Discussion: “Comparison of Statistical Methods for Assessing Spatial Correlations Between Maps of Different Arterial Properties” (Rowland, E. M., Mohamied, Y., Chooi, K. Y., Bailey, E. L., and Weinberg, P. D., 2015, ASME J. Biomech. Eng., 137(10), p. 101003): An Alternative Approach Using Segmentation Based on Local Hemodynamics

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Discussion of Rowland et al, "Comparison of Statistical Methods for Assessing Spatial Correlations between Maps of Different Arterial Properties, J Biomech Eng, **137, 101003**, October 2015": An Alternative Approach Using Segmentation Based on Local Hemodynamics

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Abstract

The biological response of living arteries to mechanical forces is an important component of the atherosclerotic process and is responsible, at least in part, for the well-recognized spatial variation in atherosusceptibility in man. Experiments to elucidate this response often generate maps of force and response variables over the arterial surface, from which the force-response relationship is sought. Rowland et al. discussed several statistical approaches to the spatial autocorrelation that confounds the analysis of such maps, and applied them to maps of hemodynamic stress and vascular response obtained by averaging these variables in multiple animals. Here we point out an alternative approach, in which discrete surface regions are defined by the hemodynamic stress levels they experience, and the stress and response in each animal is treated separately. This approach, applied properly, is insensitive to autocorrelation and less sensitive to the effect of confounding hemodynamic variables. The analysis suggests an inverse relation between permeability and shear that differs from that in Rowland et al. Possible sources of this difference are suggested.

1 Introduction

In a recent issue of this Journal, Rowland and coworkers [1] summarized many of the statistical approaches that have been developed to address the problem of local spatial autocorrelation that arises when seeking relationships between pairs of variables defined over a surface. The authors'

motivation, shared by many others in the field, was to elucidate the relation between the spatially varying hemodynamic forces at the blood vessel wall and the well-documented local variation in arterial atherosusceptibility. In the analysis reported by Rowland et al., the hemodynamic environment chosen for study was based on an average map of wall shear stress obtained from steady-flow calculations ("steady WSS", SWSS) in geometries derived from several casts of rabbit thoracic aortae; the vascular responses, obtained in immature New Zealand white rabbits, were albumin permeability, and Oil red O staining (referred to as "lesion prevalence") in hypercholesterolemia. The statistical approaches discussed in Rowland et al. were used to seek relationships between the SWSS map and average maps of permeability and lesion prevalence.

In this Discussion, we describe an alternative means to circumvent the autocorrelation problem, and its use to examine the relationship between several wall shear stress measures and vascular albumin permeability. The vessels of interest in our experiments were the proximal iliac arteries of normolipemic swine, a region and species arguably more relevant to the role of hemodynamic factors in human atherogenesis [2,3].

2 Discussion

In our porcine experiments [4,5], hemodynamic quantities were obtained from pulsatile flow calculations in geometries derived from *in situ* casts of the aortic bifurcation region of three swine, using the input flow waves measured *in vivo* for each animal. Local animal-specific wall shear stress measures were related to albumin uptake in the proximal portions of the six iliac arteries, extending from the origin of each external iliac artery to the orifice of the deep femoral artery. The hemodynamic and histologic datasets from each artery were analyzed separately. Since pulsatile

rather than steady flow was used in the simulations, it was possible to estimate hemodynamic variables that depend on the temporal variation in shear, which non-physiologic steady flow calculations cannot reveal. The maps of computed hemodynamic variables and permeability (from *en face* images) for each animal were correlated by transforming each to a common template, using an affine transformation and 12 landmarks. These landmarks consisted of three points on the transverse perimeter of the pinned out arteries at four stations: the origin of the iliac artery, the orifice of the circumflex iliac artery, midway between the orifices of the circumflex iliac and deep femoral arteries, and the orifice of the deep femoral artery. [6].

