SUPPLEMENTARY DATA

METHODS OF THE SUPPLEMENTARY DATA

Cardiac imaging

Echocardiographic examinations were performed 4 times in each patient: at screening, at enrollment and at the 1-week and 6-month visits after enrollment. We used a Vivid 7 scanner and a phase-array 2 to 4 MHz transducer (GE Healthcare). We obtained 3-dimensional apical sequences to measure LV volumes and ejection fraction and contrast-echo sequences (intravenous Sonovue, Bracco Imaging, 1-2 mL studied using pulse inversion and a mechanical index < 0.3) to rule out intraventricular thrombosis (LVT). Two level-3 echocardiography experts blindly analyzed the presence/absence of LVT as well as regional wall motion. Longitudinal myocardial strain was measured from 2-, 3- and 4-chamber long-axis B-mode sequences and averaged using the 16-segment model (EchoPac version 204, GE Healthcare). Apical strain was calculated as the mean of the apical segments. The E-wave propagation index was calculated as the ratio between the E-wave velocity time integral and the LV long-axis length.[1]

Cardiac MR imaging was performed twice, at 1 week, and at 6 months after enrollment. The imaging protocol included a cine steady-state free precession imaging of LV function (SENSE X 2, repetition time: 2.4 ms, echo time: 1.2 ms, average in-plane spatial resolution: 1.6 x 2 mm, 30 phases per cycle, 8-mm slice thickness without gap) and late enhancement imaging (3D inversion-recovery turbo gradient echo sequence, prepulsed delay optimized for maximal myocardial signal suppression; 5-mm actual slice thickness, inversion time: 200-300 and 600 ms). Images were obtained in short axis (10 to 14 contiguous slices) and 4-, 2-, and 3-chamber views. Early and late enhancement sequences were obtained 3 to 10 minutes after injection of 0.1 mmoL/kg of gadobenate dimeglumine (ProHance, Bracco Imaging) to assess mural thrombosis and quantify infarct size.[2]

Brain imaging

Brain MR was performed twice (at the 1 week and 6-month visits after enrollment) and included sagittal T_1-weighted images, axial diffusion weighted images, coronal T_2-weigthed turbo spin echo, and axial FLAIR-T_2-weigthed images. Acute or subacute diffusion weighted brain infarcts were adjudicated to the primary endpoint whenever hyperintense focal lesions exceeded 3 mm on diffusion weighted images with low apparent coefficient diffusion or pseudo normalization values were identified. Chronic ischemic injuries (not adjudicated to the primary endpoint) were diagnosed if the lesion was as intense as the cerebrospinal fluid on T_2, FLAIR weighted images, appeared surrounded by an hyperintense lineal rim of gliosis, and showed high apparent coefficient diffusion values. Only those lesions that were unequivocally dated after STEMI onset were adjudicated to the primary endpoint. All studies were interpreted by expert neuroradiologists who also differentiated these types of lesions from dilated perivascular spaces, based on their distribution and morphology.

Stasis mapping

From the echocardiograms performed at enrollment, we calculated 2-dimensional, time-resolved (2D+t) blood flow fields inside the LV using color-Doppler velocimetry (echo-CDV).[3] For this purpose, we obtained LV color-Doppler acquisitions followed by 2-dimensional cine-loops at a frame rate > 60 Hz. By imposing mass conservation, echo-CDV provides the crossbeam flow velocity, under the hypothesis of planar flow with high temporal and spatial resolutions (~0.5 mm and 5 ms).

We used the 2-dimensional+t flow fields, obtained from the echo-CDV, to integrate forced advection equations to map and quantify the residence time, R_T *[units of time],* of infinitesimal blood volumes traveling inside the LV:

$$\frac{\partial R_T}{\partial t} + \nabla \cdot (\vec{v} R_T) = 1 \qquad (1)$$

where $\overrightarrow{v}$ is the velocity field obtained by the echo-CVD at each point of space and time inside the LV. We integrated equation (1) for 8 consecutive cardiac cycles, the time a normal LV takes to fully washout.[4]

From the residence time of spatio-temporal residence time maps, we calculated the average R_T of the entire blood volume inside the LV at the end of calculation (last instant of mitral valve opening). This is a representative metric of global stasis that accounts for the full blood pool in the ventricle and has been shown to be a good index to address intraventricular stasis risk.[5-7] We found no meaningful difference in prediction of the primary endpoint on calculating R_T in seconds instead of cardiac cycles, because both R_T metrics correlated tightly (R = 0.94, pooled studies).

We designed a color-coded scale to generate video maps of RT of blood in the LV. In each frame, the color scale represents the number of cardiac cycles a blood particle has spent inside the chamber; dark blue represents "fresh" blood recently entering the LV, whereas dark red represents stasis regions in which with blood is retained for at least 4 cardiac cycles.

