Applying a Digital Twin Framework for Stroke Risk Evaluation in Atrial Fibrillation Patients

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Abstract

Atrial fibrillation (AF) carries a fivefold higher risk of cerebrovascular events, accounting for 15-18% of all strokes. Stroke prevention in clinical practice is based on the CHA_2DS_2-VASc score, which relies on general clinical risk factors and lacks enough predictive accuracy at the patient-specific level. In this study, we propose a digital twin model of the left atrium (LA) and the application of computational fluid dynamic (CFD) simulations to improve patient-specific stroke risk assessment. Simulations were performed on patient-specific dynamic LA models in sinus rhythm on three groups of subjects: 10 controls, 10 paroxysmal AF subjects and 10 persistent AF subjects. Blood velocity and regions prone to thrombogenesis based on endothelial damage were all measured in both the LA chamber and the left atrial appendage (LAA). Furthermore, the proposed approach could be used to stratify stroke risk assessment in AF patients based on a unique index integrating blood velocity derived parameters.

1. Introduction

Atrial fibrillation is the most common form of supraventricular arrhythmia worldwide. The population is aging and more people are suffering with chronic diseases, which supports current estimates [1] of a significantly higher incidence and prevalence of AF. People with AF have a fivefold greater risk of cerebrovascular events; in the medium term, this is due to structural remodelling, which manifests as greater LA dilation and extension of the LAA. This in turn leads to an alteration of the mechanical function, which impairs blood washout and promotes clot formation, especially in the LAA, by causing a chaotic and significantly reduced contractile activity of the cardiac cells [2]. In clinical settings, the CHA_2DS_2-VASc score is frequently used to evaluate stroke risk. Despite its simplicity, it is based on a small number of variables (age, sex, hypertension, diabetes, prior stroke, etc.) rather than the processes that cause thrombus formation.

The origins of thrombus development may be examined using CFD to generate blood flow patterns inside the LA. Previous study has shown that patient-specific anatomical models, LA displacement derived from imaging data and boundary conditions obtained from Doppler acquisition at the pulmonary veins (PVs) and mitral valve (MV) can all be used to simulate realistic LA blood flow 3D patterns [3].

In this study, we propose a digital twin (DT) model of the LA and the application of CFD simulations to enhance the ability to assess the risk of stroke for any specific patient. We focused our analysis on the LAA as it is the structure most at risk of thrombus formation.

2. Materials and Methods

2.1 Patients data acquisition

Thirty non-consecutive patients were enrolled in the observational registry FATA ("Fluid-dynamics in the Left Atrium in atrial fibrillation patients and in controls for Thrombogenic risk Analysis"). Patients were subdivided into three groups: 10 controls (CTRL), 10 paroxysmal AF (PAR) and 10 persistent AF (PER).

Contrast Enhanced Computed Tomography (CECT) data were obtained. Using ECG gating, ten volumes (0.4 mm pixel size, 1 mm slice thickness) covering a cardiac cycle from the end of ventricular diastole were reconstructed and used for the following study. At the MV and PVs, Doppler measurements were also collected.

2.2 Data analysis

The data processing workflow that we applied for the analysis is shown in Figure 1. Details to obtain the dynamic model are reported in [3]. Blood flow was simulated in sinus rhythm as a fluid using the incompressible Navier-Stokes Equations in the Arbitrary Lagrangian Eulerian frame of reference. The CFD model's parameters were

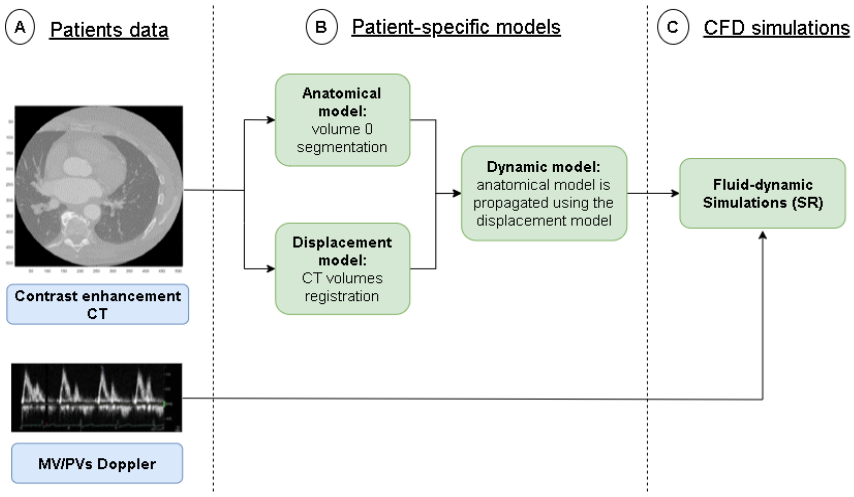

Figure 1: The workflow of the study: patient-specific contrast enhanced CT (CECT) data are processed to derive the LA anatomical and displacement models from which a dynamic model is computed; this dynamic model represents the computational domain for the CFD model in sinus rhythm (SR) using mitral valve/pulmonary veins (MV/PVs) Doppler as boundary conditions.

adjusted to include a dynamic viscosity of 0.035 poise, a density of 1.06 g/cm3, and a time step of 0.001 seconds. The simulations were performed using the LifeX software [4]. Five cardiac cycles were performed in order to exclude non-physiological initial conditions on fluid velocity.

