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Research Letter

Inhibition of the potassium channel TASK-1 in human atria to reduce arrhythmogenesis

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The potassium channel $K_{2P}3.1$ alias TASK-1 (TWIK-related acid-sensitive potassium channel 1), which is selectively expressed in human atrium, was recently identified as a potential antiarrhythmic target in atrial fibrillation.[1] TASK-1 upregulation in atrial fibrillation contributes to action potential duration shortening and initiation and propagation of arrhythmias. Interestingly, the drug-approved respiratory stimulant doxapram possesses high potency and specificity for TASK-1 inhibition and has previously demonstrated promising antiarrhythmic properties in animal models of atrial fibrillation.[1] However, effectivity in human and multicellular models requires further investigation, prompting the investigation of this study. We tested the antiarrhythmic properties of doxapram and its potential effects on contractility in multicellular human atrial trabeculae isolated from right atrial appendage biopsy specimens of 31 patients undergoing elective coronary artery bypass grafting or valve surgery. All patients gave written informed consent. The research reported in this paper adhered to the Declaration of Helsinki as revised in 2013 and was approved by the local ethics committee (University of Regensburg, Germany; 22-2802_10-101).

On average, patients were 67.1 ± 6.7 years old (mean ± SD), and 64.5% were male. Mean body mass index was 27.5 ± 4.7 kg/m^2, and mean glomerular filtration rate was 69.4 ± 20.9 mL/min. Left atrial dilation was present in 64.5% of patients, and mean left ventricular ejection fraction was 53.0% ± 11.3%. Diabetes mellitus was diagnosed in 41.9% and arterial hypertension in 93.5% of patients. In summary, the atrial tissue stemmed from patients possessing a variety of atrial fibrillation risk factors and also structural atrial changes that have been associated with an increased propensity for atrial arrhythmias. Regular contractions were elicited in atrial trabeculae by electrical field stimulation at 1 Hz (5 V for 50 ms, 37 °C). Premature atrial contractions were analyzed as a surrogate for atrial arrhythmias. To facilitate arrhythmias, the atrial trabeculae (Figure 1A) were exposed to isoproterenol (100 nM) and increased Ca_o (3.5 mM; original traces in Figure 1B). Severity of premature atrial contractions was classified by an arrhythmia severity score of 0 points (no arrhythmias) to 5 points (salvo) as described previously.[2] Interestingly, the arrhythmia severity score was reduced by wash-in of doxapram (5 μM) from 2.21 ± 0.42 to 0.55 ± 0.23 (mean ± SEM; $P < .001$; n = 21 vs 21 patients; Figure 1C). Contractility was analyzed in a separate protocol at physiologic Ca_o of 2 mM and without isoproterenol. Importantly, doxapram did not exert any negative inotropic effect. The developed force was 1.59 ± 0.34 mN/mm^2 for control vs 2.21 ± 0.21 mN/mm^2 in the presence of doxapram (n = 9 vs 6, respectively; P = not significant; Figure 1D). Also, duration of relaxation to 50% (68.81 ± 3.74 ms, control; 71.07 ± 4.82 ms, doxapram) and 90% of baseline (146.2 ± 10.60 ms, control; 144.0 ± 10.92 ms, doxapram) was unchanged by doxapram (n = 9 vs 6 respectively; Figure 1E and 1F).

At the concentration of 5 μM used in these experiments, it was shown that doxapram causes a strong inhibition of the TASK-1 current while maintaining its specificity.[1] We show here that provoked arrhythmias were effectively suppressed by application of doxapram (Figure 1B and 1C) in atrial biopsy specimens of patients with high cardiovascular risk. The lack of adverse effects on contractility or relaxation is consistent with the safety and specificity of the drug described in

