Size-dependent predilections of cardiogenic embolic transport

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NEARLY 90% OF STROKES ARE ischemic, and roughly 40% of ischemic strokes result from emboli (8). Emboli to the brain commonly originate from the heart (12). Causes of cardiogenic emboli can be divided into three main categories (21): cardiac wall and chamber abnormalities, valve disorders, and arrhythmias. Atrial fibrillation is a major cause of cardiogenic thrombus formation and embolization from the left atrial appendage (1). Intracavitary thrombus from chronic ventricular dysfunction resulting from myocardial infarction or nonischemic dilated cardiomyopathy also leads to significant increase in incidence of embolism (14). Another source is paradoxic system, or right heart, which enters the systemic circulation through an intracardiac shunt (28). In addition to spontaneous emboli, periprocedural stroke due to cardiac catheterization is surprisingly common (15). Little has been done to mechanistically describe the impact of aortic anatomy or embolus size to cardioembolic stroke risk, location, or severity, as these relationships are difficult to directly observe or physically model. Nonetheless, a posteriori data indicate that cerebral embolism may be affected by such factors (17).

It is intuitively clear that an embolus should generally favor arteries that receive the highest volumetric flow of blood. However, there may be locations or situations that result in surprising predilections. Previous investigations suggest that particles tend to favor wider diameter daughter branches at vessel bifurcations in excess of expectations based on volumetric flow, and this bias increases with increasing particle size. For example, particle transport studies through idealized (Y-shaped) in vitro bifurcations were performed by Pollanen (27) and Bushi et al. (7) and demonstrated that larger diameter particles suspended in fluid tend to preferentially enter the wider diameter daughter branch beyond the distribution of the fluid itself, even though the particles were physically small enough to easily pass through either daughter. Chung et al. (9) investigated particle transport in the cerebral arteries using an anatomically realistic in vitro model and similarly found that larger diameter emboli from the internal carotid artery favored continuation to the wider diameter middle cerebral artery than the smaller diameter anterior cerebral artery.

The objective of this study is to investigate the propensity of cardiogenic particles to be transported to the carotid and vertebral arteries supplying the head as a potential mechanism underlying cardiogenic embolic stroke etiology. Specifically, possible size-dependent predilections in particle transport are investigated, as well as cross-sectional analysis of how such trends vary between patients. To systematically explore predictions of cardiogenic embolic transport over multiple patient models, simulation-based techniques offer the greatest flexibility and data collection capabilities. Specifically, replication of in vivo aortic flow conditions through experimental setup is difficult, expensive, and time consuming. As a result, in vitro experiments are less amenable to variations of the model parameters, experimental conditions, and measurements, which are all factors that limit the ability to explore or establish underlying relationships. The study herein utilizes three-dimensional medical imaging of living patients and validated computational modeling to model patient-specific blood flow from the aortic root to the
common carotid and vertebral arteries. These data are then used to track particle transport for a range of particle sizes in these patient models.

MATERIALS AND METHODS

Imaging. Computed tomography (CT) scans utilized to provide anatomically accurate models in this study were obtained from 10 patients at the Minneapolis Heart Institute and Foundation using a SOMATOM Definition Flash scanner (Siemens, Erlangen, Germany). All images were acquired for clinical indications, and each patient provided informed consent. Image collection followed Minneapolis Heart Institute and Foundation guidelines and was approved by the Institutional Review Board. No patient had overt or known aortic disease, a finding confirmed by review of their CT scans. All patients were 65 yr or older.

Imaged-based modeling. Vessel lumen reconstructions were performed from the CT data (Fig. 1A) of each patient using a customized version of the SimVascular software (29). Paths were created along the aorta, carotid, innominate, subclavian, and vertebral arteries. In three patients, the subclavian arteries were truncated proximal to the vertebral takeoffs due to inadequate imaging of the vertebral arteries. Lumina were segmented along each path using a level set method (35). Segmentation of the aorta began as close to the aortic valve as possible. Segmentations were lofted together to create spline representations of the luminal surfaces using Parasolid (Siemens). These surfaces were combined (unioned) to create a unified geometric model (Fig. 1B). Each patient model was discretized into a nominally isotropic tetrahedral finite-element mesh (Fig. 1C) with maximal edge size between 600 and 800 μm using MeshSim (Simmetrix, Clifton Park, NY). Subsequent local refinement was performed to enhance mesh resolution in the vertebral arteries. Because the purpose of this study was to quantify embolic transport predilections occurring at the level of the aortic arch and first generation arterial branches to the head, models were truncated at the level of the common carotid and vertebral arteries. The carotid and vertebral arteries were extended to the cerebral circulation in one model (patient 7 in Fig. 2), and it was verified that these extensions did not influence the results.

