Review

Myocardial Na,K-ATPase: the molecular basis for the hemodynamic effect of digoxin therapy in congestive heart failure

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Abstract

Congestive heart failure may be deemed the epidemic of cardiology in the 21st century in the industrialized part of the world. Although new therapies improving morbidity and mortality from chronic heart failure have emerged it is likely that there is a growing role for digoxin. Thus, digoxin treatment is known to control symptoms of congestive heart failure when added to standard therapy. In this setting, we review the prevailing knowledge of the Na,K-ATPase, the cellular receptor for the inotropic action of digitalis glycosides, in relation to the hemodynamic effect of digoxin. It is concluded that if improvement of hemodynamics is needed in congestive heart failure, this knowledge should be taken into account and in many cases digoxin should be added to standard therapy. Digoxin is still the only safe inotropic drug for oral use that improves hemodynamics. Digoxin should be used to heart failure patients in sinus rhythm when they after institution of mortality reducing treatment still have heart failure symptoms, and to patients intolerant to heart failure mortality reducing drugs. Digoxin should probably in heart failure patients with sinus rhythm be given in the lowest possible dose that relieves symptoms sufficiently.

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1. Introduction

The increasing age of the population, improved survival from ischaemic syndromes and a more aggressive treatment against sudden death leaving patients with impaired heart function, cause a rapid rise in the prevalence of congestive heart failure [1]. Despite recent improvements in therapy the overall prognosis for congestive heart failure still remains very poor—similar to that seen in many cancer diseases. Thus, it is a major public health threat and will be a leading cause of morbidity and mortality in the future. Congestive heart failure may be deemed the epidemic of cardiology in the 21st century in the industrialized part of the world.

Cardiac glycosides have been widely used for the treatment of congestive heart failure for more than two centuries since William Withering published his famous monograph in 1785 [2]. Although new therapies improving morbidity and mortality from chronic heart failure have emerged—angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, beta-adrenergic receptor antagonists and low dose spironolactone—it is likely that there is a growing role for digoxin. Thus, digoxin treatment is known to control symptoms of congestive heart failure when added to standard therapy.

At the beginning William Withering used digoxin on a trial and error basis. In the middle of the last century digitalization was found to reduce congestion, and to increase cardiac output [3]. Later, acute digitalization of patients with cardiomyopathy was found to reduce heart rate, pulmonary artery pressure and increase cardiac output both at rest and during exercise [4]. In chronic left ventricular dysfunction the hemodynamic effects of digox-
in and vasodilators were enhanced when given in combination [5]. Moreover, a recent study of the effect of digitalization on left ventricular ejection fraction showed a 5–10% increase [6].

Withdrawal studies—PROVED and RADIANCE [7,8]—have demonstrated better exercise tolerance and less symptomatic deterioration in heart failure patients continuing digoxin therapy. The study designs, however, did not allow any conclusions on the effect on mortality. In 1997 the Digitalis Investigation Group (DIG) published their prospective, randomized and placebo-controlled trial on 6800 patients in sinus rhythm with a left ventricular ejection fraction less than 45% [9]. The main finding was a decreased rate of hospitalization for worsening of congestive heart failure, together with a neutral effect on all-cause mortality in the digitalis group. An observed decrease in death due to progressive heart failure was counterbalanced by an increased mortality from presumed arrhythmias.

Thus, the DIG-trial being the largest and most comprehensive study on digoxin ever defines it as an overall safe drug. On this basis digoxin is today in widespread use in patients in sinus rhythm with congestive heart failure secondary to left ventricular systolic impairment that remains symptomatic despite optimum doses of diuretics including spironolactone, ACE-inhibitors and beta-adrenoceptor antagonists [10,11]. Thus, in Europe 39–87%, overall 64%, of patients with moderate to severe congestive heart failure has been reported to be on digoxin therapy [12]. On the other hand, a few recent but relatively small and retrospective studies have again questioned the use of digoxin [13,14]. Moreover, as more beneficial drugs for the treatment of heart failure emerge a declining use of digoxin has been predicted [15–18]. Since it is unlikely, that another large-scale study will be performed to clarify possible clinical uncertainties after the DIG-trial, alternative evaluations are in demand. In this setting, an analysis of the sodium, potassium-adenosinetriphosphatase (Na,K-ATPase or Na,K-pump), the cellular receptor for the inotropic action of digitalis glycosides, becomes of importance, especially because the DIG-trial was not a hemodynamic study.

