magnitude $(X^2+Y^2+Z^2)^{1/2}$. Filtered P-wave duration was measured and calculated automatically. Heart rate (HR) and Na^+, K^+ and Ca^{2+} plasma values were also measured.

The Courtemanche model of human atrial myocyte (Fig. 1) provided the basis for the AP simulations in this study. For a complete description of the model and its validation see [5]. Since it didn't consider time-varying extracellular ion concentrations, some known dependences of currents on such concentrations were not included in the Courtemanche model. In order to discuss the hemodialysis effects on atrial AP, we included in a modified version of the model the most important of such

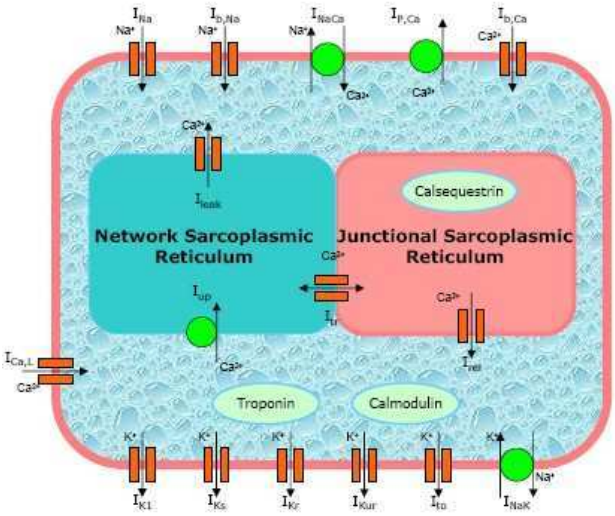

Figure 1: Schematic diagram of the Courtemanche atrial cell model. The model describes the main membrane currents and active transport mechanisms participating in the AP and the processes that regulate intracellular Ca^{2+} concentration.

dependencies, i.e. the $[K^+]_o$-dependence of I_{K1} and I_{Kr} currents, as described in most ventricular model (see, e.g., [6]).

The original Courtemanche model and its modified version were used to simulate the effects of dialysis by imposing extracellular electrolyte concentrations and heart rate to the values measured *in vivo*.

Pacing at 1 Hz was maintained for 300 s until a steady AP was reached. Action potential duration (APD) was measured as the interval between the AP upstroke and the 90% repolarization level (APD_{90}). Maximum upstroke velocity (V_{max}) was measured as the maximum value of the membrane potential first derivative, dV_m/dt.

Model differential equations were implemented in Simulink (Mathworks Inc., Natick, MA, U.S.A.). A variable order solver based on the numerical differentiation formulas (NDFs) was used to numerically solve the model equations (ode15s) [6].

3. Results

Hemodialysis-induced changes in electrolyte concentrations and heart rate are described in Table 1. These data demonstrate a substantial decrease in K^+ plasma concentration, and an increase in Na^+ and Ca^{2+} concentration.

The P wave duration slightly but systematically increased after dialysis (125±12 vs 131±9 ms, $p<0.05$), indicating a dialysis-induced slowing of intra-atrial conduction.

Table 1. Hemodialysis-induced changes in electrolyte concentrations and heart rate.

PARAMETERS	*PRE-DIALYSIS*	*END DIALYSIS*	*P*
HR (bpm)	71±7	67±8	NS
$[K^+]_o$ (mM)	5.03±0.61	3.95±0.38	<0.001
$[Na^+]_o$ (mM)	140±3.8	143±3.4	<0.05
$[Ca^{2+}]_o$ (mM)	1.13± 0.09	1.28±0.08	<0.001

The model-based analysis indicated that at the end of dialysis several features of the atrial AP are changed with respect to the beginning of the treatment (Fig. 2). Namely, the cell is more hyperpolarized (resting potential -82 vs -89 mV, beginning vs end) and the action potential duration (APD) is reduced (298 vs 279 ms). Moreover, a reduction in the maximum AP upstroke velocity coherent with experimental observations on P wave duration was observed (V_{max}= 214 vs 206 V/s).

Incorporation of I_{Kr} and I_{K1} dependence on extracellular K^+ concentration, did not appreciably affect the results on maximum AP upstroke velocity (V_{max}= 215 vs 206 V/s). On the contrary, the APD in this case kept almost constant at the end of dialysis (306 vs 311 ms, +1.6% at the end of dialysis, Fig. 3).

