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LETTER TO THE EDITOR

Stent-Induced Thromboembolism

In their report ''Enhancement of Stent-Induced Thromboembolism by Residual Stenoses: Contribution of Hemodynamics'' (Ann. Biomed. Eng. 28:182–193, 2000), S. Sukavaneshvar, G. M. Rosa, and K. A. Solen performed numerical simulations that were used to delineate the contribution of hemodynamics to thrombus accumulation and embolism, as measured *in vitro* in stents, in the presence of residual stenoses that were placed either proximal, or proximal and distal, to the stent. Their work deals with an important clinical issue pertinent to the increasing use of stents to remedy coronary heart disease. The emergence of residual stenoses gives rise to specific hemodynamic patterns which, when interacting with the stents, may elicit thrombus formation and/or embolization. Those have clinical implications that, upon deployment in an artery, may considerably affect the efficacy of the stent. Because these hemodynamic effects are intricate, and in view of the clinical implications involved, it is very important to delineate these hemodynamic effects carefully, following the governing fluid mechanical principles. The authors rely heavily on their numerical results to interpret the mechanisms that may effect thrombus formation and embolism in these stent configurations. However, the methodology chosen for the numerical simulation, the presentation of the CFD results, and their interpretation, cast some doubts regarding their validity.

The authors have chosen to exclude the geometric details of the stent from their analysis. This is surprising, as the geometry of the stent is expected to alter the flow dynamics that affect the most the thrombus formation at the wall region. As the numerical results were used to delineate the mechanisms underlying thrombus formation and embolization, and correlate them to measurements in an actual stent, the absence of these details in the numerical model is acute.

In the presentation of the CFD results, the authors have also chosen to exclude both the proximal and distal stenoses. This is unexpected, given the statement appearing in the article that ''platelets are more likely to be activated before reaching the stent region in all stenoses configurations compared with the respective controls.'' The argument given for excluding the stenoses is that by including them, the intricate details of shear stress distribution in the stent region would have been dwarfed by the much higher wall shear stress levels at the stenoses. While this is true, it could have been easily circumvented by zooming in on the area of interest. Further, the authors have found ''kinks'' in their shear stress axial distributions [Figs. 6(a) and 6(b)], which they state ''are not expected to have a significant bearing on platelet deposition on the stent.'' If this were true, it would defeat the argument that the otherwise ''dwarfed'' details in the stent region are important. Indeed, if these ''kinks'' are not artifacts of the numerical computations, they are most likely the result of a flow structure in that region, as the authors themselves state. The existence of such a flow structure could have a major impact on thrombus formation in this specific area.

Unfortunately, it is difficult to tell from the way the numerical results are presented whether such flow structures indeed exist, as the authors have chosen a peculiar format for presenting the velocity information. They present the contours of the axial velocity component only (Fig. 7), and separately the radial velocity vectors only—at the wall (Fig. 5), instead of the accepted presentation of the total velocity vectors which would have easily indicated a formation of such a secondary recirculation zone, or a possible shed vortex in this region of the stent. However, there seems to be a strong argument against the interpretation of these kinks that appear in the axial shear stress distribution [Figs. 6(a) and 6(b)], as their behavior appears inconsistent. The kinks appear in both configurations (proximal stenosis only, and the combination of proximal and distal stenoses) for $\mathrm{Re}=116$, and also for the two-stenoses configuration for the higher flow rate ($\mathrm{Re}=232$), but disappear at the higher flow rate for the proximal stenosis configuration. The latter goes unaccounted for, although if one examines Fig. 6(a) in juxtaposition with the corresponding radial velocity distribution [Fig. 5(a)], the same radial velocity distribution appears in both cases ($\mathrm{Re}=116$, and $\mathrm{Re}=232$) at the ''kink'' location, indicating a possible vortex formation (which is implicated in the shear stress ''kinks'' for all the other cases).

