Editorial Comment

New Directions for Microvascular Research in Hypertension

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The studies by Boegehold and Kotchen and le Noble et al represent directions for microvascular research in hypertension that are virtually unexplored. Although microvascular research techniques have been extensively used in the study of spontaneously hypertensive rats (SHR) and rats with renal vascular hypertension, the study by Boegehold and Kotchen will be among the first, if not the first, to use in vivo microscopy to determine to what extent vasoconstriction and vessel closure contribute to the abnormal vascular physiology of the Dahl salt-sensitive rat. The initial study on these issues by Boegehold and Kotchen is the first step in what will undoubtedly become a major area for microvascular research on Dahl rats. The study by le Noble et al is also a first step for a new direction in microvascular research in hypertensive animals. Although the use of conscious animals to independently study microvasculature and hypertension is well established, their simultaneous evaluation is essential in the translation of increased vascular resistance to specific in vivo abnormalities of the microvessels. By avoiding the potentially detrimental effects of both anesthesia and acute surgical trauma, microvascular studies in conscious hypertensive animals may allow us to better appreciate what features of past and future research on acutely prepared animals are exactly correct or potentially misleading. It is very fitting that this new direction of research involves Dr. Phillip Hutchins because he was, if not the first, one of the first investigators to study the in vivo microvasculature of SHR. Since his first study with Alice Darnell almost 2 decades past, studies of the microvasculature in virtually every organ system and type of hypertension have been published and now, with the work of Boegehold and Kotchen, the Dahl form of hypertension is included.

The studies by Boegehold and Kotchen and le Noble et al point out two ongoing issues that are common to the majority of in vivo and anatomic studies of the microvasculature. These issues are where in the microvasculature and to what extent by vasoconstriction and vascular rarefaction is the vascular resistance increased. Both of the current studies indicate that larger, rather than smaller, arterioles of the hypertensive skeletal muscle microvasculature are constricted. Because of the lack of in vivo observational and microvascular pressure measurements in Dahl rats, a great deal of additional work will be required to pinpoint the specific locus of increased resistance. However, for studies of SHR there are sufficient data to comment on several trends. Only a minority of the published reports have found constriction anywhere in the skeletal muscle microvasculature of SHR, other than the finding of temporary closure of the smaller arterioles in lower body muscles. Whether these findings are influenced by the specific vasculatures that have been studied or the possibility that muscle vasculatures are easily compromised by anesthesia and surgery is debatable. However, with similar anesthetics and various degrees of surgical manipulation, vasoconstriction of the largest and smallest arterioles in the intestinal and cerebral vasculatures of both SHR and renal vascular hypertensive rats is routinely found. If one accepts the analysis of Borders and Granger that power dissipation in the microvasculature rather than in vessel diameters per se should be used to evaluate the overall resistive properties of the microvasculature, then the larger arterioles provide the major component of total microvascular resistance. Direct measurements of microvascular pressure dissipation in the normal and hypertensive vasculatures basically support this concept. However, these measurements add the additional information that the smallest arteries have a resistance that is similar in magnitude to that of all the arterioles combined. Whether small arteries or larger arterioles are also likely to be the major sites for resistance regulation during hypertension remains to be proven by future studies. Another factor that should be kept in mind is that even if a vessel has a completely normal diameter in a hypertensive animal, this does not mean that the vessel fails to participate in the hypertensive process. To maintain either a normal or reduced diameter, calculations of both wall tension and stress indicate that virtually all vessels face a 30–50% force overload on the vessel wall, with the possible exception of those in the cerebral vasculature.

The issue of how force overload on the vessel wall interacts with normal compensatory functions and any inherited abnormalities of the resistance vessels is far from settled. However, there are past and recent studies that in combination offer a new perspective. For example, with the possible exception of the smallest...
arterioles, virtually all macroscopic and microscopic resistance vessels experience about the same proportional increase in microvasculature pressure in various vasculatures of SHR\(^{6,8}\) and, to some extent, renal vascular models of hypertension.\(^5\) Furthermore, from the largest to smallest arterioles of SHR there is about a threefold to fivefold difference in wall tension, and for a given vessel type, wall tension is 30–50% higher than in normal rats. It would be expected that the major differences in wall forces between different-sized vessels in normal animals as well as between comparable types of vessels in normal and hypertensive animals should induce some degree of vascular hypertrophy, hyperplasia, or both. However, this does not seem to occur, although the type of data to be mentioned is only currently available for the intestinal microvasculature. Miller et al\(^{10}\) have shown, using scanning electron microscopy, that the length, shape, and average diameter of vascular smooth muscle cells are almost identical from the largest to smallest arterioles of normal rats and are statistically equivalent to the same morphological indexes in hypertensive rats. Furthermore, the number of vascular smooth muscle cells per unit length of microvessel was virtually identical for equivalent types of arterioles in SHR and normal rats. In contrast, it is well established that the mesenteric arteries that precede the intestinal arterioles have an enlarged muscle due to a combination of cellular hypertrophy and hyperplasia.\(^{11,12}\) Why does such a difference exist between macroscopic and microscopic vessels during hypertension? Perhaps just as in skeletal muscle, there is a threshold overload required for vascular muscle cell growth that is exceeded in the macrovasculature but not the microvasculature. In any event, whether by differences in compensatory mechanisms or inherited characteristics, arteries and arterioles exhibit remarkably different anatomic and, presumably as a result, functional changes during hypertension.

In addition to the new microvascular research directions mentioned, an equally important directional change is occurring in the size and methodology used to study cellular mechanisms that influence the regulation of resistance vessels. In recent years, studies of isolated resistance vessels have made the transition from the macroscopic to nearly microscopic arteries and, in many laboratories, to large and intermediate diameter arterioles. The use of isolated vessels, whether of macroscopic or microscopic dimensions, has clearly shown that, when physical forces in the vessel wall can be readily controlled and measured, the ability to explore specific cellular mechanisms that regulate force development is substantially improved. Although in vivo microvascular studies have been, and are currently, exploring specific cellular mechanisms that influence vascular diameters, the correlation of microvascular cellular mechanisms to specific changes in force development that modulate the diameter responses is the mechanistic approach needed. Although such studies are difficult, they are well within the current technological capabilities available. It is my opinion that this direction for in vivo microvascular research will lead to expression of microvascular responses in terms of how specific cellular mechanisms alter vessel dimensions through changes in force development by microvessels in their natural physical and chemical environment. Studies of this type will be a fundamentally important bridge to connect concepts that evolve from the in vitro study of vascular tissues to how these mechanisms are expressed in the complex interactive system of the intact microvasculature. In addition, in vivo studies of this type will undoubtedly spawn new questions and concepts about cellular mechanisms that will require both the development of new directions for research and greater interaction between in vitro and in vivo microvascular research. What is learned from this increasing overlap of methodological approaches and interests may teach us which abnormalities in hypertension are inherited to the detriment of the organism or compensatory to protect microvascular function within the tissues.

References


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