Myocardial Na,K-ATPase: Clinical aspects

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The specific binding of digitalis glycosides to Na,K-ATPase is used as a tool for Na,K-ATPase quantification with high accuracy and precision. In myocardial biopsies from patients with heart failure, total Na,K-ATPase concentration is decreased by around 40%; a correlation exists between a decrease in heart function and a decrease in Na,K-ATPase concentration. During digitalization, around 30% of remaining pumps are occupied by digoxin. Myocardial Na,K-ATPase is also influenced by other drugs used for the treatment of heart failure. Thus, potassium loss during diuretic therapy has been found to reduce myocardial Na,K-ATPase, whereas angiotensin-converting enzyme inhibitors may stimulate Na,K pump activity. Furthermore, hyperaldosteronism induced by heart failure has been found to decrease Na,K-ATPase activity. Accordingly, treatment with the aldosterone antagonist, spironolactone, may also influence Na,K-ATPase activity. The importance of Na,K pump modulation with heart disease, inhibition in digitalization and other effects of medication should be considered in the context of sodium, potassium and calcium regulation. It is recommended that digoxin be administered to heart failure patients who, after institution of mortality-reducing therapy, still have heart failure symptoms, and that the therapy be continued if symptoms are revealed or reduced. Digitalis glycosides are the only safe inotropic drugs for oral use that improve hemodynamics in heart failure.

An important aspect of myocardial Na,K pump affection in heart disease is its influence on extracellular potassium (K_e) homeostasis. Two important aspects should be considered: potassium handling among myocytes, and effects of potassium entering the extracellular space of the heart via the bloodstream. It should be noted that both of these aspects of K_e homeostasis are affected by regulatory aspects, eg, regulation of the Na,K pump by physiological and pathophysiological conditions, as well as by medical treatments. Digitalization has been shown to affect both parameters. Furthermore, in experimental animals, potassium loading and depletion are found to significantly affect K_e handling. The effects of potassium depletion are of special interest because this condition often occurs in patients treated with diuretics. In human congenital long QT syndrome caused by mutations in genes coding for potassium channels, exercise and potassium depletion are well known for their potential to elicit arrhythmias and sudden death. There is a need for further evaluation of the dynamic aspects of potassium handling in the heart, as well as in the periphery. It is recommended that resting plasma potassium be maintained at around 4 mmol/L.

Key Words: *Digoxin; Heart; Na,K-ATPase; Potassium*

QUANTITATIVE ASPECTS OF HUMAN MYOCARDIAL NA,K-ATPase

Digitalis glycosides have been in use for the treatment of heart failure for 225 years and are still the only safe inotropic drugs for oral use that improve hemodynamics. Active sodium and potassium transport is specifically inhibited by cardiac glycosides (1) and the Na,K pump is the cellular receptor for the inotropic action of digoxin. On this basis, digitalis glycoside binding was developed as a tool for Na,K-ATPase quantification (2). This method allows quantification of muscular Na,K-ATPase with high accuracy and precision (3). Na,K-ATPase was demonstrated in the human myocardium several years ago (4), and has since been quantified in both normal and diseased myocardia. In normal human left ventricular myocardium, a Na,K-ATPase concentration of around 700 pmol/g wet weight has been found (5). The absolute amounts of the various isoforms of human myocardial Na,K-ATPase have not been determined. In human dilated cardiomyopathy, endomyocardial biopsies showed a significant decrease of approximately 40% in total Na,K-ATPase concentration (6). Later, data from available studies (6-9) were analyzed, and it was concluded that there is a consistent and significant decrease of 26% to 32% in Na,K-ATPase in the failing human heart (10). Furthermore, a close correlation between left ventricular ejection fraction and Na,K-ATPase concentration was observed (6,11), indicating that the contractile performance of the myocardium decreases in proportion to the loss of Na,K-ATPase. In the first report of Na,K-ATPase isoform expression in normal and failing human left ventricles, Allan et al (12) found no significant alteration in messenger RNA (mRNA) expression. In that study, however, the tendency toward a reduction in total Na,K-ATPase concentration was only around 10%. Furthermore, it was noted that minor changes in protein expression might be missed by studies of mRNA abundancies and that post-transcriptional factors may also be in play. However, Shamraj et al (10) found that the mRNA expression pattern was different in samples from failing human hearts. A different expression pattern in failing human left ventricles was also found for the Na,K-ATPase isoform proteins. Thus, the alpha-1 (–38%) and alpha-3 (–30%) isoforms were lower in failing human hearts than in nonfailing hearts. In parallel, an abundance of the beta-1 isoform (–39%), maximal ouabain binding (–39%) and Na,K-ATPase activity (–42%) were also lower in heart failure. Alpha-2 isoform expression only showed a small tendency toward reduction, which did not reach the level of statistical significance. At the protein level, the expression of Na,K-ATPase isoforms in the right atrium was also different

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during heart failure in humans. The alpha-1 and alpha-2 isoforms were expressed at reduced levels (13).

Occupancy of Na,K-ATPase – ie, percentage of receptors occupied by digitalis glycoside during digitalization – was first evaluated by membrane potential measurements in human atrial biopsies, revealing a 38% reduction in electrogenic effect (14). Later, occupancy in myocardial biopsies from digoxin-treated patients was determined as the relative difference in digitalis glycoside binding before and after a prolonged wash of samples in buffer containing digoxin antibody. This revealed occupancies of 24% to 35% in the human heart (5,15). In the human heart, the alpha-1 and alpha-2 isoforms have almost identical affinity for digitalis glycosides. Thus, their occupancy by digoxin during digitalization is probably also of the same order of magnitude. Using genetically manipulated mice, it was recently found that the alpha-2 isoform has a special role in calcium signalling and may thus be of special importance for the inotropic action of digitalis glycosides, whereas the alpha-1 isoform may have a special role in maintaining sodium and potassium concentrations (16). Thus, it is of interest that isoform-specific regulation of Na,K-ATPase in the heart has recently been reported (17).

