Acceptance of the 2003 Jean Hamburger Award

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Thank you, Professor de Wardener for your kind comments as well as your support and friendship for many years. I appreciate the honor of sharing the Jean Hamburger Award for clinical research from the International Society of Nephrology with my friend Stewart Cameron. I accept the Jean Hamburger Award on behalf of over 100 fellows from 27 countries who have worked and published with me for more than 30 years. There have been several major areas of our research that have focused on important clinical problems, including acute renal failure (ARF), arginine vasopressin (AVP) and body fluid volume regulation, autosomal-dominant polycystic kidney disease (ADPKD), and type 2 diabetic complications.

ACUTE RENAL FAILURE

Our ARF studies focused on the pathogenic role of increased cytosolic calcium concentration in tubular epithelial and vascular smooth muscle cells (VSMC). In proximal tubular epithelial cells (PTC), ischemic injury was associated with increased Ca^{2+} influx, mitochondrial Ca^{2+} overload, and impaired respiration. Subsequently, the Ca^{2+}-dependent protein, calpain, was found to be activated in PTC during hypoxia and associated with tubular injury. A relationship between activation of calpain and caspases also occurred in hypoxic PTC, thereby leading to caspase and interleukin-18 (IL-18)–related injury. A rise in glomerular afferent arteriole Ca^{2+} concentration also occurred during renal ischemia and was associated not only with loss of autoregulation but also increased sensitivity to angiotensin II (Ang II) and endothelin (ET). These vascular renal effects could be markedly attenuated with atrial natremic peptide (ANP) in the isolated ischemic perfused rat kidney or with intrarenal ANP in humans. Systemic ANP, however, was associated with declines in mean arterial flow pressure (MAP) in prospective randomized negative studies in patients with ARF; the systemic hypotensive effect of ANP may have obscured any beneficial renal effect.

With renal ischemia and hypoxia or sepsis, nitric oxide (NO) was shown to have a deleterious effect on tubules, in part by combining with reactive oxygen species (ROS) to form the injurious compound, peroxynitrite. On the other hand, the vasodilating effect of NO has been shown to be protective against ischemic injury.

In sepsis-related ARF, the early (16 hours after lipopolysaccharide) phase appears to be related to increased endogenous vasoconstrictors, including norepenephine (NE), Ang II, and ET, which attenuate the systemic vasodilating effect of NO at the expense of secondary renal vasoconstriction. Oxygen radical scavengers and blockade of tumor necrosis factor-alpha (TNF-α) were also shown to be beneficial early in experimental sepsis-related ARF. The later proinflammatory phase of sepsis-related ARF involves cytokine and chemokine activation associated with cellular infiltration.

NONOSMOTIC RELEASE OF AVP AND BODY FLUID VOLUME REGULATION

AVP release was shown to occur independent of osmolality and to be baroreceptor-mediated in settings of arterial underfilling secondary to either a decrease in stroke volume and/or arterial vasodilation. Thus, the term nonosmotic AVP release was coined. Further studies in experimental and human cardiac failure, cirrhosis, and pregnancy demonstrated an increase in radioimmunoassayable AVP despite a degree of hypoosmolality, which would maximally suppress plasma AVP in normal subjects. The use of V_2 vasopressin antagonists were shown to reverse the water retention, thus confirming the role of nonosmotic AVP release in edematous disorders. In experimental and human cardiac failure the nonosmotic AVP release up-regulated aquaporin 2 (AQP-2) water channels, an effect which could be reversed in the renal papilla and urine, respectively, with orally active, nonpeptide V_2 antagonists. The arterial underfilling in cirrhosis and pregnancy occurred secondary to arterial vasodilation, which was mediated, at least in part, by NO. In this regard, nitric oxide synthase (NOS) inhibition was shown to profoundly reverse the sodium and water retention in experimental cirrhosis. The failure to escape from the sodium-retaining effects of aldosterone and the resistance to ANP in edematous disorders was most consistent with diminished fluid delivery to the distal sites of action of aldosterone and ANP, an effect which occurred secondary to activation of the neurohumerol axis in response to arterial underfilling. Other studies documented the role of Ca^{2+} and opioids in the nonosmotic release of AVP, and incriminated nonosomotic AVP release in glucocorticoid and mineralocorticoid deficiency.

