

When Virchow Meets Da Vinci Correlating Thrombogenesis With Intracardiac Flow Dynamics

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Atrial fibrillation (AF) is the most common sustained arrhythmia, afflicting >5 million people in the United States alone¹ and associated with considerable morbidity because of migration of left atrial (LA) and specifically left atrial appendage (LAA) thrombi. A combination of LA anatomic, inflammatory, and metabolic changes results in abnormalities in both flow characteristics, endothelial function, and blood constituents. Thus, AF creates an hypercoagulable state in the LA by virtue of fulfilling Virchow's triad of thrombogenesis.² Although the CHADS₂ and CHA₂DS₂-VASc risk scores are clinically useful for identifying AF patients who are at high risk for thromboembolism,³ they are imperfect (C statistics 0.60–0.69).^{4,5} They concentrate on the clinical substrate and do not consider local physiological factors such as LA/LAA flow, which are likely to offer higher fidelity discrimination of those at highest risk for thrombus formation.

See Article by Markl et al

The essence of cardiology is blood flow, but noninvasive tools to comprehensively characterize intracavitary blood flow dynamics have been lacking. Cardiovascular magnetic resonance (CMR) is already recognized as the noninvasive clinical gold standard for the assessment of cardiac volumes, regional/global systolic function, fibrosis, and inflammation.^{6,7} More recently, 2D phase-contrast CMR has been shown to be clinically important for assessment of mitral regurgitation.⁸ Advancement in flow visualization have now provided us with more powerful tools for in vivo multidirectional blood flow assessment using either phase-contrast CMR, echocardiography particle imaging velocimetry, and echocardiography vector flow mapping.⁹ These novel tools enable us to verify and continue Leonardo Da Vinci's quest to study intracavitary flow dynamics¹⁰ and provide new insights regarding intracardiac flow—revealing asymmetrical spiral flow in the heart chambers and great arteries that have pivotal importance in physiological and pathological conditions.¹¹

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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The use of time-resolved, 3-dimensional, and 3-directional phase-contrast CMR (technique known as 4D flow magnetic resonance imaging [MRI]) is emerging as a valuable tool to analyze and describe intravascular velocity fields and flow characteristics. In this issue of *Circulation: Cardiovascular Imaging*, Markl et al¹² use 4D flow MRI to provide an advance in characterizing LA and LAA flow. Though no subject apparently had a thrombus, their aim was to characterize LA and LAA flow dynamics in the AF population to identify factors associated with thromboembolism.

This group has extensive expertise in acquiring and analyzing LA 4D flow MRI. Their previous studies have introduced a method to build 3-dimensional anatomic maps of 4D flow CMR LA velocity, demonstrating that global and regional LA velocity changes are associated with AF, age, and LA volume,¹³ that AF patients have a reduced LA blood flow velocities compared with controls, and that there is an inverse relationships between increased CHA₂DS₂-VASc score and LA velocity.¹⁴ In another study, they compared LA with right atrial flow characteristics in AF patients aiming to explain why left-sided thromboembolism is more frequent. Interestingly, they found no significant difference in LA and right atrial flow velocity profiles.¹⁵

In the current study, Markl et al analyze 4D flow CMR LA and LAA flow dynamics in 60 AF patients (30 while in AF and 30 while in sinus rhythm) and 15 sinus rhythm controls. Overall, they demonstrate that in healthy controls, flow velocities are significantly lower in the LAA compared with the LA body, whereas AF patients failed to demonstrate such a difference between these 2 compartments. When persistent AF patients were compared with controls, lower velocities and higher stasis were measured in both the LA and the LAA. In contrast, velocity differences between AF patient in sinus rhythm and controls were noticed only in the LA body. There was a modest correlation between transesophageal echocardiography (TEE) LAA Doppler data among the subset who underwent nonconcurrent TEE.

These findings suggest that the LAA is in a constant state of relatively low velocity/stasis both in sinus rhythm and in AF, whereas the significant velocity change imposed by AF occurs mainly in the LA body. This interesting observation is intriguing because the vast majority of nonvalvular AF thrombi are within the LAA.¹⁶ Does this mean that LA flow dynamics are more important than LAA flow dynamics with regards to thrombus formation? Does LAA emptying relate mostly to LA body flow dynamics and mechanics?