First of all, the viscous stress vector $\vec{\tau}$ exerted by the wall on the fluid should be defined:

$$\vec{\tau} = \mu\,[\nabla\vec{u} + (\nabla\vec{u})^T] \cdot \vec{n}$$

where μ is the viscosity of the blood, $\nabla\vec{u}$ the velocity gradient, and $\vec{n}$ is the unit normal vector to the wall. In general, the normal component of $\vec{\tau}$ can be subtracted from the total $\vec{\tau}$ to yield the wall shear stress ($\overrightarrow{WSS}$) vector:

$$\overrightarrow{WSS} = \vec{\tau} - (\vec{\tau} \cdot \vec{n})\,\vec{n}$$

The wall's force on the fluid per unit area is expressed by the WSS in a direction along the local tangent plane. The periodicity of the heartbeat makes it possible to calculate an averaged indicator, the time average WSS (TAWSS):

$$TAWSS = \frac{1}{T}\int_0^T \left\|\overrightarrow{WSS}\right\|_2 \, dt$$

where *T* is the total duration of the simulated cardiac cycles and $\|\cdot\|_2$ is the Euclidean norm of a vector.

Let's now consider the oscillatory shear index (OSI):

$$OSI = \frac{1}{2}\left(1 - \frac{\left\|\int_0^T \overrightarrow{WSS}\; dt\right\|_2}{\int_0^T \left\|\overrightarrow{WSS}\right\|_2 \, dt}\right)$$

This dimensionless indicator provides values in the range [0,0.5] and it is higher in places where the WSS varies significantly over the cardiac cycle. Directional flow shifts, in particular, are the major contributors to high OSI values.

Another index is the relative residence time (RRT):

$$RRT = \frac{1}{(1 - 2OSI) * TAWSS}$$

This indicator locates areas of low $\overrightarrow{WSS}$ and oscillatory flow. The blood residence period in close proximity to the wall lengthens due to the hemodynamic environment, may resulting in an inflammatory reaction in the endothelial cells.

In order to localize regions of the wall exposed to both high OSI and low TAWSS, a new index was proposed by Di Achille et al. [5] using the ratio of these two indices to characterize the degree of 'thrombogenic susceptibility' of the vessel wall. This metric is referred as endothelial cell activation potential (ECAP):

$$ECAP = \frac{OSI}{TAWSS}$$

Additionally, to measure blood stasis, the residence time T_r was defined as the time spent by blood particles inside the LA chamber. This quantity is expressed by the following expression:

$$\frac{\partial T_r}{\partial t} + \vec{v} * \nabla T_r = 1$$

Instead of solving the equation, the 3D flow velocity field obtained from the simulation was used to track the

Lagrangian flow and the time elapsed along their path was estimated. We observe that, despite possible numerical errors, solving the equation is identical to this approach [6].

A One-Way ANOVA was conducted to evaluate statistical differences between the parameters, with results expressed as mean ± standard deviation. Statistical significance was determined by a p-value of less than 0.05.

3. Results

The proposed approach was feasible in all thirty subjects and allowed the quantitative assessment of several parameters potentially able to characterize stroke risk in AF patients. On average, inside the LAA, the CTRL group showed a higher velocity (0.11 ± 0.03 m/s) as compared to PAR (0.05 ± 0.02 m/s) and PER (0.04 ± 0.02 m/s) groups ($p < 0.05$). Additionally, the mean velocity at the LAA ostium was measured, showing a higher value in the CTRL group (0.28 ± 0.05 m/s) as compared to PAR (0.14 ± 0.03 m/s) and PER (0.11 ± 0.04 m/s) groups ($p < 0.05$). Overall, the CTRL subjects showed a better washout throughout the cardiac cycle. Next step was the evaluation of CFD parameters in the LAA. TAWSS, OSI, RTT and ECAP maps in a sample patient for each group are shown Figure 2. Average values of the computed parameters in the three study groups are ported in Table 1.

