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EDITORIAL

Dofetilide as Activator of Na/Ca Exchange: New Perspectives on an 'Old' Drug

Editorial to: "Dofetilide Enhances the Contractility of Rat Ventricular Myocytes via Augmentation of Na^+–Ca^{2+} Exchange" by *Xuan-Ping Zhang et al.*

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Introduction

The paper by Zhang et al. in this issue [1] is challenging some well established concepts regarding the actions of dofetilide and adds a new dimension to the discussion of whether we can/should target the Na/Ca exchanger (NCX) in treatment of heart failure. It therefore deserves some further scrutiny and needs to be discussed in a broad perspective.

The key findings of Zhang et al. are that (1) dofetilide increases NCX currents when studied in isolation with all other ion currents blocked, (2) dofetilide increases contraction under voltage clamp pulses of fixed duration, excluding indirect effects via block of the delayed rectifier K current, I_{Kr}. The authors therefore propose that dofetilide has a positive inotropic, and lusitropic, effect by enhancing NCX activity. This raises a number of discussion points.

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Is dofetilide not the highly specific I_{Kr} blocker we thought?

Dofetilide has been developed in the late 80's and at that time identified as a new and highly potent Class III anti-arrhythmic agent. The classification was based upon the electrophysiological profile of the drug that prolonged the cardiac action potential with no effect on upstroke and resting membrane potential [2]. These characteristics result from a specific inhibition of the rapid component of the delayed rectifier K current, I_{Kr}. The selectivity of dofetilide for I_{Kr} was confirmed in studies that excluded off-target effects on a number of other cardiac ion channels. There was no block of Ca and Na current, inward rectifier I_{K1}, transient outward I_{to} and Cl currents, at 1 μM dofetilide or at concentrations that fully inhibited I_{Kr} [3, 4]. Higher concentrations of dofetilide may cause some delay of the deactivation of the slow component of delayed rectifier, I_{Ks}, but this is a matter of controversy [3].

In clinical practice, dofetilide is used in the pharmacological management and treatment of atrial fibrillation (AF). Dofetilide is efficient in conversion to sinus rhythm, and maintenance of sinus rhythm, but has some restrictions [5, 6]. Dofetilide can also be used as adjunctive therapy in patients with life-threatening ventricular arrhythmias who have an implantable cardioverter-defibrillator (reviewed in [7]). Despite the potential for inducing torsades de pointes, with the correct dosing, adjusted for renal function and QT, this risk remains low. The DIAMOND trial documented no excess mortality in patients at risk with coronary artery disease and heart failure [8] and actually improved survival in patients who were successfully converted to sinus rhythm [9].

In the experimental setting, dofetilide is used as a selective pharmacological tool to dissect I_{Kr} from other

current components in native cardiac myocytes. I_{Kr} can thus be quantified as the dofetilide-sensitive current [4].

The study by Zhang et al. in the current issue questions this specificity of dofetilide [1]. The authors found a potentiating effect of the drug on the NCX current, I_{NCX}, in myocytes from adult rat hearts. In general, I_{NCX} is not routinely included in studies of specificity of ion channel blockers. Yet there is one previous study on dofetilide which reports opposite effects: dofetilide blocked I_{NCX} [10]. This study was done in neonatal rabbit myocytes, but using similar protocols with buffered, and constant, Ca and Na levels. Thus differences in Ca regulation that are known to exist between neonatal and adult cells cannot explain the discrepancy between these observations. A species-dependent effect is possible and implies we will need to test dofetilide in different species. The evidence of an effect on NCX in rat myocytes in the current study is clear, but it is necessary to confirm this finding with tests in human myocytes before considering new interpretations of its clinical effects.

Does an increase in NCX activity have a positive inotropic and lusitropic effect?

The positive effects of I_{Kr} block on contractility have been noted before [11, 12] and ascribed to the well-known interaction between Ca handling and action potential duration. In cardiac cells, changes in amplitude and time course of the Ca transient will affect the action potential time course, and vice versa. This is because voltage-dependent ion currents that regulate Ca are also themselves regulated by Ca: the L-type Ca current through Ca-dependent inactivation and recovery, and the NCX, of which the direction and amplitude depends on Ca. From an electrophysiological perspective, the increase of Ca with dofetilide can thus be simply explained as a consequence of I_{Kr} block and subsequent prolongation of the action potential. Prolonging repolarization makes the forward mode of the exchanger less favorable and shifts the balance for Ca removal towards Ca reuptake into the SR. During the late repolarization phase, when Ca is low, the NCX may even reverse and bring Ca into the cell [13]. A sustained Ca influx through window Ca currents may further load the cell with Ca [14]. Two observations in the current study argue against such indirect effects to explain the observed positive and lusitropic effects in the rat heart. First, in the rat, the repolarizing currents are dominated by I_{to} with only a small contribution of I_{Kr}. It is noteworthy that Tande et al. did not observe a positive inotropic effect in rat papillary muscle with I_{Kr} block [11]. Second, the inotropic effect of dofetilide is still observed under voltage clamp conditions that exclude indirect effects via changes in action potential duration. This strongly supports the claim that there must be additional mechanisms.