For the two-stenoses configuration [$\mathrm{Re}=116$, Fig. 6(a)] there is also a sudden drop in the wall shear stress level toward the distal stenosis, instead of the typical increase in shear stress one expects to find due to the flow acceleration through the converging part of a stenosis. The authors implicate a flow separation point with an associated recirculation zone just upstream from the second stenosis for this sudden drop in the wall shear stress level. Although this is further supported by the radial velocity distribution presented in Fig. 5(b), it contradicts any stenosis study in the literature, e.g., Refs. 1–5, 13

and 14. This calls for a close examination of the results presented in Fig. 5, i.e., the axial distribution of the radial velocity components along the stent. These velocities were recorded at an arbitrary radial location of $r/R = 0.96$, and the magnitude of these vectors is not indicated. The location of the separation points (the appearance of significant radial velocity components in the direction of the center of the tube) do not conform to that found in the literature, e.g., Refs. 1–5, 13; and 14. Notwithstanding, the sudden emergence of the strongest radial velocity component when approaching the second stenosis (Re=232), indicating a flow separation point (as suggested by the authors), appears implausible. The appearance of a separation point is a clear indication of an instability mechanism, which is characterized by an inflection point in the velocity profile.[6,7,10] The mechanism responsible for that would be an adverse pressure gradient, i.e., a positive instead of a negative pressure gradient. This typically happens in a diverging geometry, but hardly ever in a converging geometry (unless one actively injects fluid through a port at this location). Such a flow phenomenon, though, could be induced by the model thrombus, which is presented later in the article.

A conceivable explanation for this anomaly may be found in the possibility that this is a result of a numerical artifact, rather than an actual flow phenomenon. The authors have used a uniform grid of 10,000 nodes (200 axial nodes and 50 radial nodes.) Such a density of the numerical mesh is just about what is needed, and commonly employed, in this type of numerical simulations in order to resolve spatial changes. The use of a uniform density mesh could be advantageous if CPU resources are not an issue, provided that a sufficiently fine wall region mesh is replicated throughout the model geometry. However, if the latter goes unfulfilled, it could lead to erroneous numerical results. The authors reason their choice of a uniform density mesh by the need for a higher mesh resolution in the core-flow regions because of the thrombus models they have employed. While this could benefit the numerical solution at the core-flow region, the near-wall results may suffer because the uniform mesh density employed may have been too coarse for the numerical solution to converge to a meaningful result in the near-wall region. Unfortunately, any numerical artifact generated by the solution in the wall region could then propagate to the rest of the mesh. In other words, a much higher density than the 10,000 nodes grid used might be needed, in order to successfully solve this problem with a uniform density mesh.

Further, the authors offer a puzzling criticism of the use of a progressive density mesh: ''The conventional approach is to use fewer computational nodes with a progressively-increasing mesh density in the radial direction from the center towards the wall to provide more accurate modeling of the near-wall region while minimizing CPU time.'' This statement is only partially accurate. The use of a progressively increasing mesh density towards the wall does not decrease the number of computational nodes; in fact, in most cases it will increase their number. The reason for using a progressive density mesh towards the wall, besides the trade-off between the number of computational nodes and the number of iterations needed for numerical convergence which could definitely minimize CPU time, is chiefly because of the steeper velocity gradient in the near-wall region, and the higher spatial resolution needed to successfully resolve these changes numerically. This aspect of numerical simulations of stenotic flows was already recognized by Daly[4] in 1976: ''mesh points are concentrated radially near the arterial wall and axially near the stenosis. The radial concentration near the wall is intended to resolve boundary-layer features, particularly *reverse flow features, shear stress distributions* and pressure variations in the vicinity of the stenosis. The axial variation in mesh resolution is designed to efficiently isolate the flow near the stenosis as much as possible from end effects.'' This is further reiterated by Thornburg *et al.*:[11] ''The location and spacing of the mesh points, not the accuracy with which the grid equations are evaluated, affects the accuracy and stability of the discretized flow equations . . . It is desirable for the grid to vary smoothly near regions of large gradients where grid clustering occurs.''

