Uremic Cardiomyopathy—An Endogenous Digitalis Intoxication?


Since the days of Richard Bright (1), it has been common knowledge that the heart is a target organ in uremia, and by the beginning of the 20th century it had been recognized that heart failure and cardiac death were frequent in renal patients (2).

Despite the common occurrence of failing heart function, as early as 1937 Mason had reported that the contractile force of frog hearts was augmented when exposed to the serum of uremic dogs, but not of control dogs (3). This was confirmed in the study of Nivatpumin (4). One potential explanation for the paradoxical initial increase in cardiac inotropy, later followed by pump failure, was the presence of a hypothetical, endogenous, digitalis-like substance that had been found in other systems, e.g., erythrocytes (5). Indeed, Penpargkul (6) and Fiehn (7) documented inhibition of the sarcolemmal Na,K-ATPase in the heart of uremic animals and we found similar inhibition of this enzyme also in extracardiac organs, e.g., the inner ear membranes (8).

Around this time, inhibitors of the ouabain-sensitive Na$^+$,K$^+$-ATPase, called “digoxin-like” (9), were also found in the urine and serum of uremic and of volume-expanded patients (8,9). Serum of uremic patients interfered with the radiourbidium assays for digitalis (10); this observation and the reduced inotropic dose-response relationship to digoxin in uremic animals (11) led several authors to the conclusion that in uremic animals endogenous digoxin-like substances were present, presumably in supranormal concentrations. The presence of endogenous digitalis in normal mammals had been postulated half a century ago (12).

Based on the finding of (an) endogenous inhibitor(s) of Na$^+$-K$^+$-ATPase, Bricker (13), Nutbourne et al. (14), and Blaustein et al. (15) proposed the ingenious hypothesis that this inhibitor constituted part of a homeostatic feedback system, the task of which was to maintain the constancy of the extracellular fluid spaces (16) and of blood pressure (17).

Digitalis-like substances are widely distributed in nature and almost certainly have important functions, as suggested by the fact that the substance in the phylogenetically-distant foxglove fits onto the mammalian receptor—although, clearly, weird coincidences can never be completely excluded.

There have been numerous attempts to isolate and chemically characterize the hypothetical endogenous “digitalis,” i.e., inhibitor of the Na$^+$-K$^+$-ATPase. The quest to identify the chemical nature of the substance was for a long time painfully frustrating, but finally rewarding (18,19).

Ouabain, the long-known arrow poison of the African ouabaio tree and of the Strophantus gratus plant, was identified as a new steroid hormone that is synthesized in the zona fasciculata of the adrenal cortex, in the extreme case illustrated by ouabain-producing adrenal tumors, ouabainomas, causing hypertension. Apparent triggers for the synthesis are ACTH, alpha adrenergic and dopaminergic (20) stimulation, angiotensin II, vasopressin, as well as systemic hypoxia and physical exercise (21). Ouabain is also found in the hypothalamus as a neurosteroid and can be detected in the circulation. Its concentration is elevated in congestive heart failure and renal failure (21,22).

Ouabain antibodies or the newly discovered antagonist PST 2238 (23) inhibit ouabain-induced hypertension in experimental models. Of considerable importance with respect to the following is the recent observation that ouabain (and other cardiotonic steroids) act not only as inotropic agents and as inhibitors of the Na$^+$-K$^+$-ATPase, but also trigger intracellular signaling cascades. In the heart muscle, ouabain causes a Ca$^{2+}$-dependent early gene response (c-fos, c-jun), stimulates Ras and p42/44, and increases protein biosynthesis (24). In vascular smooth muscle cells, both ouabain and marinobufagenin also stimulate proliferation at concentrations lower than those normally required to alter intracellular ion concentrations (25).

What is really exciting is the identification of additional cardiotonic steroids with overlapping
but partially differing actions. While it is still unclear whether digoxin is present in mammals (21), endogenous bufadienolides (bufo = toad) have been clearly identified, particularly marinobufagenin which—as the name indicates—was originally isolated as an amphibian venom from toads, where it interestingly exerts antimicrobial activity (26). In contrast to ouabain, marinobufagenin exhibits greater affinity to the ouabain-resistant α1 subunit of Na⁺-K⁺-ATPase (27) which, interestingly, is the isoform that exhibits a loss of function mutation in the Dahl rat in which marinobufagenin (but not ouabain) increases natriuresis, apparently in a compensatory effort to overcome the impairment of sodium excretion (28). It thus acts as a natriuretic hormone. In experimental diabetes, the plasma levels of marinobufagenin are increased (29) and the substance is also involved in a rat model of preeclampsia (30).

The plasma levels of a related endogenous digitalis, telocinobufagenin, are elevated in renal failure as well (31) and are even higher than those of marinobufagenin. Marinobufagenin is a marker of congestive heart failure severity (32) and is elevated after myocardial infarction (33).