Boundary conditions. A physiologic volumetric flow waveform (Fig. 1D, inset) from Olufsen et al. (26) was mapped to the aortic root morphology of each patient using a plug profile as consistent with in vivo measurement (30). The waveform was measured distal to the aortic valve using two-dimensional phase contrast MR but was scaled to have a time-averaged flow rate of 4.9 l/min for all patients. The purpose of this normalization was to use the same cardiac output for all patients to better isolate the influence of aortic anatomy when comparing particle distributions between patient models. To investigate the impact of this normalization, cardiac output was varied for each patient to determine sensitivity of the distribution results to changes in flow rate from the heart, as reported below.

At the outlets, single element Windkessel models were coupled to the three-dimensional computational domain to represent the respective downstream vascular bed. The resistance of each Windkessel model was set to produce an expected mean flow rate to each arterial bed. The mean flow to each outlet \( Q_e \) was obtained as follows. Based on measurements of mean aortic flow distribution (4), 65% of aortic flow was nominally distributed to the descending aorta. The
remaining 35% was distributed according to vessel area to the aortic arch branch arteries, as validated in (37). Subsequently, the resistance at each outlet \( R_e \) was set according to \( R_e = P/Q_e \). Mean brachial pressure was used for \( p \). Depending on relative size differences among the subclavian, carotid, and vertebral arteries between the patients, flow distributions to the carotid and vertebral arteries ranged between 10 and 18% over the patients, which is consistent with in vivo measurements (4).

Flow solver. Blood was modeled as an incompressible, Newtonian fluid by the Navier-Stokes equations with density \( \rho = 1.06 \text{ g/ml} \) and viscosity \( \mu = 4 \text{ cP} \). It is widely accepted that blood behaves as a Newtonian fluid in the larger arteries under physiologic shear rates (10). However, typical blood viscosity values can range between 3.5 and 4 cP, and therefore, sensitivity of our results to changes in blood viscosity was tested as reported below. An in-house finite element flow solver was used to solve for spatiotemporally resolved velocity fields (Fig. 1E). The finite element method is well suited for cardiovascular simulation since an unstructured discretization can be used to accurately model complex vascular geometries. The weak form of the Navier-Stokes equations can be written to include the resistance boundary conditions at the domain outlets as derived in Vignon-Clementel et al. (32). The resulting equations are solved using a modified version of the finite element flow solver released with the SimVascular software package (29). This solver uses a stabilized finite element formulation (31, 34) based on the streamline-upwind Petrov-Galerkin equations (6) with same order pressure and velocity interpolation. The discretization is semidiscrete, leaving integration in time handled by a generalized \( \alpha \)-method (16), which is implicit, second-order accurate, and unconditionally stable. This solver has been used and validated in hundreds of peer-reviewed publications, including targeted validations of arterial blood flow modeling (2, 3, 18, 19, 20). The average mesh size was roughly 10 million tetrahedral elements. Particle distribution results were confirmed to be grid independent.

Embolic model. Embolic particles were modeled as spherical and coupled to the fluid dynamics by the Maxey-Riley equation (23)

\[
\left( \rho_p + \frac{1}{2} \rho_f \right) \frac{d \bar{u}(x(t))}{dt} = \left( \rho_p - \rho_f \right) \bar{g} + \frac{3}{2} \rho_f \frac{D \bar{u}(x,t)}{Dt} - \frac{9}{2} \frac{\mu}{a^2} (\bar{v}(x,t) - \bar{u}(x,t)),
\]