The six pairs of maps, each from a different artery, provide more useful data than a single pair of average maps. The availability of multiple individual dose-response datasets permits an alternative approach to the autocorrelation problem, eliminating the need to perform a complex and admittedly imperfect analysis to overcome it. In Himburg et al. [4], the shear exposure in each vessel (ca. 5000 pixels) was binned into tertiles according to magnitude, and the average shear and average permeability in each bin were computed. Owing to the nonuniformity of shear within the branch, the pixels comprising each bin were generally not contiguous, and autocorrelation was not an issue since only a single data point was extracted from each tertile (the process was repeated for up to ten shear bins, with results not significantly different from those reported in [4]). The reduction of the shear and permeability distributions to only three data points in each vessel, each data point representing multiple uncorrelated regions of the wall, effectively eliminates autocorrelation effects and circumvents issues around the use of a single decorrelation length, a concern noted by Rowland et al. in describing their own work.

Furthermore, the aggregation of data points based on a local hemodynamic variable (rather than on

proximity to one another) offers a further advantage in the presence of uncorrelated confounding hemodynamic variables. As noted above, most of the regions formed by the former segmentation were not contiguous; rather, they were comprised of multiple unconnected subregions of vessel wall. Each subregion was necessarily exposed to similar levels of the shear measure of interest, but not of the uncorrelated confounding variable. As the subregions are combined to form a single region in which the measure of interest remains fairly uniform, the distribution of the confounding variable becomes broader, and similar to that in the other regions, effectively diminishing its confounding effect on the correlation sought.

Among the hemodynamic variables considered in Himburg et al., the closest to that examined in Rowland et al. was time-average wall shear stress magnitude, TAWSS. As Rowland et al. point out, it is important to examine individual-level correlations prior to aggregation, to confirm the absence of an "ecological fallacy". In the present case, linear regressions between normalized uptake and TAWSS were performed for each vessel. The confidence interval derived from the slopes of the individual correlations confirmed an inverse relation between the two variables ($p = 0.025$). Having to this extent established the consistency of the individual responses, the data were pooled to generate the inverse correlation reported in Himburg et al. ($p = 0.0014$, $r^2 = 0.48$).

3 Concluding remarks

The relation between hemodynamic stresses and vascular response was studied by generating paired maps of computed stress and measured response in individual arteries, and averaging the response in each distinct vessel over regions exposed to similar levels of the hemodynamic variable of interest. This

approach circumvents the autocorrelation problem and the considerable complexity of addressing it, and reduces the effect of uncorrelated confounding variables. Our conclusion, that there is evidence of a weak (~$TAWSS^{-0.118}$ over the experimental range of shear) inverse relationship between albumin uptake and shear, differs from that in Rowland et al. There are many differences between the two experiments that could explain this, apart from the differences in data analysis methodology: the use in Himburg et al. of multiple flow field simulations based on measured animal-specific flow waves and regional geometries, rather than an average map of steady flow calculations onto a single idealized geometry; the choice of swine rather than the immature rabbit as the experimental animal; and the choice of the proximal iliac artery rather than the intercostal ostia as the vascular region of interest. The presence of a modest shear effect on endothelial permeability is in itself not surprising, given the numerous in vitro studies using endothelial monolayers that demonstrate a cellular responsiveness to many hemodynamic variables at the genomic, molecular and morphological levels.

Although their dataset did not permit it, Rowland et al. note that "Ideally, [flow and histology] datasets should be paired at the individual level", yielding "maps of both variables … in multiple subjects". As the present work demonstrates, we are in strong agreement with the authors in that respect. The concept is not novel; indeed, we first followed that principle some time ago [7] to examine the relationship between pulsatile shear stress and intimal thickness in a set of ten human aortic bifurcations. In those early experiments, the fluid dynamic environment at the vessel wall was estimated from laser Doppler anemometry measurements in flow-through casts of each bifurcation, since few facilities at the time possessed enough computing power to support reasonably realistic flow simulations. With the current state-of-the-art of computational simulation, the attractiveness of this approach is even greater.

Acknowledgments

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