In view of the unsettled involvement of the putative inhibitor of Na⁺-K⁺-ATPase in the uremic syndrome, it was sensible to address the issue whether the recently identified marinobufagenin was the long-sought “endogenous digitalis.” Therefore, the authors examined whether the infusion of marinobufagenin (10 μg/kg per d) into conscious rats reproduced the increase in blood pressure and heart weight seen in uremia and also reproduced cardiac hypertrophy, fibrosis, and impaired diastolic relaxation (34). The authors then went one step further and measured the expression of the sarcoplasmic ATPase, which is responsible for uptake and sequestration of cytoplasmic calcium in the control of diastolic relaxation, known to be abnormal in uremia (35,36). Finally, they assessed cardiac fibrosis and measured oxidative stress.

To provide evidence for a causal role of marinobufagenin, the authors used two strategies. First, they infused marinobufagenin to sham-operated rats to achieve the concentrations seen in subtotally nephrectomized rats and to assess whether the above pathologies were reproduced by marinobufagenin.

Second, they immunized rats before subtotal nephrectomy against BSA-conjugated marinobufagenin to block the effect, if any, of elevated endogenous marinobufagenin by the apparently induced neutralizing antibodies.

What were the results? Infusion of marinobufagenin doubled the plasma concentration and urine excretion of marinobufagenin to the level seen after partial nephrectomy, and this was abrogated by immunization against marinobufagenin. There were no significant changes in the concentration of ouabain-like substances. In parallel with both maneuvers, i.e., marinobufagenin infusion and partial nephrectomy, the concentrations of carbonylated proteins as evidence of oxidative stress increased in plasma and heart tissue. Importantly, there were no confounding effects on aldosterone and parathyroid hormone concentrations. Marinobufagenin caused some increase in blood pressure, but less than partial nephrectomy.

The changes of heart morphology and function were impressive: left ventricular wall thickness by echocardiography was significantly elevated after subtotal nephrectomy, and was accompanied by reduced systolic and diastolic left ventricular (LV) volumes and increased fractional shortening. These findings were abrogated by preimmunization with marinobufagenin. Invasive measurements showed increased maximal velocity of rise in LV pressure (dP/dt) and some evidence of impaired diastolic LV function. Infusion of marinobufagenin tended to move the parameters in the same direction.

Cardiac fibrosis after partial nephrectomy, a well-known sequela of uremic cardiomyopathy (37), was reproduced by infusion of marinobufagenin and abrogated by preimmunization.

In the heart, both partial nephrectomy and infusion of marinobufagenin downregulated the α1 and α2 Na⁺-K⁺-ATPase isoforms, activated extracellular signal kinase, and downregulated sarcoplasmic reticulum calcium ATPase, which is crucial for diastolic Ca²⁺ reuptake and relaxation.

The findings, if confirmed, introduce a new paradigm, i.e., endogenous cardiotonic steroids as a pathogenetic factor in the genesis of cardiac dysfunction observed in uremia. These findings
also indicate that the effect of these substances goes beyond that of simple inotropic agents and involves intracellular signal cascades triggered by Na⁺-K⁺-ATPase located in caveolae as well described by others (24,25). The study provides evidence of increased oxidant stress, well-documented also in the genesis of LV hypertrophy as an important intermediate step (38), which may be relevant because antioxidant interventions have been shown to block effects of cardiotonic steroids (39). The action of endogenous cardiotonic steroids may provide an explanation for the enigma that control of preload, afterload, and sympathetic activity failed to prevent LV hypertrophy in subtotally nephrectomized rats (40).

It looks as if the authors hold a smoking gun. It is a sound principle in science to wait for confirmation of data by independent investigators, but admittedly the data reported so far appear to be consistent, plausible, and promising. As all good papers do, this paper raises many questions. Where is marinobufagenin synthesized, how is its synthesis regulated, what are the relative roles of synthesis and potentially excretion in the generation of increased plasma levels in uremia? What are the relative roles of telocinobufagenin (31) and marinobufagenin? What is the interaction, if any, with ouabain? What is the interaction with known agents operative in the genesis of cardiomyopathy such as blood pressure, aldosterone, anemia, parathyroid hormone, and others? And finally what intervention strategies will be successful: antioxidant strategies (41), blockade of the renin-angiotensin system in view of the fact that angiotensin II pathways are involved in stimulating marinobufagenin (42), or specific antagonists as developed for ouabain (23)?

And beyond the confines of nephrology: if such Na⁺-K⁺-ATPase inhibitors have been conserved during evolution so long—from foxglove to Homo sapiens—it is difficult to believe that the only reason why nature preserved them was to make life difficult for nephrologists. The substance must obviously have more basic physiologic regulatory functions that so far escape us. The future will hopefully give the answer to the question of what role it plays in normal physiology.

References


35. Kennedy D, Omran E, Periyasamy SM, Nadoor J, Priyadarshi A, Willey JC, Malhotra D, Xie Z, Shapiro JI: Effect of chronic renal failure on cardiac contractile function, calcium cycling,