where the Faxen second-order corrections and Basset-Boussinesq memory term, which decays quickly at finite Reynolds numbers (24), have been neglected. In Eq. 1, \( \bar{v} \) is the particle velocity, \( \bar{u} \) is the blood velocity, \( \bar{g} \) is the gravity vector, \( a \) is the particle radius, \( \mu \) is the blood viscosity, \( \rho_p \) and \( \rho_f \) are the particle and blood densities, and \( \mathbf{x} \) is the position of the particle. Therefore, image-based blood flow modeling (Fig. 1, A–E) is performed to obtain velocity field data over space and time, \( \bar{u}(x,t) \). Particle trajectories are then modeled according to the above differential equation for a range of particle sizes, starting locations and starting times. In accordance with the derivation of Eq. 1 in Maxey (23), the spherical shape of particles was maintained for the fluid-particle coupling. However, expected plastic (and elastic) deformation was accounted for when computing the coefficient of restitution (COR) due to particle-wall impacts. Particle-wall impacts were based on a linear visco-elastoplastic model (36) using measured material properties of thromboemboli and the aorta (33). Specifically, a damping ratio was computed as a function of impact velocity and material properties of the aorta (thickness: 3 mm; elastic modulus: 1.0 MPa; bending stiffness: 10 kPa; and Poisson ratio: 0.5) and of the embolus (elastic modulus: 1.0 MPa; yield strength: 10 kPa; and Poisson ratio: 0.5). This damping ratio along with typical collision velocities was used to obtain a COR, which was generally >0.5. The COR was varied to simulate uncertainties in material properties of the arterial walls or emboli, as reported below.

Particles were introduced at the model inlets (immediately distal to the aortic valve) to represent cardiogenic emboli ejected from the heart. While sources of cardiac emboli are multifactorial, it is expected that on average such emboli are ejected from the left ventricle with no preferred positioning when exiting the aortic valve. It is further assumed that a cardiogenic embolus would exit the aortic valve with velocity near that of the blood velocity at the position and time the embolus is ejected. Therefore, since blood has a nominal plug profile at the aortic root, particles were released with uniform distribution over the inlets of the models at five times throughout systole: at the time of peak flow rate and roughly the times at which flow rate was 30 and 60% of the peak during both the acceleration and deceleration phase of systole. For each release, particles were given initial velocity of blood at the respective release location and time. Moreover, the strategy by which particles were released into the model (both timing and the initial velocity of each particle) was varied as reported below.

RESULTS

The 10 patient models reconstructed from CT angiography are shown in Fig. 2, and main dimensions are given in Tables 1 and 2. These patients demonstrated a broad range of aortic anatomy. The trajectories of various sizes of particles originating from the aortic root were tracked using the methods described above. For each patient, particle diameter ranging from 0 to 4 mm, in increments of 250 \( \mu \text{m} \), were seeded uniformly at the aortic root with initial velocity equal to the blood velocity at the respective release location. For each particle size, several thousand particles were introduced throughout systole. This high density of particles was used for sampling purposes only; interparticle interactions did not exist. Visualization of particles released at 60% peak systole for three particles sizes is shown for the sample model above in the Supplemental Video S1 (Supplemental Material for this article is available online at the Am J Physiol Heart Circ Physiol website).

The foremost bifurcations directing cardiac emboli to the cerebral vs. peripheral arteries are the aortic arch branch
arteries. The percentage of particles embolic to the aortic arch branch arteries, and specifically the arteries to the head (L/R common carotid/H11001 L/R vertebral), was quantified. The percentage of particles embolic to the branch arteries is plotted in Fig. 3 as a function of particle size for each patient model. The values listed have been normalized by blood flow distribution to the branch arteries so that a distribution ratio of 1.0 is equivalent to particles being distributed proportion to blood flow. Small particles (diameter of \( \leq 250 \mu m \)) were distributed to the branch arteries according to volumetric blood flow distribution. As particle size increased, there was significant increase of particles embolic to the branch arteries for all patients. Upon averaging over all patients, peak particle transport to the branch arteries occurred for 1.275 \( \times 10^{-0.25} \) mm diameter particles, and the total percentage of released particles embolic to the branch arteries was 60 \( \times 10^{-1.3} \%), which was nearly twice the percentage of cardiac output to these arteries. Of the particles that

