

Council's Corner: Hypertension Issues - a personal view



Hermann Haller
Hannover Medical School
Clinic of Nephrology and Hypertension
Carl-Neuberg-Straße 1
30625 Hannover, Germany

I have not always been a “vascular “person. When I first entered the field of hypertension research as a young doctoral fellow my research topic was the effects of the hypothalamus on the kidney.

Under the supervision of Wolfgang Oelkers who had trained at the MRC Unit in Glasgow I tried to find out whether and how ACTH influenced RAAS. Besides the fact that we found a small but significant effect of ACTH on the renin-angiotensin system, the most important lesson was the rigorous training of clinical research and the enthusiasm of working with patients. So I entered hypertension research as an endocrinologist with a profound belief in the importance of the RAAS in hypertension. However, when I entered Nephrology and the research group of Armin Distler and Thomas Philipp in 1983, it was all blood vessels, and contraction which mattered in the pathogenesis of hypertension. As today, the concept of hypertension in 1983 was that it is either (1) an increased vaso-constriction in arterioles or (2) an increased activity in the heart or (3) the increased sodium uptake in the kidney or (4) a mechanism influenced by the altered circuits in the brain. So, as of today, the kidneys, vascular tone and the brain were supposed to be the culprits either alone or together in the pathogenesis of hypertension. My research group was concentrating on increased contractility. Thomas Philipp had described that vascular receptors in hypertensive patients were more responsive to catecholamines and my first task was to address intracellular signalling in vascular smooth muscle cells. It was well-known that calcium is important in the regulation of cellular contractility and since the first measurements of intracellular free calcium had just been made possible by the introduction of fluorescent dyes I tried to measure intracellular free calcium in patients with essential hypertension. The hypothesis was that a disturbance in intracellular calcium signalling, either by calcium influx through membrane channels or by an increased release from intracellular stores is altered in hypertensive patients. This assumption was supported by the antihypertensive effects of calcium channel blockers in patients with essential hypertension. Since vascular smooth muscle cells were not accessible in our hypertensive patients, we used what we thought at that time to be a circulating contractile cell type i.e. the platelet from hypertensive patients. I learned the method in the laboratory of Fritz Bühler and Paul Erne in Basle and we were able to demonstrate that intracellular free calcium concentration in patients with essential hypertension was increased and that it could be manipulated both to increase and to decrease in accordance with changes in blood pressure. I still believe that a disturbance in vascular smooth muscle cells is important in the pathogenesis of hypertension. At the time there was a raging debate whether this is an intrinsic alteration of contractility or whether there are structural alterations in the vessel wall which mediate the increase in resistance. The excitement of the scientific discussions and the battles which were fought between functional and structural believers is still a fond memory.

The vascular hypothesis of hypertension, although still important, has lost some ground in the era of genetics. Most genetic alteration and possible candidate genes which have been associated with high blood pressure and hypertension have been found in the kidney. The last example is uromodulin which shows a strong association both with hypertension and the progression of renal disease. Most likely uromodulin, which is a tubular surface molecule interacts with transporters in the renal tubules and influences thereby sodium uptake and, possible, fibrosis. This indicates that at least in some patients with hypertension the kidney and sodium still play a major role. This hypothesis is strongly supported by the fact that most monogenetic forms of hypertension have been associated with sodium transport and renal mechanisms. However, recently the first monogenetic disease which is caused by a dysregulation in vascular smooth muscles has been described. Friedrich Luft and his research group, where I had the privilege to be a member of 20 years ago, found and described the first “vascular” gene in a monogenetic form of hypertension and brachydactily. The gene codes for phosphodiesterase-3 and, in families with hypertension, is hyperactive and leads to an increased breakdown of cyclic GMP. To what extent these genetic disturbances contribute to the increased vascular resistance in patients with so-called essential hypertension remains to be identified. At least in one genome-wide analysis PDE-3A has been found to be associated with hypertension. This makes it possible that some patients have a vascular disturbance as the cause of hypertension.