Progressively mesh density in the radial direction is even of a greater importance in the case of turbulent simulations for two reasons. First, the velocity gradient is steeper in a turbulent velocity profile. Second, the distance of the first computational node away from the wall in the two-equations k-ε family of turbulent models should be in the proximity of $y^+ \leqslant 1$ (y^+ being the nondimensional viscous sublayer height).[12] In numerical simulations that attempt to resolve flow conditions where flow separation and recirculation zones are expected this is crucial, as the instability that may induce a flow separation emerges within the near-wall region.[9] Thus, the use of a uniform density mesh may lead to erroneous results because of the lack of spatial resolution, even if a large enough number of computational nodes is employed. In addition, steady flow simulations tend to smear out spontaneous vortex formation which may be induced by flow instabilities. The strategy to circumvent this when the flow is steady is to run the problem as an unsteady simulation, with an inlet boundary condition of an essentially steady flow profile, which is slightly perturbed.[2]

Another aspect pertinent to numerical simulations which involve areas of flow reversal and recirculation, is the fact that these areas are characterized by low levels of shear stress. The non-Newtonian nature of the blood is

pronounced at low shear stress levels (below 100 s^{-1}).[8] Thus, it is advantageous to conduct the numerical simulation with a viscoelastic fluid model for the blood behavior, e.g., the Casson model, or use actual whole blood data, to characterize better the dynamic behavior of the blood in the low-shear regions. This is even more important in flow studies that attempt to model thrombus formation.

Danny Bluestein

Program in Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, New York

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Authors' Response

Dr. Bluestein has expressed some concerns about certain aspects of our paper entitled ''Enhancement of Stent-induced thromboembolism by residual stenoses: Contribution of hemodynamics.'' In that paper, we report a study of the effects of stenoses on stent-associated thrombosis and embolization. This letter is in response to his concerns.

One of Dr. Bluestein's concerns was associated with the fact that we did not include the geometric details of the stent itself in the computational model of the fluid dynamics. To respond to that criticism, it is important to restate the scope of our study. The complete modeling of the thrombosis/embolization process (a goal toward which we are working) would, indeed, include the monitoring of the wall geometry (including the stent) and small-scale fluid mechanics. That process model would begin with a description of the stent geometry, because initial stent thrombogenecity is influenced by the geometry of the stent as supported by scanning electron microscopy histological sections, etc., presented by other groups[4] and by our own data showing the thrombogenic nature of microscopic flow disturbances in general[7] and wire junctions in stents specifically.[8] However, the ''perforated'' stent structure initially seen by the blood is quickly altered by subsequent growth of the thrombus on the stent, which alters the geometry of the entire ''wall'' (and, hence, the associated flow patterns) in a dynamic fashion. Thus, a correct model would follow the minute-by-minute changes in the wall resulting from the growth of thrombus; the associated fluid mechanics would also be recalculated each minute to account for the evolving wall profile. But details about dynamic thrombus growth are not yet available (we are in the process of acquiring such data), and this detailed process model is not ready. For that reason, describing the wall for the first few minutes of the process (i.e., the stent geometry), without describing the wall throughout the remainder of the process would have been of little value. Instead, this paper was designed to examine the influences provided by stenoses—influences which are relatively constant-throughout the process—and the *overall* effect that those influences have on the intensity of stent-induced thrombosis/embolization. Thus, our only venture into that area with this study was to preform cursory predictions of how mature model thrombi might interact with the flow disturbances associated with stenoses.

Dr. Bluestein expresses concern that we did not display (graphically) the fluid mechanics in the stenoses regions themselves (i.e., the converging region, the apex, and the diverging region). First, the stenoses were outside the regions of interest (which was the stent region). Instead of showing the high shear in the stenoses, we chose to zoom in (as Dr. Bluestein recommends) to the stent area to present the fluid mechanics ''details'' there, where the entering flow streams cause flow attachment, separation, and recirculation. Second, the fluid mechanics in stenoses have been determined and presented before,[12] and nothing of value would have been accomplished by

presenting them. For example, it is well known that the shear stresses in the throat of the stenoses are high, which gave rise to our suggestion that platelets are likely to be activated by the upstream stenoses before they reach the stent.