1 The aortic arch branch arteries are nominally considered to be the innominate, left carotid, and left subclavian arteries. For patient 2, the left vertebral branched directly from the aortic arch as well.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>AsAo</th>
<th>AoArch</th>
<th>DAo</th>
<th>Innom</th>
<th>L CCA</th>
<th>L Subclavian</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.03</td>
<td>4.10</td>
<td>2.61</td>
<td>0.86</td>
<td>0.44</td>
<td>0.37</td>
</tr>
<tr>
<td>2</td>
<td>6.74</td>
<td>5.28</td>
<td>3.31</td>
<td>1.12</td>
<td>0.71</td>
<td>0.62</td>
</tr>
<tr>
<td>3</td>
<td>5.65</td>
<td>3.83</td>
<td>3.79</td>
<td>0.81</td>
<td>0.26</td>
<td>0.73</td>
</tr>
<tr>
<td>4</td>
<td>9.24</td>
<td>5.22</td>
<td>4.33</td>
<td>3.73</td>
<td>0.19†</td>
<td>0.62</td>
</tr>
<tr>
<td>5</td>
<td>7.51</td>
<td>4.46</td>
<td>3.89</td>
<td>1.47</td>
<td>0.48</td>
<td>0.88</td>
</tr>
<tr>
<td>6</td>
<td>8.40</td>
<td>5.89</td>
<td>5.14</td>
<td>1.29</td>
<td>0.65</td>
<td>1.04</td>
</tr>
<tr>
<td>7</td>
<td>5.93</td>
<td>6.32</td>
<td>4.87</td>
<td>1.15</td>
<td>0.47</td>
<td>0.60</td>
</tr>
<tr>
<td>8</td>
<td>8.31</td>
<td>6.10</td>
<td>5.16</td>
<td>2.03</td>
<td>0.46</td>
<td>0.84</td>
</tr>
<tr>
<td>9</td>
<td>7.32</td>
<td>4.85</td>
<td>5.39</td>
<td>1.07</td>
<td>0.50</td>
<td>2.86</td>
</tr>
<tr>
<td>10</td>
<td>10.32</td>
<td>6.68</td>
<td>5.17</td>
<td>1.59</td>
<td>0.43</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Ascending aorta measurement (AsAo) was made half way between the aortic valve and innominate origin, aortic arch measurement (AoArch) was made half way between the left carotid and left subclavian artery, and descending aorta (DAo) was measured at approximately the same transverse location as the aortic root. Innom, innominate; L CCA, left common carotid artery. Branch arteries were measured \( \pm 1 \) diameter distal to their origin.

The increased predilection of cardiogenic particles to the branch arteries of the aortic arch translated to an increased predilection for embolization to the carotid and vertebral arteries, as shown in Fig. 3B. These data have similarly been normalized by volumetric flow to these arteries for each patient. On average, particles sized 1.42 \( \pm 0.51 \) mm showed greatest predilection for the carotid and vertebral arteries, and the total percentage of released particles embolic to these arteries was 41 \( \pm 15 \%), which was roughly twice the percentage of cardiac output to these arteries. Of the particles that

Data provided are for the innominate, left common carotid, and left subclavian arteries. *Patient 4 had a bovine arch as well as an aortic arch origin of the left vertebral artery. Consequently, measurements based on the left common carotid were instead based on the left vertebral artery for this patient.

**Table 2. Distance in centimeters, along the aorta centerline, of the aortic arch branch arteries measured from the model inlet**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Innom</th>
<th>L CCA</th>
<th>L Subclavian</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.67</td>
<td>6.81</td>
<td>8.16</td>
</tr>
<tr>
<td>2</td>
<td>8.16</td>
<td>9.39</td>
<td>12.18</td>
</tr>
<tr>
<td>3</td>
<td>8.78</td>
<td>10.18</td>
<td>12.18</td>
</tr>
<tr>
<td>4</td>
<td>8.75</td>
<td>11.77*</td>
<td>20.53</td>
</tr>
<tr>
<td>5</td>
<td>7.58</td>
<td>8.75</td>
<td>12.02</td>
</tr>
<tr>
<td>6</td>
<td>9.48</td>
<td>11.17</td>
<td>12.83</td>
</tr>
<tr>
<td>7</td>
<td>6.26</td>
<td>6.98</td>
<td>7.99</td>
</tr>
<tr>
<td>8</td>
<td>9.13</td>
<td>10.87</td>
<td>12.09</td>
</tr>
<tr>
<td>9</td>
<td>9.25</td>
<td>10.48</td>
<td>12.36</td>
</tr>
<tr>
<td>10</td>
<td>9.92</td>
<td>11.83</td>
<td>13.53</td>
</tr>
</tbody>
</table>

Data provided are for the innominate, left common carotid, and left subclavian arteries. *Patient 4 had a bovine arch as well as an aortic arch origin of the left vertebral artery. Consequently, measurements based on the left common carotid were instead based on the left vertebral artery for this patient.

