Structural Abnormalities of the Resistance Vasculature in Hypertension

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In this number, Bund and Lee [1] provide a timely review concerning some of the problems associated with measurement and discussion of the structural abnormalities in the resistance vessel which are associated with hypertension. The review has three parts. First, the authors describe the various methods which have been used to measure the structure of resistance vessels, and the limitations involved. Second, the authors review current ways of classifying the structural abnormalities which are found. Third, the authors discuss the extent to which the structural changes have functional consequences.

In the first part, the authors identify the paradox that although there is general agreement that resistance vessel structure is altered in hypertension compared to normotensive controls, it is a difficult quantity to measure. In vivo studies of vascular resistance measured under conditions of complete relaxation provide a sensitive comparison of apparent resistance vessel diameter, but are difficult to interpret, since any differences could be due to differences in vascular architecture rather than structure of the individual vessels. In vitro studies of isolated resistance vessels have the advantage of precise measurements of vascular dimensions without fixation artefacts, but suffer from the difficulty that there is no clear agreement as to the length to which vessels should be set. Histological studies have the advantage of allowing global analysis, but may be compromised by unintended activation of vessels

during fixation, and lack of knowledge of the intravascular pressure during the process. None of the methods is therefore perfect, and the authors conclude correctly that it is unwise to draw strong conclusions alone on the basis of results from one method. Nevertheless, if measurements are confined to a comparison of the ratio of wall thickness to lumen diameter 'wall:lumen' (or, with measurements of tunica media thickness, 'media:lumen'), ratios at a given lumen, all methods are in agreement that this parameter is increased in hypertension, at least in the more proximal resistance vessels. The difficulty arises as soon as comparison is to be made of lumen diameters, or of the wall (media) cross-sectional areas, since here all of the methods are faced with the fundamental problem of comparing vessels from different individuals. Vascular architecture differs between individuals even of the same strain, and substantial differences in architecture between strains have been documented [2]. Thus, for example, a 'third branch' in one animal may be at a different level in another.

Bund and Lee allude to the problem of vessel comparison between individuals, but do not give an indication of how this could be solved beyond reference to the 1965 work of Short [3], who studied the entire human mesentery. A less time-consuming method can, however, be envisaged to obtain a global and reliable measurement. It would, for example, be possible to perfusion-fix a whole

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vascular bed (e.g. the mesenteric vascular bed) and assess the vascular structure statistically. That is, measurements could be made of randomly selected vessels in sufficient number to allow precise estimates of average dimensions. One approach would be to use the fractionator technique [4] to select a known fraction of the material, and then measure all arteries within this fraction following the principles described previously by Skov et al. [5] for measurements of the structure of renal afferent arterioles. The results would allow statements about average resistance vessel lumen diameter and average media:lumen ratio, and could thus address the question of whether there has been growth. This is to some extent similar to the approach of Short [3], but would have the advantage that the use of the fractionator would obviate the need to examine the whole vascular bed as he did, while the techniques of Skov et al. [5] allow the vasculature to be fixed while relaxed and under known intravascular pressure.

In the second part of their review, the authors take issue with the current use of the terms 'hypertrophic', 'eutrophic' and 'hypotrophic' remodelling to describe structural abnormalities which are associated with, respectively, increased, unaltered and decreased vascular mass as previously recommended by Mulvany et al. [6]. The authors emphasise the limitations raised by Mulvany et al. and conclude that there are so many reservations that the terms become meaningless. Instead they refer to the approach proposed by Folkow [7] to simply provide information about the measurements made. Thus if it was found that lumen diameter was reduced by 10%, and media:lumen ratio was increased by 20%, and (hence) calculated media cross-sectional area was essentially unchanged (−1%), this would be given as 'L (−10%), M:L (+20%), MCSA (−1%)'. Mulvany et al. would have referred to this as 'inward eutrophic remodelling'. Although Bund and Lee's approach has the advantage of purity, it implies a degree of precision which is hardly achievable in practice. More importantly, their approach loses what I see as the conceptual advantage of the approach of Mulvany et al., which emphasises that observed increases in media:lumen ratio do not necessarily imply growth [8], and may indeed be associated with a reduced amount of material [5]. This may be of importance when trying to understand the mechanisms of remodelling. Thus the growth mechanisms observed in cell culture experiments may not be relevant to resistance vessel remodelling in hypertension, if hypertension is in fact associated with eutrophic or hypotrophic processes, a concern supported by recent experiments [9].

For this reason, despite the numerous caveats given by Mulvany et al. [6] and repeated by Bund and Lee, I should be loathe to recommend dropping the description of remodelling being hyper-, eu- or hypotrophic. It would, however, probably be more satisfactory if, in contrast to the original recommendations of Mulvany et al. [6], the term remodelling was taken just as a morphological term to refer to structural differences without preconditions, i.e. regardless of whether the altered structure is due to altered synthesis, altered apoptosis, rearrangement of material, altered cell number, altered cell volume, or altered elastic modulus. Moreover, it could be argued that the calculations of growth index and remodelling index [10] – in the example above these would be −1 and 103%, respectively – are more precise than measurements warrant. Thus, I would accept that many of Bund and Lee's objections are correct, but their proposed nomenclature also has the difficulty of implying unobtainable precision, nor is it particularly easy to understand. On the other hand, in my view, the concepts of hyper-, eu- and hypotrophic remodelling are readily understandable, and are relevant to relating abnormal vascular structure to pathological processes.

In the third part, the authors refer to the ongoing discussions as to whether structural change has functional consequences. Despite the clear implication of the Laplace relation that an increased wall:lumen ratio should (for a given degree of smooth muscle activation and given wall stress) give a stronger narrowing, it has been surprisingly difficult to demonstrate this. Under *in vivo* conditions, support is only found under conditions of heroic efforts to minimize feedback mechanisms [11], and even under *in vitro* conditions evidence has been lacking [12]. Thus, the concept that an increased pressor response causes increased pressure, and compensatory increased wall:lumen ratio that in turn helps to maintain the pressure at the increased level appears to be fallacious. Instead, as pointed out previously [13, 14] it seems more fruitful to recognize that blood pressure is determined by a large variety of factors (e.g. the factors responsible for water homeostasis [15]), and that the blood vessels are the effector organ of this blood control system. If these extra-vascular factors call for a sustained requirement for vascular narrowing and/or raised intravascular pressure, the resistance vessels remodel to allow them to maintain the reduced lumen with normal activation level and normal wall stress. The end result is that hypertension is associated with altered vascular structure ('the hallmark of hypertension'), but normal levels of sympathetic and plasma renin activity. But it is not the resistance vessels which are

the 'cause' of hypertension, the cause is due to the mentioned extracellular factors which are calling for the high blood pressure.

In conclusion, Bund and Lee are to be thanked for providing a framework for reconsidering how we should be measuring structure of the resistance vasculature. As they

point out, the pitfalls are numerous, and interpretations are often at best simplistic and at worst incorrect. Given the huge amount of effort now being devoted to unravelling the mechanisms of vascular growth, it is clearly important that we develop better methods for determining what actually happens in the intact organism.

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