

Cardiac Glycosides and Cardiomyopathy

Paolo Manunta, Mara Ferrandi

Digitalis-like steroids and related agents have been a mainstay in the treatment of congestive heart failure ever since the publication, in 1785, of Withering's seminal monograph on foxglove. Heart failure refers to the clinical syndrome that results when the heart is unable to pump sufficient blood to keep up with the metabolic demands of the body. Congestive heart failure is characterized by excessive neuronal and hormonal-mediated fluid retention, expanded intravascular volume, high pulmonary and systemic venous pressures with consequent dyspnea (shortness of breath) on exertion, reduced exercise tolerance, and fatigue. Most heart failure patients also have impaired ventricular systolic function and depressed cardiac output; these are the patients most often treated with digitalis glycosides. These drugs are positive inotropic agents and enhance cardiac contraction. The "cardiotonic steroids" cause cardiac muscle to lose K^+ and gain Na^+ because they inhibit the Na^+K^+ -ATPase, a plasma membrane protein, present in all cells. The Na^+ pump uses the energy from ATP to extrude Na^+ and to maintain the large Na^+ electrochemical gradient across the plasma membrane.

How does inhibition of the Na^+ pump augment cardiac contraction? The discovery of the Na^+ - Ca^{2+} exchanger and sarcoplasmic reticulum Ca^{2+} ATPase (Serca) has provided the missing link between Na^+ pump inhibition and delivery of Ca^{2+} to enhance contractility.¹ An increase of Na^+ - Ca^{2+} exchanger at the plasma membrane and/or a reduced Serca activity may contribute to increased intracellular Ca^{2+} concentrations leading to increased contractility. In 1997, the Digitalis Investigative Group reported on a controlled, randomized trial of digoxin in 6800 patients with congestive heart failure being treated with diuretics and angiotensin-converting enzyme inhibitors.² The study led to the conclusion that digoxin therapy reduces hospitalization of patients affected by heart failure and confirmed the overall efficacy of digoxin therapy in patients with congestive heart failure and normal sinus rhythm. Yet, for unknown reasons, digoxin benefits only some patients. Clearly, some means of identifying the potential impact of digoxin before its administration would be extremely useful. The presence of endogenous cardiac glycosides, including marinobufagenin (MBG)³ and

endogenous ouabain (EO)⁴ in the human circulation, should be taken into account. EO is not plant ouabain, but a related that remains structurally unclear compound.

The article published in this issue of *Hypertension* by Kennedy et al⁵ is in keeping with the hypothesis of a new function of the endogenous cardiac glycosides. The authors investigated the role of marinobufagenin in uremic cardiomyopathic, suggesting that the increased levels of MBG are implicated in the development of a uremic cardiomyopathy associated with diastolic dysfunction, cardiac hypertrophy, and systemic oxidant stress. In particular the administration of 10 $\mu\text{g}/\text{kg}$ per day of MBG for 4 weeks caused increased blood pressure, cardiac fibrosis, and systemic oxidant stress associated with decreased cardiac Serca2a expression. All these effects were attenuated following immunization against MBG.

Evidence has been provided by this group, and by others, that cardiotonic steroids activate intracellular signaling pathways through Na/K -ATPase-Src-Ras-ROS and extracellular signal regulated kinase within restricted membrane subdomains, referred to as caveolae. This signal has genomic effects leading to changes in gene expression involved in the hypertrophic growth response. These data have shifted the focus of cardiotonic steroids from their pharmacological effects on the enzymatic function of the Na/K -ATPase to intracellular signaling functions triggering growth and cell proliferation.

Similarly, longer term infusion of plant-derived ouabain (15 $\mu\text{g}/\text{kg}$ per day for 18 weeks), at doses that just double the plasma levels (from 0.3 to 0.7 nmol/L), produced hypertension and cardiac hypertrophy in rats.⁶ Moreover, a growing number of studies suggest that elevated levels of endogenous cardiac glycosides, such as EO,⁴ may have a primary role in cardiac dysfunction and failure:

1. In young offspring of hypertensive individuals, plasma EO levels positively correlate with certain indexes of diastolic cardiac dysfunction that precede the development of hypertension and left ventricular hypertrophy.⁷
2. Approximately 30% of whites with uncomplicated new onset of essential hypertension show increased concentrations of EO associated with reduced heart rate and greater left ventricular mass and stroke volume.⁸
3. Among patients with more advanced hypertension, the circulating levels of EO are directly related to both blood pressure and total peripheral resistance and inversely related to cardiac index.⁹
4. Among patients with idiopathic dilated cardiomyopathy, high circulating levels of EO identify those individuals predisposed to progress more rapidly to heart failure.¹⁰ Moreover, patients on digoxin therapy display higher levels of EO compared with patients without therapy and this difference persists when all the confounders are taken into account. This suggests that EO may contribute to digoxin toxicity.

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From the Division of Nephrology (P.M.), Dialysis and Hypertension, University "Vita-Salute" San Raffaele, Milan, and Prassis Sigma-Tau Research Institute (M.F.), Settimo Milanese, Italy.

Correspondence to Paolo Manunta, MD, Division of Nephrology, Dialysis and Hypertension, University "Vita-Salute" San Raffaele, Via Olgettina, 60, 20132 Milan, Italy. E-mail manunta.paolo@hsr.it

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In agreement to these points, the study of Kennedy et al is extremely interesting in view of the fact that volume expansion appears to play a key role in cardiac hypertrophy associated with renal failure and MBG concentrations appear to increase following volume expansion. Taken together, these data strongly support an important role for endogenous glycoside, EO and MBG, in the pathogenesis of cardiomyopathy.

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