**Fig. 3. Distribution of cardiogenic emboli to the branch arteries of the aortic arch (A) and specifically to the carotid and vertebral arteries (B) plotted as a function of particle size. Plots at left are normalized by volumetric flow to the branch arteries for each patient (Pat), and similarly the plots at right are normalized by volumetric flow to the carotid and vertebral arteries. These trends indicate strong predilection of medium-sized (\( \sim 1 \) mm) cardiogenic particles to become embolic to the superior circulation.**
reach the carotid and vertebral arteries, the percentage that were embolic to the right arteries is shown in Table 3 for each patient. These percentages are based on summing particles of all sizes that reached the carotid and vertebral arteries. In the rightmost column, the percentage of particles to the right carotid and vertebral arteries has been normalized to account for differences in right vs. left volumetric flow resulting from differences in diameter among right vs. left carotid and vertebral arteries. Specifically, the rightmost column was computed as \( \frac{N_R}{N_L} \), where \( N_R \) and \( N_L \) are the number of particles to the left and right, respectively, common carotid and vertebral arteries, and \( R_R \) and \( R_L \) are the equivalent resistances of the left and right, respectively, common carotid and vertebral arteries. In 6 of the 10 cases, cardiogenic emboli appeared to favor the right carotid and vertebral arteries (once normalized); in all 6 of these cases the base of innominate and left carotid arteries were separated along the aortic arch. In the four cases where particle transport to the left carotid and vertebral arteries was dominant, the innominate and left carotid arteries shared a common origin.

To test the robustness of the distribution trends to model parameters, the following variations were considered: cardiac output, coefficient of restitution for particle-wall impacts, the strategy by which particles were released into the model, blood viscosity, and the direction of gravity. These variations were performed for the majority, or all, of the patient models and these results are summarized for a representative case (patient 1) in Fig. 4. Cardiac output was varied from 4.2 to 4.9 l/min (Fig. 4A). This range is within the normal range of cardiac output at resting conditions of persons aged 65 and older without overt cardiac conditions (5), as considered in this study. For the release strategy comparison (Fig. 4B), two main strategies were considered as follows: releasing particles at five uniformly spaced times during systole and releasing particles based on flow rate to maintain a uniform spatial density of particles into the model. In both cases, the release locations were uniform over the aortic root, which assumes that cardiogenic emboli on average has no preferential positioning when exiting the heart. Both of these release strategies produced essentially equivalent distribution trends. It was nominally assumed that cardiogenic emboli are ejected from the heart with a velocity equal to the velocity of blood at each specific release location and time. Due to the uncertainty in this assumption, the ejection velocity (magnitude and direction) was varied randomly. Specifically, each component of \( \mathbf{u}(\mathbf{x}, 0) \) was multiplied by a random number from a \( \beta \)-distribution (parameters: \( \alpha = 6, \beta = 1 \)) to obtain \( \mathbf{v}(\mathbf{x}(0)) \). These

### Table 3. Percentage of cardiogenic particles to the right carotid and vertebral arteries

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Absolute Percentage</th>
<th>Normalized Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80%</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>3</td>
<td>73%</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>32%</td>
<td>45%</td>
</tr>
<tr>
<td>5</td>
<td>46%</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>7</td>
<td>48%</td>
<td>54%</td>
</tr>
<tr>
<td>8</td>
<td>73%</td>
<td>73%</td>
</tr>
<tr>
<td>9</td>
<td>79%</td>
<td>82%</td>
</tr>
<tr>
<td>10</td>
<td>73%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Values in rightmost column have been normalized to account for differences in volumetric flow between the right vs. left arteries as described in the text.
Transport of small to medium-sized cardiogenic particles to the branch arteries of the aortic arch, and subsequently to the carotid and vertebral arteries, increased substantially over expectations based on volumetric flow. While this trend held for all patients, there was significant variation in distributions between patients indicating some patients may have aortic anatomy that places them at an inherently higher risk of cardiogenic particles being transported to the aortic arch branch arteries and subsequently arteries supplying the head. Indeed, flow parameters such as cardiac output and relative flow distribution to the aortic arch branch arteries vs. descending aorta were maintained across patient models. As exemplified in Fig. 4, these distributions were robust to large changes in modeling parameters that may be considered uncertain. Therefore, increased predilection of small to medium-sized cardiogenic emboli to the upper extremities appeared to be a consistent and robust trend; however, variability of this trend between patients appears to be due mainly to anatomical differences between patients. Relative flow distribution to the carotid and vertebral arteries was not held fixed across patients, and greater variability among patients was observed for the distributions in Fig. 3B. Nonetheless, small to medium-sized cardiogenic particles were transported to the carotid and vertebral arteries in excess of expectations based on volumetric flow in all patient models.