AUTOSOMAL-DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

The accumulation of the largest population of ADPKD patients in the world allowed the delineation of the natural history of this most frequent, life-threatening, hereditary renal disease affecting 12 million patients worldwide. The most treatable complication was found to be the early onset of hypertension at a mean age of 29 years, which occurs prior to loss of renal function. When compared with essential hypertension patients, the renin-angiotensin-aldosterone system (RAAS) was significantly more activated in patients with ADPKD. Moreover, in ADPKD left ventricular hypertrophy (LVH) was found to have a frequency of 50% at age 40 years, an important clinical finding since in the era of renal replacement therapy cardiovascular complications have become the most frequent cause of death in ADPKD patients. The hypertension in ADPKD patients correlates with the degree of kidney enlargement and the rate of progression to end stage renal disease (ESRD). Angiotension converting enzyme inhibitors (ACEI) were shown to have a significantly greater reversal of LVH and antiproteinuric effect than calcium channel blocker (CCB) in the ADPKD patient. Aggressive blood pressure control to a goal of 125/75 mm Hg was found in a 7-year prospective randomized study to more significantly reverse LVH in ADPKD patients as compared to a blood pressure goal of 135/85 mm Hg. In an epidemiologic study, the progression rate of ADPKD to ESRD was shown to be significantly slower in the most recent decade as compared to the previous decade; the only detectable differences were the more frequent use of ACEI therapy and better blood pressure control in the recent time period. Insight into the phenotypic heterogeneity of ADPKD in the same family, and thus with the same mutation, has been found to be influenced by the prevalence of parenteral hypertension and other modifying genes. On this background, a clinical ADPKD network has been formed by the National Institutes of Health (NIH) to examine the effect of RAAS blockade on early and advanced ADPKD on renal cystic growth and rate of renal functional deterioration, respectively.

APPROPRIATE BLOOD PRESSURE CONTROL IN TYPE 2 DIABETES MELLITUS (ABCD) TRIAL

As with ADPKD, our studies in diabetes mellitus were primarily undertaken in patients, particularly the prospective randomized ABCD trial in 950 type 2 diabetes patients. The hypertensive (>140/90 mm Hg for average of 12 years) cohort study included 470 patients, while the normotensive study included 480 patients followed for 5 years. In addition to comparing standard (<140/90 mm Hg) versus aggressive (<130/80 mm Hg) blood pressure control, the affect of ACEI versus CCBs was also examined relative to renal, cardiovascular, eye, and neurological complications. The hypertensive ABCD study demonstrated (*1*) stable renal function with both levels of blood pressure control in normoalbuminuric and microalbumuric patients, (*2*) decreased myocardial infarctions with ACEI versus CCB, (*3*) 5 mL/min/year decrease in renal function with both blood pressure goals in patients with overt diabetic nephropathy, and (*4*) decreased mortality with the more aggressive blood pressure control. In the normotensive ABCD cohort, there were no differences between the ACEI and CCB treatments; however, the more aggressive blood pressure control demonstrated significantly (*1*) decreased progression to incipient nephropathy (30 to 300 mg/day albumin excretion), (*2*) decreased progression from incipient to overt nephropathy (>300 mg/day albumin excretion), (*3*) decreased progression of retinopathy, and (*4*) decreased incidence of strokes. In type 2 patients with peripheral vascular disease, the more aggressive blood pressure control was associated with a significant decrease in cardiovascular complications.

The opportunity to work with fellows from numerous countries over the more than 30 years has been an extremely productive, rewarding, and enjoyable experience. I am honored to accept the Jean Hamburger Award for contributions in research with a particular emphasis on patient-oriented investigations on behalf of these research fellows.

Finally, the love and support of Barbara and my family have been the primary foundation for both my professional and personal life.