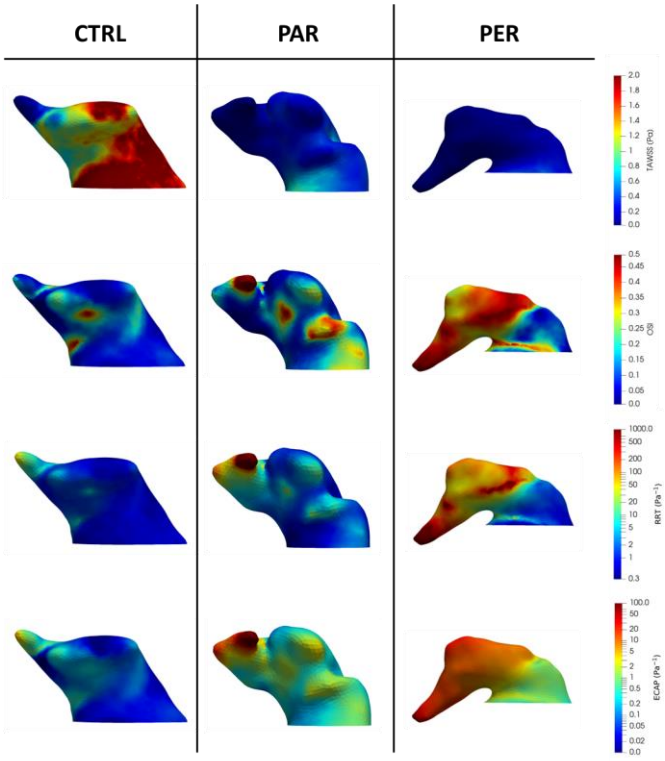

Figure 2: LAA analysis in one representative subject for each group: Time-average wall shear stress (1st row), Oscillatory shear index (2nd row), Relative residence time (3rd row), Endothelial cell activation potential (4th row).

The residence time T_r was then evaluated considering the velocity field computed from the CFD simulations.

In Figure 3, one representative subject for each group is shown.

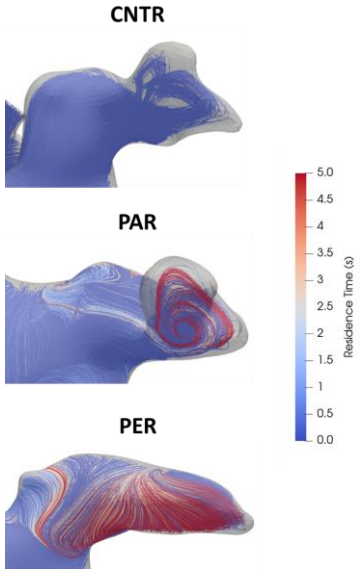

Figure 3: Residence time analysis in one representative subject for each group.

In general, the lowest T_r values were observed around the PVs inlets, where blood enters the chamber and the velocity reaches moderate values (70-80 cm/s). The residence time computed in the LA body didn't show differences among the groups, maintaining its value around 1 second (assumed as 1 cycle). In fact, despite an impaired atrial activity in AF subjects, T_r rarely surpasses 2 cycles in this area of the chamber. Furthermore, unlike the LA body, the LAA exhibits a notable degree of diversity when comparing normal with AF subjects; while in the normal subject the T_r remains around 1 cycle within the LAA, in the paroxysmal AF its value reaches 5 cycles at the tip of LAA, and it is even worse for the persistent AF. However, there is greater heterogeneity in the proximal T_r distributions, particularly in the AF subjects. A similar behavior was found for each subject of each group.

4. Discussion and conclusion

Our main finding is that, when comparing AF subjects to the controls within the LAA, on average, WSS is consistently lower and OSI, ECAP, and RRT are consistently larger, with significant differences for WSS, ECAP, and RRT. This indicates a higher likelihood of

Table 1: Mean CFD values of the LAA for each group (*CTRL vs both PAR and PER).

Parameters	CTRL	PAR	PER	p-value*
TAWSS (Pa)	0.78 ± 0.35	0.28 ± 0.16	0.18 ± 0.07	< 0.05
OSI	0.20 ± 0.07	0.22 ± 0.06	0.25 ± 0.06	0.2
RRT (Pa^{-1})	9.09 ± 7.66	112.79 ± 97.25	123.83 ± 143.68	< 0.05
ECAP (Pa^{-1})	0.93 ± 0.63	3.96 ± 3.28	4.77 ± 2.08	< 0.05

slower and more variable blood flow affecting the LAA in AF patients compared to controls. Low WSS and high OSI flow combined may thereby activate the LAA wall's endothelial cell layer, attracting platelets and leukocytes. In turn, this triggers venous thrombus mechanisms that activate the coagulation cascade, resulting in the formation of a local clot that may induce ictus [7].

Regarding CFD parameters, in recent years several papers have measured ECAP from the blood velocity field [8,9]. Despite the main focus was not to create a DT model for assessing the risk of stroke and the studies used different CFD models, we found similar ECAP values.

Although the residence time T_r was determined by tracking the Lagrangian flow, very similar values were found in Durán and coll. [10]. The larger Tr seen in the AF patients is consistent with the notable variation in LAA velocity among groups.

With all of these indices available, stroke risk assessment could be improved on a quantitative and patient-specific basis, allowing for personalized blood clot prevention treatment and facilitating physicians to schedule examinations. Indeed, by weighting each parameter, a new clinical score might be generated.

In conclusion, our results show a substantial difference between those with AF and those with mild or no heart illness but no AF symptoms. This implies that our method may provide a digital twin model to assess the stroke risk in individuals with AF. Moreover, an original index that measures the risk of stroke may be created using the computed parameters.

Acknowledgments

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