Dr. Bluestein is concerned about our statement that the small ''kinks'' in our computed wall shear stress distributions are not expected to affect platelet deposition on the stents. First, he questions whether the kinks actually are a result of flow structure, as opposed to being artifacts of the calculations and suggests that a plot of total velocity vectors would have answered that question. We stated in the paper that the kinks are due to the presence of additional, small recirculation zones in that region. Such secondary and minor recirculation zones have been reported by Freitas in certain cases[3]). In fact, our plots of total velocity vectors do suggest such a structure, but only very near the wall, and the region and the magnitude of the velocity changes are small. We could have tried to generate a close-up view of a total velocity vector plot to see those structures, but such an effort seemed unwarranted. We concede that the kinks may have some effect on platelet deposition (our original statement of no effect may have been too absolute), but the variations in wall shear stress produced by them are small compared with those of the larger recirculation zones in the stent region. Further, the flow parameter which appeared to vary most dramatically was the radial velocity proximal to the downstream stenosis, which was not greatly affected by these small kinks.

It is possible that there may be some vortex shedding in the regions associated with the kinks, as suggested by Dr. Bluestein, but it was not very apparent in the qualitative flow visualization experiments conducted as part of this study, and hence an unsteady CFD model was not set up to study dynamic vortex shedding phenomena. Further, Bluestein *et al.* noted that vortex shedding occurred only at $\mathrm{Re} \geqslant 375$ in their study,[1] so it is unlikely that there was vortex shedding in our study where $\mathrm{Re} < 250$ for all cases. However, since the stenosis characteristics used in our study were slightly different from those used by Bluestein, future studies using high-resolution DPIV and intricate unsteady CFD models could attempt to probe this issue further using the Bluestein study[1] as a guide.

The conjecture that these kinks were a result of some numerical anomaly due to insufficient grid resolution seems unlikely, since the reattachment length predictions from the model matched well with those obtained from flow visualization (Table 2 in Ref. 6). Also, simulations were conducted at three mesh densities (6400, 8100, and 10,000), and the solution did not vary significantly between the two higher mesh densities. The authors do not dispute the merits of a progressively dense mesh in the appropriate situation, but since the solution was stable at the higher mesh densities, the use of a progressively dense mesh for this situation was not considered necessary.

Dr. Bluestein expressed surprise at our report that the radial velocity increased towards the center of the conduit near the downstream stenosis, which we have attributed to a separation point in that region. The point at which flow separates from the wall in that region will be associated with an increase in the radial velocity component and a decrease (to zero) of the axial velocity component, as was computed. It must be noted that this point occurs just proximal to the converging section of the stenosis; it is *not within* the converging section of the stenosis. Hence, the argument as to whether such a point can occur within the converging section of a stenosis is moot. Bluestein's statement that flow separation ''hardly ever [occurs] in a converging geometry'' ignores the very common occurrence of separation points *proximal* to flow obstructions (where convergence is not gradual), which are well known and are presented in several standard fluid mechanics textbooks.[9]

Dr. Bluestein pointed out that progressive mesh density is particularly useful in the case of turbulent flow simulations, implying that we should have employed this technique when we used the turbulent model. It may be noted that our turbulent simulations were conducted using the k-ε-RNG model and not the standard two-equation k-ε model. It is well known that many of the standard two-equation k-ε models (e.g., k-ε, k-w^2, etc.) provide relatively poor predictions of flow parameters near the wall.[5,10] Thus, the k-ε-RNG model (employed by FLUENT versions 4.3 and above) was used, because the renormalization group theory improves near-wall predictions of the k-ε model,[2,3,11] and such composite models are generally considered to be state of the art in commercial CFD codes. Further, the first computational node in our study was at $Y^+ = 0.477$, and hence adheres to the condition $Y^+ \leqslant 1$ (based on the following values: $\tau_W = 2\ \mathrm{N\,m^{-2}}$, $y = 32\ \mu$, $\mu m = 0.003\ \mathrm{kg\,m^{-1}\,s^{-1}}$, $\rho = 1050\ \mathrm{kg\,m^{-3}}$). In any case, the requirement that the first computational node must adhere to $Y^+ < 1$ for accurate solutions applies to the standard two-equation k-ε models. The authors are not aware of such a condition for composite models such as the k-e-RNG model.

We acknowledge, as suggested by Dr. Bluestein, that the use of more accurate models (such as the Casson model) for shear-dependent blood viscosity would yield more accurate results for regions of low shear.

Ken Solen

Professor of Chemical Engineering, Brigham Young University, Provo, UT

Sivaprasad Sukavaneshkar

Research Scientist, Utah Artificial Heart Institute, Salt Lake City, UT

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