The changes in blood residence time in the LV during the entire calculation period is shown in video 1 of the supplementary data for a patient with a stroke and in video 2 of the supplementary data for a patient without any primary endpoint. Video 3 of the supplementary data shows the changes in of residence time in a healthy volunteer for comparison.

Sensitivity analysis

To avoid verification bias we performed a sensitivity analysis following current recomendations.[12] For that purpose, we used multiple imputation by chained equations of the missing values of the individual events that constitute the primary endpoint in the patients with stasis imaging lost to follow-up. These 1000 imputed datasets were used for analyses of the primary endpoint, and median metrics of diagnostic performance and their 95%CIs were calculated using Rubin's rule.

Table 1 of the supplementary data

Performance of stasis imaging and sensitivity analysis

Model performance						
Index	c-index	Threshold	Sensitivity	Specificity	PPV	NPV
Residence time	0.82 (0.71-0.92)*	> 2.76 cycles	1.00 (0.94-1.00)	0.54 (0.36-0.78)	0.44 (0.36-0.61)	1.00 (0.96-1.00)
Apical strain	0.75 (0.62-0.82)*	−8.11 %	1.00 (0.82-1.00)	0.47 (0.17-0.84)	0.40 (0.31-0.68)	1.00 (0.91-1.00)
Residence time + apical strain	0.86 (0.73-0.95)*	0.11	1.00 (0.88-1.00)	0.54 (0.37-0.91)	0.44 (0.37 -0.77)	1.00 (0.94-1.00)
Sensitivity analysis						
Index	**c-index**	**Threshold**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Residence time	0.75 (0.64-0.88)*	> 2.74 cycles	0.90 (0.77-1.00)	0.43 (0.29-0.57)	0.41 (0.33-0.50)	0.93 (0.81-1.00)
Apical strain	0.70 (0.57-0.85)*	−9.3%	0.87 (0.74-1.00)	0.31 (0.18-0.44)	0.36 (0.29-0.43)	0.86 (0.70-1.00)
Residence time + apical strain	0.80 (0.69-0.91)*	0.20	0.92 (0.84-1.00)	0.47 (0.32-0.61)	0.48 (0.40-0.56)	0.92 (0.84-1.00)

PPV, positive predictive value; NPV, negative predictive value.

*$P < .05$; thresholds selected by Youden's criterion weighting sensitivity.

Values are shown for bootstrap values of 2000 replicates of 1000 bootstrap imputed datasets.

VIDEO LEGENDS

Video 1 of the supplementary data. Changes in residence time in a patient who was diagnosed with mural thrombosis 1 week after enrollment. The RT map is colored and overlaid over a B-mode of the 3-chamber view of the LV. Flow colors account for the time each blood volume spends inside the LV, from dark blue (blood entering in the LV) to dark red (blood spending more than 4 cycles inside the chamber). As time evolves, due to deficient blood mixing and stagnation near the apex, the hue of blood shifts toward red colors. The study was performed at the time of enrollment.

Video 2 of the supplementary data. Changes in residence time in a patient free of events. The RT map is overlaid over a B-mode of the 3-chamber view of the LV. Flow colors are identical to those represented in video 1 of the supplementary data. Notice that contrary to what is shown in that video, adequate blood mixing and washout are depicted by low values of residence time near the apex.

Video 3 of the supplementary data. Changes in residence time in a healthy volunteer. In this case, optimal blood mixing and washout is shown in the entire chamber.

REFERENCES OF THE SUPPLEMENTARY DATA

1. Harfi TT, Seo JH, Yasir HS, et al. The E-wave propagation index (EPI): A novel echocardiographic parameter for prediction of left ventricular thrombus. Derivation from computational fluid dynamic modeling and validation on human subjects. *Int J Cardiol.* 2017;227:662-667.

2. Mollet NR, Dymarkowski S, Volders W, et al. Visualization of ventricular thrombi with contrast-enhanced magnetic resonance imaging in patients with ischemic heart disease. *Circulation.* 2002;106:2873-2876.

3. Garcia D, Del Alamo JC, Tanne D, et al. Two-dimensional intraventricular flow mapping by digital processing conventional color-Doppler echocardiography images. *IEEE Trans Med Imaging*. 2010;29:1701-1713.

4. Benito Y, Martinez-Legazpi P, Rossini L, et al. Age-dependence of flow homeostasis in the left ventricle. *Front Physiol.* 2019;10:485.

5. Delgado-Montero A, Martinez-Legazpi P, Desco MM, et al. Blood stasis imaging predicts cerebral microembolism during acute myocardial infarction. *J Am Soc Echocardiogr.* 2020;33:389-398.

6. García-Villalba M, Rossini L, Gonzalo A, et al. Demonstration of patient-specific simulations to assess left atrial appendage thrombogenesis risk. *Front Physiol.* 2021;12:596596.

7. Martinez-Legazpi P, Rossini L, Perez Del Villar C, et al. Stasis mapping using ultrasound: A prospective study in acute myocardial infarction. *JACC Cardiovasc Imaging.* 2018;11:514-15.