Excess aldosterone as a mechanism of resistant salt-sensitive arterial hypertension

IMPACT PARAGRAPH

As Max Planck stated in 1923, “Science does not recognize national borders; its limit is simply the limit of human knowledge.” Knowledge is universal in nature, and it is critical in order to stay competitive in an ever-changing world. Academic research, the most important source of cutting-edge knowledge, along with government and industry, is the critical pedal to build a knowledge-based economy in any country. In this respect, basic research is the basis for economic innovation.

Even if they do not offer an immediate commercialized solution to cardiovascular problems, the findings presented within this thesis provide novel insights that may have potential implications for clinical practice and future research in cardiovascular diseases.

Because of the high prevalence and poor rate of blood pressure control, arterial hypertension (HT), and in particular drug-resistant hypertension (RH), is the major cause of mortality and early disability worldwide. It is a major risk factor for stroke, coronary heart disease and heart failure with an estimated cost of €169 billion in the European Union[1]. The disease burden and related costs of HT are thus substantial and call for continuous effort to control this condition. In this respect, the identification of the cause of HT and the underlying pathophysiology is crucial since it allows achieving cure of the HT, especially in younger patients, or, when this is not feasible, a better control of blood pressure and a better prevention of specific target-organ damage and cardiovascular events by a more targeted pharmacological treatment.

Previously considered a rare disease, recent prevalence studies demonstrate that PA is a very common and vastly underdiagnosed etiology of HT, particularly RH[2–4]. It is caused by inappropriately high aldosterone production, relatively autonomous of renin-angiotensin system and non-suppressible by sodium loading. Such inappropriate production of aldosterone causes HT, cardiovascular damage, sodium retention, suppression of plasma renin, and increased potassium excretion that (if prolonged and severe) may lead to hypokalemia[3]. Lack of mechanistic knowledge has impaired the development of effective preventing strategies and timely diagnostic strategies. This results in late, or even missed diagnoses with raising development of RH and cardiovascular complications.

The first objective of this thesis was to demonstrate the crucial importance of identification of PA in resistant hypertensive patients, a well-characterized subgroup of HT patients with distinct demographics, comorbidities, and metabolic abnormalities. Our findings suggest that adrenal vein sampling (AVS), the key procedure for PA subtyping, is feasible and

allows identification of unilateral PA in RH patients, a challenging PA phenotype owing to the need of multiple antihypertensive drugs potentially confounding AVS results. Moreover, AVS-guided adrenalectomy allows biochemical cure and resolution of RH in those with underlying PA, with a prominent clinical benefit in spite of severity of HT and presence of hypertension-mediated organ damage.

To further understand the positive effect of biochemical cure of PA, we assessed the impact of surgery on health-related quality of life (both in Mental and Physical components) and, for the first time, depression status of patients suffering from PA. In agreement with previous studies, we confirmed that patients with PA have an impaired health-related quality of life compared with normal population and that PA affects the quality of life by worsening the mental component and the depression status. The biochemical cure of PA by surgery improves the mental component of health-related quality of life and depression status at 1 month after adrenalectomy and at long term. In the long term, surgery determines an improvement also in the physical component of health-related quality of life of PA patients, confirming the beneficial effect of adrenalectomy.

Finally, since the pathophysiology of HT is not always clear, elucidation of the role of environmental influences, especially the role of dietary salt intake and the salt sensitivity of BP, is urgently needed. Recent studies have demonstrated that sodium and water homeostasis is far more complicated than previously assumed and emphasized the role of sodium storage and the immune system in sodium balance[5–7]. In this respect, to gain further insight into the mechanisms by which salt increases BP, we have investigated if extracellular skin Na^+- storage occurs in humans affected by PA, a suitable model to explore the changes in skin-Na^+ content in relation to aldosteronism and its surgical correction. Our results suggested that Na^+ is stored in the skin of PA subjects without concomitant water retention, suggesting that a certain amount of Na^+ is osmotically inactive and implying that tissue-specific regulatory mechanisms might control the release and storage of Na^+ from a kidney-independent reservoir. Importantly, Na^+ accumulation in the skin seems to be reversible after unilateral adrenalectomy, but not medical treatment.

The presence of a third compartment, in which sodium can be stored without concurrent water retention, is of a crucial importance in HT and even more in PA. In fact, given the currently disappointing status of blood-pressure control worldwide, which derives from both imprecise knowledge of the underlying mechanisms and the pathophysiologic diversity of hypertensive patients, it is evident that mechanistic investigation of extracellular tissue Na^+ storage, is front-of-the-edge research that can have a huge impact

from multiple standpoints, including identification of novel diagnostic and prognostic markers and more specific therapeutic targets for pharmacologic interventions.

References

1. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: Epidemiological update 2016. Eur Heart J. 2016; 37:3232–45.
2. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gidding SS, Judd E, Lackland DT, Laffer CL, Newton-Cheh C, Smith SM, Taler SJ, Textor SC, Turan TN, White WB. Resistant hypertension: Detection, evaluation, and management. A scientific statement from the American Heart Association. Hypertension. 2018; 72:e53–90.
3. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016; 101:1889–916.
4. Rossi GP, Seccia TM, Gallina V, Muiesan ML, Leoni L, Pengo M, Ragazzo F, Caielli P, Belfiore A, Bernini G, Cipollone F, Cottone S, Ferri C, Giacchetti G, Grassi G, Letizia C, Maccario M, Olivieri O, Palumbo G, et al. Prospective appraisal of the prevalence of primary aldosteronism in hypertensive patients presenting with atrial flutter or fibrillation (PAPPHY Study): rationale and study design. J Hum Hypertens. 2013; 27:158–63.
5. Titze J, Lang R, Ilies C, Schwind KH, Kirsch KA, Dietsch P, Luft FC, Hilgers KF. Osmotically inactive skin Na+ storage in rats. Am J Physiol - Ren Physiol. 2003; 285:F1108–F1117.
6. Rakova N, Jüttner K, Dahlmann A, Schröder A, Linz P, Kopp C, Rauh M, Goller U, Beck L, Agureev A, Vassilieva G, Lenkova L, Johannes B, Wabel P, Moissl U, Vienken J, Gerzer R, Eckardt KU, Müller DN, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na+ balance. Cell Metab. 2013; 17:125–131.
7. Machnik A, Dahlmann A, Kopp C, Goss J, Wagner H, Van Rooijen N, Eckardt KU, Müller DN, Park JK, Luft FC, Kerjaschki D, Titze J. Mononuclear phagocyte system depletion blocks interstitial tonicity-responsive enhancer binding protein/vascular

endothelial growth factor c expression and induces salt-sensitive hypertension in rats. Hypertension. 2010; 55:755–761.