In the current set of data, increased Ca influx through reverse NCX is a highly probable scenario. For any modulation of NCX, increase or decrease, the effect on Ca availability for the cardiomyocyte, and thus on contractility, will depend on the net flux of Ca during the cardiac cycle. A net gain implies that the NCX predominantly operates in the reverse mode. In rat, the species being studied, this is not unlikely. Typical for rat myocytes are the high intracellular Na levels, which promote reverse NCX and Ca loading during diastole, especially at low heart rates [15, 16]. In the current study, the cellular recordings of Ca were obtained at a cycle length of 2 s, corresponding to a heart rate of 30 bpm, which may indeed create these conditions. This is however quite different from the in vivo situation for the rat, with a heart rate of 300–400 bpm, and also different from the Langendorff recording obtained at 200 bpm.

There are a few more caveats and missing data to firmly anchor the interpretation of the current data set. First, there is a missed opportunity to actually record the NCX currents during the voltage clamp experiments, or document promotion of Ca influx and Ca efflux more directly. Second, the data are missing to see whether there was an increase in SR Ca content, or rather an increase in direct Ca influx. The cellular recordings do not give information on the time course of shortening and Ca that would allow this distinction. Lastly, the use of KB-R7943 as a tool to identify the NCX contribution is not ideal. KB-R7943 is not as highly specific as some of the newer NCX inhibitors [17] and in the intact myocyte experiments (Fig. 3 in the study by Zang et al. [1]), its effect could as well correspond to a reduction of Ca current. In the next data set though (Fig. 5 in [1]), Ca current was already eliminated. The decrease of cell shortening and Ca transients on application of KB-R7943 is then consistent with a block of NCX, implying that the inotropic effect of dofetilide results from enhanced NCX.

Can we then deduce from these data that activation of NCX will always have a positive inotropic and lusitropic effect? The Ca handling and net movement of Ca by NCX in rat ventricular myocytes at low frequency are quite distinct from non-rodent species with long action potentials, including humans. In larger mammals, NCX mainly operates in the forward mode during a single cardiac cycle and net movement of Ca is efflux [18], compensating for Ca influx via the Ca channel [19]. This explains why overexpressing NCX with adenoviral gene transfer in rabbit myocytes depletes the cells of Ca and impairs contractility [20]. The authors refer to studies in heart failure reporting an increase in NCX activity, to highlight the potential benefit of NCX activation, i.e. to improve contraction with additional Ca influx and to improve relaxation by more Ca

efflux. While it is correct that NCX upregulation is interpreted as a compensatory mechanism, there are consequences to it that are not beneficial at all. Upregulation of NCX is one of the mechanisms in heart failure that reduces the SR content and thus contractility [21, 22]. Upregulation of NCX is also seen as one of the major mechanisms contributing to the increased susceptibility to arrhythmias in heart failure [23, 24].

Pharmacology of NCX so far has typically focused on NCX inhibitors, that might have a role as part of an antiarrhythmic or inotropic support therapy [25, 26]. Such drugs indeed increase SR Ca content, reduce potentially arrhythmogenic currents, but have also unfavorable effects on relaxation [27]. A role for activation of NCX in the setting of heart failure is currently not truly considered and the current paper thus opens an interesting debate.

Perspectives

If confirmed, dofetilide as an activator of NCX may be an exciting novel experimental tool. In the brain, activation of NCX is apparently part of a protective pathway during ischemia [28, 29] and pharmacological activators of NCX would be an interesting tool to further test this pathway. With dofetilide, in the correct experimental circumstances, we could have such a tool. Dofetilide could possibly also be the starting point for development of other, perhaps better, NCX activators that may have a place in certain conditions of ischemia.

Should we re-think the use of dofetilide in the clinical cardiology setting? Dofetilide is currently a fully integrated part of the antiarrhythmic strategy to treat AF. Its efficiency and safety, within boundaries, are well established. Yet from a theoretical point of view, an associated NCX activation may offset its beneficial effects. I_{Kr} blockers like dofetilide cause QT prolongation and enhance the susceptibility to triggered arrhythmias, one of the known risks. A higher NCX activity may further increase the likelihood of afterdepolarizations triggering ventricular arrhythmias [23, 24]. Increasing Ca influx via reverse mode NCX promotes Ca overload and spontaneous Ca release. During this release, increased forward NCX will produce a more potent inward current to cause delayed afterdepolarizations. These mechanisms become particularly important during β-adrenergic stimulation. Assuming that dofetilide increases NCX activity as suggested in the current study, we may have an additional mechanism apart from I_{Kr} block that contributes to the torsadogenic potential of dofetilide. If it is confirmed that also in humans dofetilide increases NCX activity, a search for analogues without this effect may further improve the safety profile of this drug.

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