4. Discussion and conclusions

These results indicate slowing of the intra-atrial conduction as a possible consequence of hemodialysis-induced changes in electrolyte concentrations. This data is obtained directly by high resolution P wave averaging registration, and measurement of P wave duration. The model reconstruction of AP after the dialytic session shows a reduction of the maximum upstroke velocity of

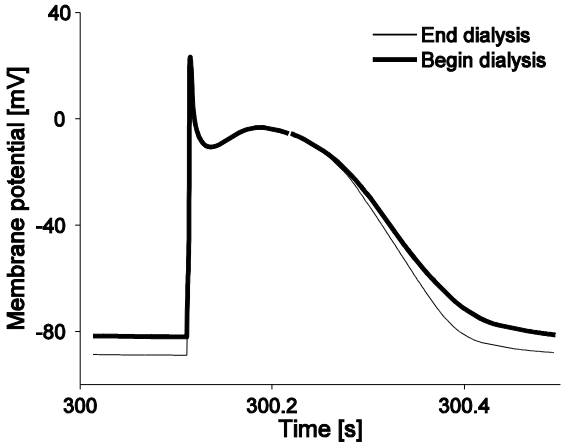

Figure 2: APs generated by the Courtemanche model in the begin and end dialysis conditions.

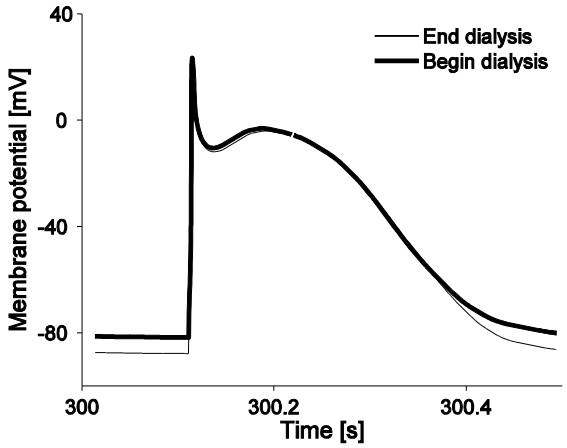

Figure 3: APs generated by the modified Courtemanche model in the begin and end dialysis conditions.

AP, and this value is the best indicator of conduction velocity, at least in the short term.

The model based analysis seems to show a reduction in AP duration, but this data is not confirmed by the modified version of the Courtemanche model. Since the dependence of membrane currents on the extracellular K^+ concentration cannot be neglected when dealing with the dialysis conditions, where such concentrations are significantly varying, our results suggest that no dialysis does not significantly affect atrial APD. An eventual dialysis-induced shortening of the effective refractory period (ERP) should be further investigated. In fact, it has been shown both experimentally and computationally that under non-physiological K^+ concentrations APD and ERP can be "uncoupled", that is ERP can diminish while APD is increasing [8,9].

In conclusion, our data suggests that hemodialytic session induces acute electrophysiological modifications in the atrial myocite, like a reduction of intratrial conduction velocity, that can favour atrial fibrillation onset and maintenance.

Acknowledgements

The authors would like to thank Henggui Zhang for help in debugging the model implementation.

References

[1] Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of Diagnosed Atrial Fibrillation in Adults: National Implications for Rhythm Management and Stroke Prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. *JAMA* 2001 May 9;285(18):2370-5.

[2] Genovesi S, Pogliani D, Faini A, Valsecchi MG, Riva A, Stefani F, Acquistapace I, Stella A, Bonforte G, DeVecchi A, DeCristofaro V, Buccianti G, Vincenti A. Prevalence of Atrial Fibrillation and Associated Factors in a Population of Long-Term Hemodialysis Patients. *American Journal of Kidney Diseases* 2005 November;46(5):897-902.

[3] Shiroshita-Takeshita A, Brundel BJ, Nattel S. Atrial fibrillation: basic mechanisms, remodeling and triggers. *J Interv Card Electrophysiol* 2005 September;13(3):181-93.

[4] Guidera SA, Steinberg JS,. The signal-avareged P-wave duration: a rapid and non-invasive marker of risk of atrial-fibrillation. J Am Coll Cardiol 1993; 21:1645-1651

[5] 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 July 1;275(1):H301-H321.

[6] Luo CH, Rudy Y. A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes. *Circ Res* 1994 June;74(6):1071-96.

[7] Shampine LF, Reichelt MW. The MATLAB ODE Suite. *SIAM Journal on Scientific Computing* 1997;18 :1-22.

[8] Downar E, Janse MJ, Durrer D. The effect of "ischemic" blood on transmembrane potentials of normal porcine ventricular myocardium. Circulation 1977; 55(3):455-462.

[9] Ferrero JM, Trenor B, Rodriguez B, Saiz J. Electrical activity and reentry during acute regional myocardial ischemia: insights from simulations. Int. J Bifurc Chaos 2003; 13(12):3703-3715

Address for correspondence

Stefano Severi
Biomedical Engineering Laboratory – D.E.I.S., University of Bologna
Via Venezia 52, I-47023 Cesena – ITALY
E-mail: stefano.severi@unibo.it