When LA and LAA velocity data were stratified by CHA₂DS₂-VASc groups, Markl et al revalidate their previous finding that LA velocities have inverse correlation with CHA₂DS₂-VASc score. In contrast, the correlation of

CHA₂DS₂-VAsC score with LAA velocities was less pronounced. Another intriguing finding is that 38% of AF patients had LA peak velocities in the normal range and 60% had normal range LAA peak velocities! These normal range velocities were even found in the highest risk group of CHA₂DS₂-VAsC ≥ 4 .

The CHA₂DS₂-VAsC scoring system for guiding thromboembolism risk has recognized limitations, although it is a validated and easy-to-apply clinical risk score. Could AF patients with high CHA₂DS₂-VAsC but normal LA 4D flow velocities be at lower risk for thrombus formation? Or is it that flow is just one element in the equation of thrombus risk prediction.

LAA Doppler TEE studies have demonstrated that flow characteristics are important in the development of LA/LAA thrombus formation.² If 4D flow CMR flow dynamics are to be incorporated into a clinical risk score, we need prospective studies demonstrating an association with hard clinical end points, such as thromboembolism and evidence of LA thrombus formation. We also need 4D CMR flow data acquisition study reproducibility and stability data over time in patients with permanent AF. Moreover, other individualized anatomic and physiological data also need to be integrated for better risk prediction. For example, certain LAA morphology (Chicken wing versus Cauliflower, Cactus, etc) seem to convey variable thromboembolism risk.¹⁷ Finally, flow characteristics constitute only one aspect of Virchow's Triade of thrombogenesis. Other local and systemic factors should not be overlooked. Thus, a combination CHA₂DS₂-VAsC score that focuses on patient demographics with 4D flow CMR that focuses on the patient's specific organ physiology may increase the fidelity of our current stroke predication algorithm.

Comparing TEE velocities to 4D flow MRI is an important yet nontrivial task. Indeed, TEE evidence of spontaneous echo contrast in the LA and low LAA ejection velocities has been correlated with increased risk of stroke in AF.¹⁸ Nevertheless, the differences between 4D flow CMR and echocardiography techniques impose difficulty in comparing velocity values from these 2 modalities. Spatially, 4D flow MRI-acquire velocities are derived from the whole LA, whereas TEE measures pulse wave velocities only in a specific location (gate). TEE has higher temporal resolution, capturing the velocities along the whole cardiac cycle from a single heartbeat, whereas 4D flow CMR velocities are prospectively collected over several heartbeats, sometimes missing part of the cardiac cycle, as shown in the current study where data covered 85% to 90% of the RR-interval and missed a fraction of late ventricular diastole that include the atrial systole (relevant in the controls and AF in sinus rhythm). In the current study, 4D flow CMR velocities were 20% slower than TEE velocities. It might well be that these technical differences are the basis for these discrepancies, the nonconcurrent acquisition (interval between CMR and TEE was 41±68 days), or the acquisition under different conditions (eg, conscious sedation for TEE). Nevertheless, 4D flow CMR allows us to noninvasively study LA and LAA flow and to better understand complex flow dynamics to which we were previously blind.

Finally, the impact of mitral regurgitation (MR) needs further detailing. Three patients in the current study had severe MR; yet, data regarding the number of patients with moderate

or greater degrees of MR and the impact of MR on 4D flow CMR dynamics are lacking. Prior studies have shown that significant MR is protective against clinical thromboembolism and for LAA thrombus formation.¹⁹ MR will introduce higher LA velocities, will increase peak velocity, and reduce stasis and increase the cohort variability. Eccentric jets of MR directed into the LAA may be still another important finding.

The current study by Markl et al represents an important step in bringing 4D flow CMR data to the attention of the cardiovascular community and advancing the potential application of CMR to the AF population. 4D flow CMR is a remarkable tool for characterizing flow with abundance of data output. The prolonged (10–20 minute) acquisition time and expertise needed for velocity reconstruction, manual segmentation, velocity field maps calculation, and visualization are other impediments. This study raises important questions that need to be addressed. It might be that this encounter between Virchow's thrombogenesis theory and Da Vinci's quest to delineate intracardiac fluid dynamics will lead us to further understand the pathophysiology of cardioembolic phenomena in AF and, thereby, advance patient care.

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Disclosures

None.

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