Unlike in vitro studies, dense sets of particles can be released in silico without concern of interparticle interactions. The presence of large numbers of emboli in vivo would be catastrophic and mostly unrealistic. Nonetheless, distributing particles densely in space or time in silico enables spatiotemporal dependences to be readily explored without the need for multiple simulations, enabling connections between release location or release time with stroke risk to be more readily observed and conveyed. While the heart and aortic valve leaflets were not directly modeled in our analysis, our modeling tacitly assumed that a cardiogenic embolus is equally likely to be located anywhere over the aortic root area when ejected from the heart. Particles were released uniformly in time; however, it may be considered desirable to release particles based on instantaneous flow rate to maintain a uniform influx of particles into the model over time when analyzing particle distribution trends. Such a release strategy is equivalent to performing a large number of simulations releasing cardiac emboli randomly in the outflow from the left ventricle. Thus, resulting distribution trends, when normalized by the total number of particles released, can be interpreted as the probability a randomly placed cardiogenic embolus of particular size is transported to the branch (or head-bound) arteries. Nonetheless, it was shown in Fig. 4B that releasing uniformly in time produced distribution trends nearly identical to those obtained from maintaining a uniform particle density influx into the model.

Because the majority of cardiogenic emboli are thrombotic, particles used herein were given the nominal density (1.1 g/cm³) of thrombus or cellular-based emboli. Expected variations in density of thrombus are relatively small; however, reported material properties of the aorta and thrombus vary significantly. These variations in material properties, in addition to variations in impact velocities with the vessel wall, manifest in variations in the coefficient of restitution for embolus-wall collisions ranging from ~0.5 to 1.0 using the model of Yigit et al. (36). In all cases considered, the overall upper convex trend of particle distribution to the branch arteries with particle size did not change as a result of these relatively larger variations in embolus or material wall properties. Larger diameter particles were more preferentially distributed to the descending aorta when particle-wall elasticity increased, which likely resulted from greater deflection of the particles from the outer aspect of the ascending aorta diminishing their preferred positioning to continue up into the branch arteries.

The observed predilections of embolic transport to the branch arteries for a particular patient appeared relatively robust to variations in cardiac output (Fig. 4A). This supports our hypothesis that aortic anatomy may be a primary factor influencing the predilection of cardiogenic emboli to the branch arteries. Since the particles were modeled as thromboemboli with density near that of whole blood, buoyancy effects appeared to have relatively negligible influence to particle distributions. Namely, the orientation of gravity, or its presence at all, did not substantially change the observed distribution trends. For embolic bubbles that may be introduced perioper-
ative, buoyancy is expected to have more significant influence, which would be consistent with clinical observation. However, perioperative flow conditions may be substantially different, and more difficult to model, than those considered herein.

The finding that emboli are preferentially transported to aortic arch branch arteries in excess of volumetric flow may be considered contrary to previous findings (7, 9, 27), which demonstrated that at vessel bifurcations, especially those with sharp angulation as considered here, particles are preferentially transported to the wider diameter artery (descending aorta in this case) and this predilection increases with particle size. We hypothesize that the potential mechanism for the observed trends herein could originate from the curvature of the aorta and pulsatile nature of aortic flow, coupled with inertial effects of the particles. The inertial and drag forces on small particles \((\approx 100\,\mu\text{m diameter})\) appear to result in relatively negligible deviations in particle distribution vs. volumetric distribution of blood flow. Medium-sized particles on the other hand \((\approx 1\,\text{mm diameter})\) carry sufficient inertia to cause them to be pushed along the upper aspect of the arch, which positions them to continue up the branch arteries. While larger diameter particles are generally pushed towards the upper-outer aspect of the aorta during systole as well, they lag the motion of the blood. Therefore, these particles do not typically reach the branch arteries before diastole sets in, or at least under strong anterograde flow conditions. As a result, these sized particles spread in the aorta during diastole diminishing any preferred positioning that would increase their transport to the upper branch arteries during the subsequent systolic push. Furthermore, the inertia of larger diameter particles transversing the aortic arch resists abrupt redirection into the aortic arch branch arteries.