2. Myocardial Na,K-ATPase

In 1997 Jens Christian Skou was awarded the Nobel Prize in chemistry for his discovery of the Na,K-ATPase in peripheral nerves of the shore crab [19,20]. The membrane-bound Na,K-pump mediating the active transport of Na and K across the cell membrane has been identified in virtually all animal tissues including the human myocardium. It is specifically inhibited by cardiac glycosides, and is thus the cellular receptor for the inotropic action of digoxin. The partial inhibition of the Na,K-pump during digitalization leads to a rise in intracellular Na, which is sufficient to reduce Ca-efflux via the Na/Ca-exchange system in the cell membrane. The resulting increase in cytoplasmatic and hence sarcoplasmatic Ca thus enhances the force of contraction. A further inhibition of the Na,K-pump due to digoxin-intoxication or pre-existence of reduced Na,K-pump concentration caused by disease, may on the other hand lead to hyperkalaemia causing arrhythmias, and to intracellular Ca accumulation and acidosis eliciting cell necrosis [21,22]. Various isoforms of the Na,K-ATPase with either low (alpha 1) or high (alpha 2) sensitivity to digitalis glycosides have been identified, and recently also different functional roles for these isoforms have been found in the myocardium of genetically manipulated mice: Heterozygous alpha 1 hearts with reduced amount of alpha 2 were hypercontractile, whereas heterozygous alpha 2 hearts with reduced amount of alpha 1 were hypercontractile, and furthermore inhibition of the alpha 2 isoform in heterozygous alpha 1 hearts increased contractility. Thus, the alpha 1 isoform is of special importance for maintaining Na- and K-concentrations, whereas the alpha 2 isoform has a specific role in Ca-signalling during cardiac contraction [23]. In the conducting system of the heart an alpha 3 isoform has been identified. Furthermore, the isoforms have been found to undergo regulation with physiological and pathophysiological conditions [24].

The Na,K-ATPase was demonstrated in the human myocardium several years ago [25], and has since then been quantified in both normal and diseased myocardium. Thus, in normal human left ventricular myocardium a Na,K-ATPase concentration of around 700 pmol/g wet weight has been found [26]. Hitherto, it has not been possible to quantify the absolute amounts of the various isoforms of myocardial Na,K-ATPase. In human dilated cardiomyopathy endomyocardial biopsies showed a decrease of around 40% in total Na,K-ATPase concentration [27]. Furthermore, a close correlation between left ventricular ejection fraction and Na,K-ATPase concentration was observed [27,28] indicating that the contractile performance of the myocardium decreases in proportion to the loss of Na,K-ATPase. This reduction has been reported to take place throughout the alpha-isoforms [29,30]. Digoxin therapy causes a decrease in functional Na,K-pump concentration of around 25% due to specific inhibition of the Na,K-ATPase [26,31]. Moreover, studies using experimental animals indicate that myocardial Na,K-ATPase is influenced also by other drugs used for treatment of congestive heart failure. Thus, potassium loss during diuretic therapy as well as hyperaldosteronism induced by heart failure has been found to reduce the Na,K-ATPase, whereas ACE-inhibitors may stimulate Na,K-pump activity [22,32,33]. Thus, proper digitalis therapy demands a meticulous balance between beneficial and deleterious effects on extra- and intracellular ion concentrations. Thus, if too few Na,K-pumps are inhibited by digoxin it may be too little to obtain effect—if too many Na,K-pumps are
occupied too few may be left to maintain basic electrolyte balance across the membrane.

Some decades ago development of tolerance to chronic digoxin therapy was suspected. This expectation came from the finding of Na,K-ATPase upregulation in various tissues e.g., erythrocytes. However, when Na,K-ATPase was later studied in the target organ for the inotropic action of digoxin, the human myocardium, no evidence for development of tolerance at the digoxin receptor level was found [27]. The studies on receptor level were in accord with PROVED and RADIANCE [7,8] showing deterioration when digitalization was discontinued. They were also in agreement with a hemodynamic study showing that discontinuation of digoxin after long-term therapy was associated with significant reduction in cardiac output as well as increase in pulmonary pressure—effects that were restored when digoxin was readministered [34]. Thus, there is no reason to expect any development of tolerance to digoxin therapy.