Recent studies using experimental animals indicate that myocardial Na,K-ATPase in addition to digoxin is also influenced by other drugs used for treatment of heart failure. Thus, potassium loss during diuretic therapy has been found to reduce myocardial Na,K-ATPase, whereas angiotensin-converting enzyme (ACE) inhibitors may stimulate Na,K pump activity (18,19). Furthermore, hyperaldosteronism induced by heart failure has been found to decrease Na,K-ATPase activity (20). Accordingly, treatment with the aldosterone antagonist spironolactone may also influence Na,K-ATPase activity.

CLINICAL ASPECTS AND PERSPECTIVES

Digitalization

Heart failure has been deemed the epidemic of cardiology in the twenty-first century in the industrialized world (21,22). Despite recent improvements in therapy mainly arising from clinical trials, the overall prognosis for heart failure still remains very poor. Hence, clinical trials, which are usually based on a trial and error concept, have generally only been able to add a few months to a life expectancy of only a few months or years in severe heart failure. In this setting, there is a pressing demand for elevation of results from basic research into clinical application in the search for a breakthrough in heart failure research.

When addressing the importance of Na,K pump regulation in heart failure, Na,K pump knowledge must be integrated with results from studies of other pumps and pathways involved in sodium, potassium and calcium homeostasis in the human heart. When this is obtained, a more rational approach to the treatment of arrythmias and inotropic incompetence in heart failure may become possible. Ideally, the myocardial Na,K pump, as well as other pumps and pathways, should be assessed in every patient with heart failure. This, however, would require myocardial biopsies and complex biochemical evaluations, and is not feasible in clinical practice. Thus, currently the most rational approach is to integrate the results of basic ion research more extensively into the design of future clinical heart failure studies.

One major aspect of reduced myocardial Na,K pump concentration in heart failure as well as of inhibition of a part of prevailing Na,K pumps by digitalization is the influence on intracellular Na (Na_i) homeostasis. Only recently have significant increases of a few millimoles per litre in Na_i been described in the failing rabbit heart exposed to volume and pressure overloading (23), as well as in the failing human heart (24). Whereas these observations seem in good accord with a decrease in Na,K pump concentration, an increased sodium influx has also been found to be of importance (23). If increased sodium influx develops together with decreased Na,K pump concentration, this probably means that the remaining Na,K pumps are set at a higher level of activity. This is feasible because at resting conditions only a small percentage of Na,K pumps are usually active, whereas all pumps can be recruited when stimulated (25). It implies, however, that only a reduced capacity for sodium handling is available when in demand. A rise in Na_i during, for example, ischemia, may secondarily limit calcium and hydrogen extrusion from myocytes, inducing arrhythmias and further progression of heart failure due to cell necrosis. Thus, whereas a minor Na_i increase may cause inotropy, a further rise may be deleterious.

Furthermore, a major aspect is the influence on hemodynamics. The hemodynamic aspects of digitalization in relation to the Na,K pump were recently reviewed (22). In heart failure, the reduction in Na,K pumps may initially be considered adaptive maintenance of contractile capacity. In accordance with the Digitalis Investigation Group (DIG) trial (26), which shows a beneficial effect of digoxin on morbidity without affecting mortality in heart failure patients, it is recommended that digoxin be given to heart failure patients who still have heart failure symptoms after institution of mortality-reducing therapy. Therapy should be continued if symptoms are revealed or reduced. Digoxin is still the only safe inotropic drug for oral use that improves hemodynamics.

Potassium

Another important aspect of myocardial Na,K pump affection in heart failure is its influence on K_e homeostasis. Two important aspects should be considered: potassium handling among myocytes and effects of potassium entering the extracellular space of the heart via the bloodstream. The latter comes into play during exercise, for example, when plasma potassium may rise to around 8 mmol/L and subsequently decrease to around 3 mmol/L immediately after cessation of exercise in healthy normal human subjects. Moreover, it should be noted that both of these aspects of K_e homeostasis are affected by regulatory aspects, eg, regulation of the Na,K pump in myocardial and skeletal muscle by physiological and pathophysiological conditions, as well as by medical treatments (18,27). Thus, digitalization has been shown to affect both aspects (28,29). Furthermore, in experimental animals, potassium loading and depletion are also found to significantly affect K_e handling (30-32). The effects of potassium depletion are of special interest because this condition may occur often in heart patients due to treatment with diuretics (33). However, it also occurs in other conditions such as potassium depletion induced by cisplatin treatment for cancer (34). The plasma potassium response to exercise is further moderated by physical conditioning and disease (35,36). It has recently been shown that ankyrin B mutation associated with reduced myocardial Na,K-ATPase causes long QT syndrome and sudden cardiac death during exercise in experimental animals (37). In human congenital long QT syndrome caused by mutations in genes coding for potassium channels, exercise and potassium depletion are well known for their potential to elicit arrhythmias and sudden death (38-41). Thus, because disturbed

K_e homeostasis may induce arrhythmias in many heart patients, there is a need for further evaluations of the dynamic aspects of potassium handling in the heart as well as in the periphery. In clinical practice, plasma potassium values should be evaluated not only as a static parameter; evaluations of the dynamic plasma potassium changes might also prove to be of clinical importance. In accordance, it is recommended that resting plasma potassium be maintained around 4 mmol/L (42).

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