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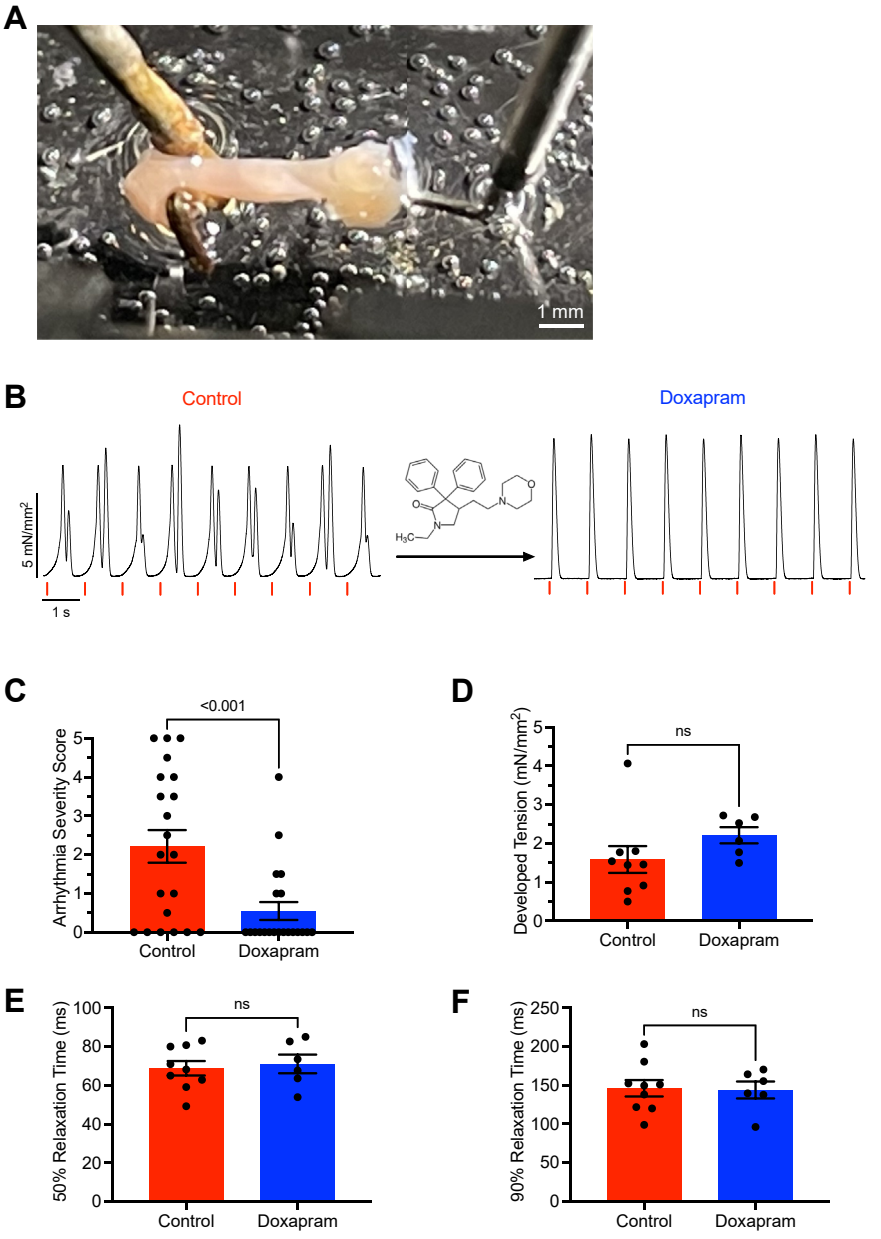

Figure 1

A: Isolated human atrial trabecula attached to a force transducer. **B:** Original trace of developed tension at 1 Hz electrical stimulation (*red lines*; Ca_o 3.5 mM, 100 nM isoproterenol [control]). Arrhythmias can be detected (*left*) and are suppressed by addition of 5 μM doxapram (*right*, *chemical structure above arrow*). **C:** Arrhythmia severity is reduced by doxapram (n = 21 control vs n = 21 doxapram), Wilcoxon test. **D:** Developed tension at physiologic Ca_o (2 mM) normalized to trabeculae cross-sectional area is unchanged by doxapram (n = 9 control vs n = 6 doxapram). **E**, **F:** Duration of relaxation to 50% and 90% of baseline, respectively, was unaltered by doxapram (n = 9 control vs n = 6 doxapram), Student *t*-test. N always indicates number of patients. ns = not significant.

previous animal studies. However, translation into patients requires further investigation in the form of clinical studies.

In summary, doxapram demonstrated strong antiarrhythmic effects in isolated human atrial trabeculae without impairing contractile function. Doxapram is approved as a drug to stimulate respiration in humans. This study highlights the potential for repurposing doxapram as an atrial antiarrhythmic agent, which could have clinical implications.

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