3. Clinical implications

Digoxin was for a long time considered first line therapy for heart failure together with diuretics. It should however be noted that the effects of long-term treatment with thiazides or loop-diuretics in chronic heart failure have never been assessed in prospective, randomized, blinded studies. Thus, it cannot at present be excluded that such diuretic treatment due to its negative effects on electrolyte homeostasis and Na,K-pumps [22] may be less beneficial than digoxin. Diuretics should clearly be used when fluid overloading is present, but it may be more rational to reduce this use to the absolute minimum and to add digoxin.

The DIG-trial demonstrated improvement of morbidity e.g. decreased rate of hospitalization for worsening of heart failure and an overall neutral effect on mortality of digoxin in congestive heart failure [9]. This observation and the subsequent studies of the effect of adding beta-adrenoceptor antagonists and aldosterone antagonists to heart failure treatment, indicates that digoxin should be administered to heart failure patients in sinus rhythm when they after institution of mortality reducing treatment still have heart failure symptoms. In clinical practice a number of patients may be intolerant to the heart failure mortality reducing drugs at least in target dosages due to e.g., renal insufficiency, hypotension and/or asthmatic lung disease. In such patients digoxin is clearly needed. In severe congestive heart failure relief of symptoms may be more important than prolongation of life. Thus, digoxin should always be considered as supplemental therapy in such patients. Before the DIG-trial there was a growing concern that digoxin might raise intracellular Ca to the level that might induce cell death. The initial decrease of Na,K-pump concentration in the early phase of heart failure or during digitalization causing intracellular Ca accumulation may enhance myocardial contractility. In terminal heart failure however, a further decrease in Na,K-pump concentration—or digitalis intoxication—causing intracellular Ca overloading and hyperkalemia may be deleterious. Thus, it was clearly a relief that the overall outcome of the DIG-trial was a neutral effect on mortality. However it is probably advisable to occupy the lowest possible number of myocardial Na,K-pumps during digitalization. In heart failure patients with sinus rhythm digoxin should probably be discontinued if no symptomatic benefit is gained. Lack of response may be the outcome of myocardial Na,K-ATPase concentration already being reduced to its minimum by the disease per se. Digoxin therapy should probably be avoided in patients with recent myocardial infarction. Of course the few well-known contraindications for the use of digoxin should always be respected.

Ideally the myocardial Na,K-ATPase should be assessed before digitalization. This, however, requires a myocardial biopsy, complex biochemical evaluations and is not feasible in clinical practice at present. Thus, to avoid dangerous over-reduction in Na,K-pump transport capacity, digoxin should probably in heart failure patients with sinus rhythm be given in the lowest possible dose that relieves symptoms sufficiently. This is in accordance with a recent clinical evaluation indicating that heart failure patients should be maintained at relatively low plasma-digoxin level [35]. It should be noted, that the traditional therapeutic range for plasma-digoxin was developed not to assess efficacy but toxicity. If symptomatic relief is obtained at a plasma-digoxin level below standard therapeutic range it should probably not be raised unless further improvement is in demand and obtainable.

In congestive heart failure myocardial norepinephrine concentrations is increased and autonomic dysfunction reduced by digitalization. It is of interest that low dosages of digoxin may attenuate neurohumoral activation without much effect on hemodynamics [34]. It should also be noted that baroreceptor abnormalities in heart failure may be associated with over-activation of the Na,K-ATPase at baroreceptor level. Thus, inhibition of this Na,K-ATPase by digitalization may normalize baroreceptor function. On the other hand, with the advance of ACE-inhibitors and beta-adrenoceptor antagonists, the neurohormonal effects of digoxin are probably less marked due to the effects of these drugs per se. In determining the place of digoxin in the era of neurohormonal modulation it has been a special concern that the DIG-trail was performed before beta-adrenoceptor antagonists came into general use in heart failure treatment. In modern use of digoxin as outlined above, however this concern in our view does not seem to carry weight enough to withhold heart failure patients from symptomatic relief by digoxin.

The fear of digitalis intoxication may have lead many physicians not to initiate or to withdraw digoxin therapy. In the DIG-trial however, toxicity was not a frequent problem and did not lead to many hospitalizations, or to significant increase in the need for drug discontinuation.
Moreover, dangerous digoxin intoxication is today effectively and easily treated by administration of digoxin-specific antibody fragments [36].

It may be concluded that if improvement of hemodynamics is needed in congestive heart failure, the prevailing knowledge of myocardial Na,K-ATPase should be taken into account and in many cases digoxin should be added to standard therapy. Digoxin is still the only safe inotropic drug for oral use that improves hemodynamics. Further studies of myocardial Na,K-pumps in relation to hemodynamics may provide further evidence for the continued use of digoxin.

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References