The vascular hypothesis of hypertension was dramatically influenced by the identification of NO and its role in vascular regulation in the early nineties. All of a sudden, the endothelium and its altered state in hypertension were of central interest. The endothelial cells are not only important in regulating vascular tone by secreting NO but also basic constrictive substances bound as an interface between the blood and the vessel wall they play a role in cardiovascular disease in general. These cells and their regulation became of central interest to my research group. We strongly believe that unravelling the disturbances of the endothelial cells will not only help us to understand hypertension but also the pathogenesis of chronic vascular disease. Numerous studies have shown that the endothelium is changed in patients with hypertension. However, it was and still is much more difficult to find out whether these are primary intrinsic differences or whether the endothelial cells are the first culprit of an increase in hypertension. After a long time in endothelial cell research I tend to believe that endothelial cells do not have a primary alteration in patients with hypertension but are suffering from the increased stress by hypertension and other risk factors in these

patients. However, it cannot be ruled out that the endothelial cells may have a different responsiveness in patients with a genetic basis for hypertension and are more susceptible to damage. After all, PDE-3 is also strongly expressed in endothelial cells.

One property of the endothelium which has been a research interest of mine in the last few years may be of central importance in the pathogenesis of hypertension. It is only recently that the early reports of inflammation and its relationship with hypertension have been confirmed and extended in a more rigorous manner. We now have a multitude of studies demonstrating that the pathogenesis of hypertension is intricately linked to specific inflammatory mechanisms. This work which was pioneered by Harrison and others suggests that hypertension is a specific immunological response and that T-lymphocytes and monocytes are directly linked to an increase in blood pressure. In this inflammatory response the endothelium also plays a major role. Leucocytes within the blood stream have to enter the vascular wall through the endothelial cell layer. The secretion of chemokines and the expression of adhesion molecules are important steps in this set of events. How the inflammatory cells induce an increase in high blood pressure and whether the endothelial cells are involved in either the generation of epitopes which induce the immunological response or whether they are mostly responsible for the immigration of white blood cells into the vessel wall remains to be solved. However, I believe that the interaction between the inflammatory mechanisms and the vessel wall are of wider importance in the pathogenesis of hypertension.

In recent years the neuronal circuits especially the sympathetic system have become more important in the pathogenesis of hypertension. As always, the introduction of a novel device to interfere with a specific pathogenetic mechanism has led to a lot of activity. Without addressing first the issues of the underlined pathophysiology we (especially in Germany) embarked enthusiastically on interventional procedures in patients with severe hypertension. I strongly believe that the sympathetic nervous system plays an important role in hypertension. The intimate relationship between neuronal cells and the vasculature, the tubulus system and other organs makes it more likely than not that the nerve fibres strongly influence the behaviour of sodium reabsorption and contractility. This relationship has been shown in elegant pathophysiological studies by DiBona and others. However, because this relationship is so delicate and balanced, it is important to find out which mechanisms are responsible and to define patients most likely to have hypertension on the basis of increased sympathetic tone and who therefore may benefit from medical therapy.

So based on my view of hypertension, what role does the kidney play? As I am a nephrologist I believe that this is most likely a central one. Classically, it was the increase in sodium absorption on the one hand and the release of ACE-active hormones on the other which kept the kidney in the centre of blood pressure regulation and hypertension. Genetic studies in families with monogenetic hypertension have strongly shown that a variety of elements are involved in tubular sodium reabsorption and the pathogenesis of hypertension. We have been concentrating on specific defects in transport systems and signalling molecules. However, in the last couple of years we have found that these mechanisms may be even more complicated.

In summary, my view on hypertension has been strongly influenced by my scientific life with hypertension. I was once fully convinced that vascular resistance is the culprit in the disease and my centre of the hypertensive universe. However, over the years, endothelium, nerve fibres and renal cells have appeared and make a more complex picture. It is like in a museum: the older I get the more I am interested in the complexity of baroque paintings and consider my favourite renaissance paintings to be one-dimensional. However, complexity is no excuse for not finding out how it works. And that is still the real challenge: which of these mechanisms we have so successfully described and characterized over the last 30 years is active in our hypertensive patient?

- Hermann Haller

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Cheol-Ho Kim

Seoul National University Bundang Hospital
Seoul National University College of Medicine
Seoul, South Korea

It was my great pleasure to be elected as an ISH Council Member in 2012. One of my main aims of joining Council was to act as a link between the ISH 2016 Seoul Biennial Scientific Meeting Local Organising Committee and the ISH leadership and maximise the opportunities for scientific exchange at this event. Since my election, I have been working with my local colleagues to determine the main theme and topics to be discussed at the meeting (Hypertension Seoul 2016).

Hypertension Seoul 2016
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