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EDITORIAL COMMENT

Will Secretoneurin Be the Next Big Thing?*

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Heart failure (HF) and arrhythmias are monumental public health challenges associated with suffering, death, and high resource utilization. Currently available treatments are inadequate and costly. Furthermore, we lack highly reliable and readily measurable indices for predicting which HF patients are at greatest risk for arrhythmias and sudden death. In this issue of the *Journal*, Ottesen et al. (1) present evidence that secretoneurin, a small peptide measurable in circulating blood, provides prognostic information for stratifying mortality risk in patients with HF and life-threatening arrhythmias. Their story presents tantalizing but incomplete information to suggest that secretoneurin exerts protective actions in pathologically stressed myocardium by inhibiting the calmodulin-dependent protein kinase II (CaMKII).

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SECRETONEURIN: WHAT COULD IT ADD CLINICALLY?

Ideally, a biomarker reflects activity of a pathway centrally important to the disease under investigation, thereby providing therapeutic insights. The small sample sizes used here prevent clear conclusions for judging secretoneurin's clinical utility as a biomarker for HF or ventricular arrhythmias. However, the exciting data in 143 patients hospitalized for acute HF and 155 patients with sudden cardiac death due to ventricular arrhythmias suggest that secretoneurin holds promise for predicting mortality in these groups.

In this study, circulating biomarkers previously validated in large clinical trials, specifically troponin and natriuretic peptides, were less predictive of death than secretoneurin, but this apparent superiority of secretoneurin may not hold up in larger studies. One intriguing aspect of secretoneurin as a biomarker for heart disease is that it seems to represent activity of a cellular pathway that is distinct from troponin or natriuretic peptides. Here Otteson et al. (1) extend earlier findings to demonstrate that secretoneurin reduces ryanodine receptor-mediated "leak" of Ca^{2+} from intracellular (sarcoplasmic reticulum) stores, a phenomenon linked to HF and triggered arrhythmias (2–4). Furthermore, at concentrations 1,000 to 10,000 times greater than measured in plasma, secretoneurin has the capacity to inhibit CaMKII activity.

CA^{2+} SIGNALING AND CAMKII PLAY KEY ROLES IN HF AND ARRHYTHMIA

Loss of normal myocardial Ca^{2+} homeostasis is a well-established fundamental characteristic of structural heart disease. Defective intracellular Ca^{2+} homeostasis contributes to mechanisms that promote myocardial dysfunction and arrhythmias. Because Ca^{2+} is a key signal for coupling myocardial cell membrane excitability with myofilament contraction, it is not surprising that HF and arrhythmias occur together in patients and in animal models.

A serine-threonine kinase abundant in the heart, CaMKII's best understood physiological roles are related to phosphorylation of proteins involved in myocardial excitation-contraction coupling and pacemaking. CaMKII seems to behave as a turbocharging signal during extreme physiological stress, but one that is dispensable based on the viability of various genetic mouse models where CaMKII is inhibited or deleted (5–7). CaMKII expression increases in failing myocardium. Under cellular conditions present during HF (e.g., prolonged intracellular Ca^{2+} transients and elevated reactive oxygen species), CaMKII reorders into a molecular conformation with constitutive activity (8,9). The increased expression and activity of CaMKII in failing myocardium favors the twin

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scourges of mechanical dysfunction and arrhythmias (10). There is now abundant evidence that myocardial CaMKII inhibition can improve contraction and suppress arrhythmias, at least in part, by quelling excessive sarcoplasmic reticulum Ca^{2+} leak in animal models (5-7) and in failing human myocardium (11,12). Thus, identifying and characterizing biomarkers with molecular connections to CaMKII are of great interest to the HF and arrhythmia communities.

IS CAMKII INHIBITION BY SECRETONEURIN DIRECT OR INDIRECT?

The new findings by Otteson et al. (1) provide evidence that secretoneurin interacts with a CaMKII pathway in healthy and injured cardiomyocytes. First, the authors interestingly observe that secretoneurin binds CaMKII and the Ca^{2+}-sensing, CaMKII-activating protein calmodulin. However, these direct effects on CaMKII activity are of low potency and do not provide a strong case that secretoneurin inhibits CaMKII primarily by direct binding in vivo. Using in vitro CaMKII activity assays, Otteson et al. found that secretoneurin at concentrations ~10,000-fold greater than were measured in plasma could inhibit CaMKII by 20% to 30%. Using an alternative measure of CaMKII activity, CaMKII autophosphorylation, they also found measurable inhibition at secretoneurin concentrations ~1,000-fold greater than in circulating plasma. However, recent studies have cast doubt on the fidelity of the CaMKII autophosphorylation epitope (phosphorylation of Thr 287 in CaMKIIδ) for reporting CaMKII activity because, at least some, commercially available antibodies are sensitive to off-target binding in myocardium (13). In this study, secretoneurin was effective when added to the perfusate for isolated hearts at a concentration of ~200 nM, ~1,000-fold greater than circulating secretoneurin measured in patients (0.1 to 0.2 nM) (1,14). All told, the low potency of secretoneurin as a direct inhibitor of CaMKII casts doubt on the concept that secretoneurin impacts myocardial biology primarily by this mechanism.

In contrast, Otteson et al. (1) provide more convincing evidence that secretoneurin at concentrations closer to those detected in patient plasma (10- to 100-fold higher) reduced sarcoplasmic reticulum Ca^{2+} leak and enhanced sarcoplasmic reticulum Ca^{2+} content. Excessive sarcoplasmic reticulum Ca^{2+} leak can promote arrhythmias and HF, so this aspect of secretoneurin signaling could provide insights into future therapies. Furthermore, sarcoplasmic reticulum Ca^{2+} leak activates CaMKII by calmodulin calcification and binding, so secretoneurin may indirectly inhibit CaMKII at plasma concentrations measured in patients with myocardial disease. Based on these findings, I suspect that secretoneurin is more likely to inhibit CaMKII-mediated signaling by an indirect, as yet incompletely defined action that reduces sarcoplasmic reticulum-mediated leak of Ca^{2+} into the cytoplasm. It seems probable that the "direct" target of secretoneurin in myocardium is upstream to CaMKII.

OPEN QUESTIONS AND NEXT STEPS

The exciting work by Otteson et al. (1) presents new and important questions. Will secretoneurin provide clinically useful information in patients with HF and arrhythmias, above and beyond current biomarkers? What is the mechanism by which secretoneurin reduces sarcoplasmic reticulum Ca^{2+} leak? What is the secretoneurin signaling pathway, and can secretoneurin and/or other molecular elements of this pathway be exploited for future therapies? More research into the biology of secretoneurin will be required to answer these questions.

Based on our experiences with other biomarkers relevant to structural heart disease, we can anticipate that the road from fundamental discovery to potential clinical application, as a biomarker or a therapeutic signal, may be long and complex. The studies by this group on secretoneurin make an important contribution, in part, because they provide new insights into a pathway with the potential to promote HF and arrhythmias by activating CaMKII.

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