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EDITORIAL

MBEC special issue on microcirculation "engineering principles of vascular networks"

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The (micro)circulation is a very prominent example for the interplay of physical factors with molecular and cellular processes in generating and maintaining crucial structural and functional features of organs and systems in the body. In this special issue, various aspects of this interaction are explored in an attempt to better understand the "engineering principles of vascular networks". An adequate understanding of these principles and their representation in quantitative models will allow meaningful predictions of clinically relevant parameters, as done in the present issue in the article by Wijngaard et al. [18] on subendocardial perfusion in the presence of epicardial artery stenosis.

Since the heart is the first functionally active organ of the embryo, blood flow and to a lesser degree, blood pressure are established very early during prenatal development. Their spatial and temporal (pulsatility) patterns entail relevant information on the functional behaviour of the vascular system. Therefore, it is very logical that these signals are used intensively to control vascular growth and differentiation in order to establish adequate hemodynamic conditions [5, 11]. Direct cellular sensors for both blood flow rate and blood pressure are difficult to envisage and the related physical quantities which elicit responses of vessels and vascular cells (Fig. 1) are most likely shear stress (related to flow rate) and circumferential wall stress (related to blood pressure).

The importance of shear stress (flow) for the control of vascular network design is evidenced by the fact that it is addressed in a larger fraction of the articles in this special issue [6, 7, 11, 14]. A key feature is the translation of shear stress into a biological response. Thus, shear stress elicits the release of molecules such as H_2O_2 and nitric oxide, that cause flow-mediated dilation. In this issue, Liu et al. [6] show that the cytoskeleton of endothelial cells, directly exposed to the flowing blood, are a critical component herein. Shear stress is not always steady, as in organs such as the heart, where blood flow is pulsatile due to the contraction of the myocardium. This pulsatile flow modulates the release of nitric oxide, a labile molecule that can be detected by a catheter-type sensor [2].

Shear stress also relates to the best known engineering concept for vascular design, 'Murray's law [10]: If the shear stress is the same in all vessels of a vascular bed, the overall energy requirement for blood flow and maintenance of the blood and the vessels is minimal. Minimizing energy consumption, however, is a goal which is secondary to the fulfillment of the central biological requirements of the circulation, e.g., adequate distribution of oxygen, low capillary pressures and a large regulatory capacity in the distal arterial tree. Therefore, living circulatory systems show substantial deviations from Murray's predictions as discussed in this special issue by Renemann and Hoeks [14]. One obvious example is the arterio-venous difference of average shear stress levels [13]. Also, it was stated by

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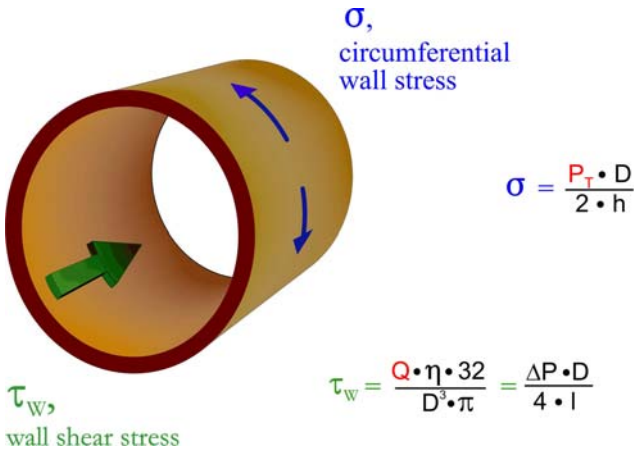

Fig. 1 Fundamental physical stresses derived from blood flow which act on vessels (P_T transmural pressure difference, D vessel diameter, h wall thickness, Q blood flow rate, η blood viscosity, ΔP pressure difference along a unit vessel length, l vessel length)

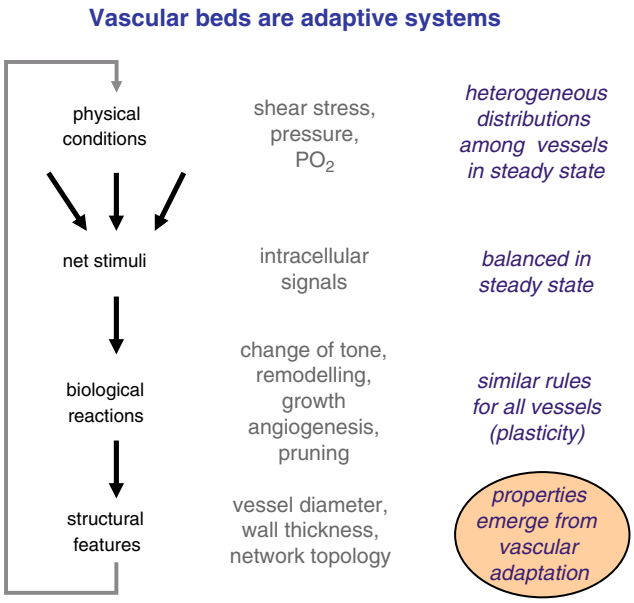

Fig. 2 Scheme for the adaptation of vascular networks. *Left column* gives the different levels involved, while in the *middle column*, corresponding examples are listed. *Right column* indicates relevant characteristics of the different levels. It is of central importance, that the emergent properties of the system are fully dependent on the internal reaction patterns. Since there are no locally imposed limits with respect to the resulting structural or functional network properties, the biological reactions have to be finely balanced under physiological conditions. In pathophysiological settings, where either the reaction patterns are changed or the boundary conditions leave the suitable range (e.g., hypertension, or arterio-veneous shunts) vascular reactions may lead to unfavorable properties of vascular beds. The scheme shown would also represent the basic outline for suitable computational models of vascular adaptation

Rodbard as early as 1975 [15] and later analyzed theoretically by Hacking et al. [3] that an isolated vascular adaptation to shear stress involves the risk of positive feedback loops eliminating parallel flow pathways and thus severely compromising tissue oxygen supply.

Such observations show that in order to better understand the engineering principles of the vascular system more factors than shear stress alone have to be taken into account, most notably blood pressure (circumferential stress) and the metabolic state of the tissue [12]. Also, the diversity of reactions at the biological level has to be represented in more detail in functional or engineering concepts. Examples are the discussion of the importance of vascular tone in the remodeling response of resistance arteries to hypertension in the present issue [8] and the earlier demonstration of the requirement for information transfer along vessel tress, e.g., by conduction of electrical signals [12]. The role of vasomotor control and its regulation is addressed by the studies of Duncker et al. [1] and by Trzeciakowski and Chilian [16] in this issue. Also, van den Akker et al. [17] dissect the process of vascular remodeling down to the interaction of smooth muscle cells with collagen, a stiff component that forms the backbone of the vessel wall.

Improvements of the available concepts describing the role of physical factors as determinants of (micro)vascular structure and function will probably entail a number of components: (1) A better assessment of the physical forces and effects under different normal and pathological states. (2) A better representation of the biological reaction patterns to these forces. (3) Improved computational models (Fig. 2) which allow interpreting the impact and role of individual mechanisms (both on the physical and the biological level) in a quantitative fashion.

Taken together, this volume provides a framework for understanding the engineering principles which appear to govern the development and adaption of the highly adaptive and dynamic entity, we are interested in, i.e., the vascular system [4, 9]. Future work will be directed to coordinating these principles with a view to providing robust models which can be used for predicting therapies which may be beneficial in the treatment of vascular pathology.

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