generalized use are its price and the usual concerns regarding the introduction of a new antiarrhythmic for use in the ED.

CONFLICTS OF INTEREST

J Cosin-Sales has received fees from Cardiome for presenting papers.

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Additive Effects of Exenatide, Glucose-insulin-potassium, and Remote Ischemic Conditioning Against Reperfusion Ventricular Arrhythmias in Pigs

Efectos aditivos de la exenatida, la glucosa-insulina-potasio y el condicionamiento isquémico a distancia frente a las arritmias ventriculares de la reperfusion en cerdos

To the Editor,

We have previously demonstrated that combination therapy with remote ischemic conditioning (RIC) and metabolic treatment (glucose-insulin-potassium [GIK] or exenatide [a mimetic of the incretin glucagon-like peptide-1]) result in additive protection against infarction in situ pig hearts, due to different impacts on key cardioprotective pathways. However, any proarrhythmic effect of this treatment would limit its clinical applicability. In this work, we analyzed the electrocardiographic recordings obtained in our previous study, conducted in an in situ pig model of transient coronary occlusion, to assess the effects of combining RIC with either GIK or exenatide on ventricular ischemia-reperfusion arrhythmias. The effects of these combinations on ventricular arrhythmogenesis were unknown.

In brief, 46 hybrid farm pigs (25-30 Kg) were anaesthetized with intravenous propofol-lipuro 1% and fentanyl and submitted to 40 minutes of left anterior descending coronary artery occlusion followed by 2 hours of reperfusion (n = 7–10/group), as previously described. The animals were included in the following groups: control, RIC, glucose-insulin-potassium (GIK), exenatide, RIC + GIK or exenatide + RIC. Electrocardiographic and hemodynamic recordings were analyzed to determine the incidence of ventricular tachycardia (VT) (4 or more consecutive premature beats of ventricular origin, heart rate faster than 100 beats/min, wide QRS durations [> 120 ms]), sustained VT (lasting more than 30 s) and ventricular fibrillation. Connexin 43 expression was assessed in cardiac extracts obtained 5 minutes after reperfusion from additional animals (n = 4/group). Results are expressed as mean ± SEM. Arrhythmias and Western blot data were analyzed by nonparametric Kruskal Wallis tests and hierarchical ANOVA, and stepwise regression analysis and 1-way ANOVA, respectively.

Contrary to previous reports, in our porcine model none of the 3 individual treatments tested was able to modify the incidence of arrhythmias during myocardial ischemia-reperfusion. However, combined treatment with GIK and RIC significantly reduced the total incidence of VT during reperfusion (Figure 1A) and the number of sustained VT during this phase (Figure 1B). Factorial analysis demonstrated that combination therapy (2 treatments) was the most effective treatment in reducing the number of VT during reperfusion (43.30 ± 7.30, 37.27 ± 4.87, and 22.21 ± 4.08 for none, 1 and 2 treatments, P < .05). However, an important

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Figure 1. Total number of ventricular (A) and sustained VT (> 30s) (B) during reperfusion in pigs from the 6 experimental groups. Exe, exenatide; GIK, glucose-insulin-potassium; RIC, remote ischemic conditioning; VT, ventricular tachycardia. *P < .05 indicates significant differences vs control animals.
limitation of this work is the use of a single electrocardiogram lead to
diagnose VT. This might have induced confusion with other entities
such as atrial tachycardia or rapid idioventricular rhythms. To
minimize such bias, we took care to include, in the VT definition,
criteria such as heart rate and QRS width. On the other hand, no
changes were observed with any of the tested treatments on the
incidence of VT during the ischemic phase or on the incidence of
ventricular fibrillation either during ischemia or reperfusion.

Myocardial connexin 43 and its phosphorylation play a key role
in arrhythmogenesis. An increase in connexin 43 levels or in its
phosphorylation would induce an improvement in gap junctional
communication and action potential propagation, and thus might
explain the reduction in reperfusion VT seen with combined
therapy. However, ischemia-reperfusion associated with connexin
43 dephosphorylation in the area at risk 5 minutes after
reperfusion (Figure 2) was not modified by any treatment. In
contrast, previous studies demonstrated that RIC is associated with
increased connexin 43 phosphorylation 2 hours after reperfusion
in the area at risk in rat hearts. Our data thus exclude a role for
improved connexin 43-mediated communication in the observed
protection against ventricular arrhythmias.

This study demonstrates that a combination of RIC with
metabolic treatments lacks any proarrhythmic effect. In fact,
combination therapy (especially RIC + GIK), has a protective effect
against reperfusion arrhythmias, independently of its actions on
connexin 43 phosphorylation. In this regard, although a number of
experimental cardioprotective therapies have been tested in the
clinical setting in patients with acute myocardial infarction, few
have been demonstrated to improve clinical outcomes. From the
present study it is difficult to guarantee the effectiveness of these
treatments in patients, but combination therapy is expected to
increase the likelihood of success.

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