In the majority of patient models, cardiogenic particles were transported to the right head-bound arteries in greater excess than the left head-bound arteries. This was also observed in several preliminary patient models where modeling was extended only to the carotid and subclavian arteries. Right hemisphere propensity of cardiogenic emboli has been demonstrated clinically and by retrospective analysis of stroke patients (17). However, left hemisphere propensity of cardiogenic embolism has also been reported (25). The study by Kim et al. (17) included a far greater number of cardiogenic embolisms \((123\,\text{cases})\) than the study of Meyer et al. (25) \((20\,\text{cases})\). In addition, the most common etiology of cardiogenic embolism in (17) was atrial fibrillation, which is the predominant etiology of cardiogenic embolism in the general population, whereas the most common etiology in the study by (25) was prosthetic heart valve. Prior observations of right hemisphere propensity are supported by our finding that as cardiogenic emboli move up the outer aspect of the arch the innominate artery is first in line and thus supplied with the greatest number of particles. Consistent with this observation, when the innominate and left carotid shared a common origin, this positioning bias becomes diminished and moreover the left carotid has an orientation more aligned with the trajectories of incoming emboli. Indeed in such cases (and these cases only), more particles were transported to the left carotid than right carotid per volumetric flow. The two cases that demonstrated greatest predilection for particle transport to the left head-bound arteries were patient 2 and patient 6. These two patients also showed relatively exaggerated peaks in particle transport to the head (Fig. 3B). This is because particles transported to the left carotid will be directly transported to the head, whereas those transported to the innominate may be transported to the head or subclavian artery. More data are need to confirm if these trends hold for larger patient populations.

A main limitation of this study is that we used a one-way coupled particle dynamics model. This model assumes that an individual embolus does not significantly alter blood flow conditions in the great arteries. This assumption is reasonable for a small to medium sized embolus, which is one or more orders of magnitude smaller than the diameter of the arteries considered. This assumption may break down for the larger diameter emboli considered \((2\,\text{mm diameter})\). In addition, larger diameter particles are more sensitive to variations of the particle-wall collision model, and therefore, distribution data for the larger diameter emboli are expected to become less certain as particle size increases. However, the finding that certain sizes of particles exhibit increased predilection for the aortic arch branch arteries and head-bound arteries is based on particle sizes well within the scope of our one-way coupled model. Therefore, the main conclusion that there exists an increased predilection of cardiogenic particles to the cerebral vs. peripheral arteries results from data that we expect are within the applicability of our modeling assumptions. The eventual decrease in predilection of larger diameter emboli to the cerebral arteries is expected and thus any uncertainties in the exact distribution of these sized particles less consequential.

In this study the arterial walls were modeled as noncompliant for the purposes of modeling the blood velocity field; vascular compliance was only accounted for in the particle-wall collision model. Aortic deformation is typical on the order of 5% (13), and deformation occurs in a nearly simultaneous fashion since the pulse wave velocity is large compared with the extent of the vasculature being modeled. Therefore, changes to the velocity field are expected to be moderate, and similar to the flow scaling comparison in Fig. 4A, have negligible influence to particle distributions. Notably, we have previously investigated particle tracking from velocity data of rigid vs. distensible patient-specific vascular models (11) and have observed that vessel compliance has relatively negligible change to transport patterns. Based on these considerations, the rigid-wall assumption employed here for velocity field modeling is expected to have minimal influence to observed distribution patterns and to the main conclusions of this study.

Conclusions. The trajectories of cardiogenic emboli were tracked through anatomically accurate models of the aorta and aortic arch branch arteries using simulation-based techniques. The results indicated strong predilection of medium-sized \((\approx 1\,\text{mm})\) cardiogenic emboli to the aortic arch branch arteries and subsequently the arteries to the head. Only particles reaching relatively larger diameters tended to prefer the descending aorta in excess of expectations based on volumetric flow. The increased transport of small to medium-sized particles to the upper branch arteries was consistent across all patient models considered. These findings may indicate an important mechanism in the etiology of cardiogenic embolic stroke.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
AUTHOR CONTRIBUTIONS

Author contributions: R.S.S. and S.C.S. conception and design of research; I.A.C., N.N., and S.C.S. performed experiments; I.A.C. and S.C.S. analyzed data; I.A.C., R.S.S., and S.C.S. interpreted results of experiments; I.A.C. and S.C.S. prepared figures; S.C.S. drafted manuscript; I.A.C., R.S.S., and S.C.S. edited and revised manuscript; I.A.C., N.N., R.S.S., and S.C.S. approved final version of manuscript.

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