

# ACUTE CARDIOPROTECTIVE EFFECTS OF DEXRAZOXANE DURING DOXORUBICIN PERFUSION IN ISOLATED GUINEA-PIG HEARTS

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## INTRODUCTION:

The cardiotoxicity of doxorubicin (DOX), one of the most widely used anticancer drugs, has been recognized for many years. The long-term cardioprotective effects of dexrazoxane (DEX) against DOX cardiotoxicity has been well-established and linked to a prevention of oxygen radical formation. DOX has been shown to increase action potential duration (APD) in guinea-pig ventricular myocytes and papillary muscles (Wang & Korth, 1995; Wang et al., 2001). An excessive increase in ventricular APD, which reflects QT prolongation, may lead to potential life-threatening arrhythmias called torsade-de-pointes. DOX has also been shown to induce dual inotropic effects in guinea-pig ventricular papillary muscles (Matsushita et al, 2000). However, little is known about protective properties of DEX upon the acute cardiac effects of DOX. Thus, the aim of the present study was to investigate the effects of DEX 100  $\mu$ M and DOX 30  $\mu$ M, perfused either alone or in combination, on coronary flow, inotropism and electrophysiological parameters in Langendorff perfused guinea-pig hearts.

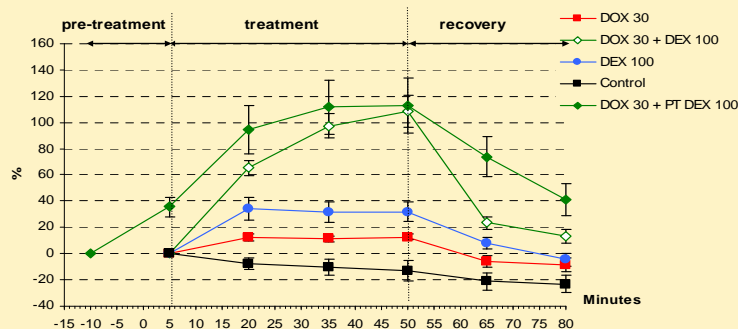
## MATERIALS AND METHOD:

✓ Isolated guinea-pig hearts were perfused according to Langendorff method, at a constant pressure of 60 mmHg, with a Krebs-Henseleit buffer containing  $\text{NaHCO}_3$  25 mM and  $\text{CaCl}_2$  1.8 mM (pH 7.4) at 36.5-37.0 °C and gassed with 95%  $\text{O}_2$ -5%  $\text{CO}_2$ .

✓ After a 45 min stabilization period and a 5 min vehicle perfusion ( $\text{H}_2\text{O}$  0.1%), DOX 30  $\mu$ M, DEX 100  $\mu$ M or both drugs in combination were perfused in Krebs-Henseleit buffer during 45 min followed by a 30 min recovery period. An additional group was also performed in which a 15 min DEX 30  $\mu$ M pre-treatment was applied before the addition of DOX 100  $\mu$ M and this combined DOX and DEX superfusion was followed by a 15-min DEX 30  $\mu$ M post-treatment and a 15 min recovery. A control group perfused with Krebs-Henseleit buffer allowed to study time-matched evolution of measured parameters.

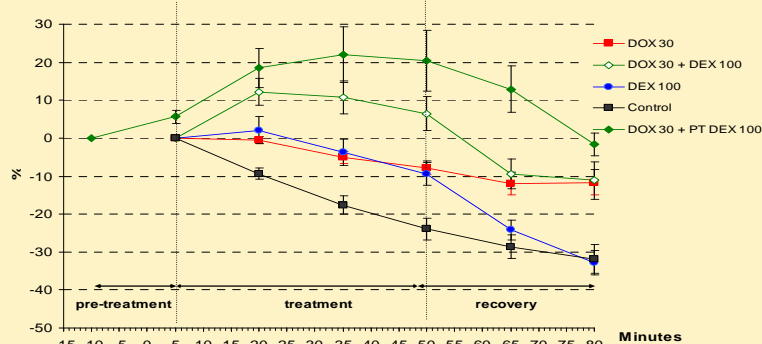
✓ Parameters exposed in this study were: coronary flow for vasodilatory effects, left ventricular pressure amplitude (LVP amplitude) for inotropic effects, and QTc and APD<sub>90</sub> (measured on monophasic epicardial action potentials) for effects on cardiac ventricular repolarization.

### Coronary flow



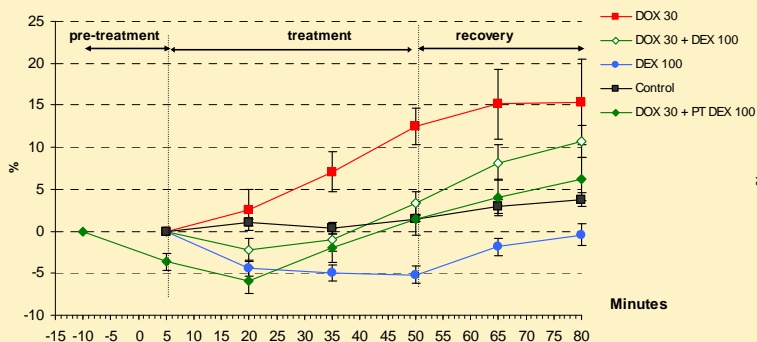
- ⇒ Continuous decrease in control conditions ( $-13 \pm 8\%$  in 45 min).
- ⇒ Reversible moderate increase with DOX 30  $\mu$ M ( $+13 \pm 2\%$ ).
- ⇒ Reversible increase with DEX 100  $\mu$ M ( $+32 \pm 7\%$ ).
- ⇒ Synergic vasodilatory effect of DOX 30  $\mu$ M + DEX 100  $\mu$ M ( $+109 \pm 12\%$ ).
- ⇒ Faster but not higher increase after pre-treatment with DEX 100  $\mu$ M ( $+113 \pm 21\%$ ).

### LVP amplitude



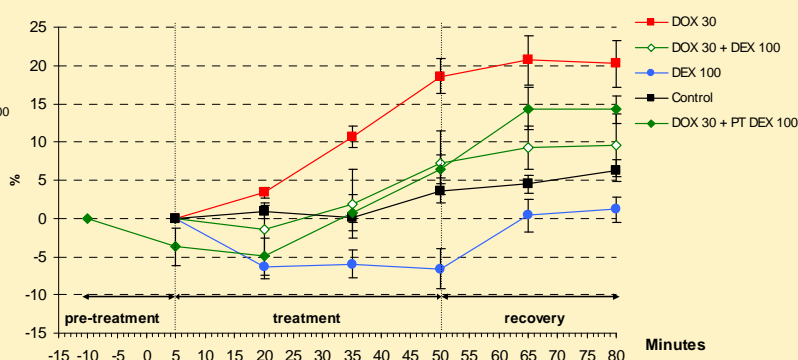
- ⇒ Continuous decrease in control conditions ( $-24 \pm 3\%$  in 45 min).
- ⇒ Lower decrease with DOX 30  $\mu$ M ( $-8 \pm 2\%$ ).
- ⇒ Lower decrease with DEX 100  $\mu$ M ( $-9 \pm 3\%$ ).
- ⇒ Synergic positive inotropic effect of DOX 30  $\mu$ M + DEX 100  $\mu$ M ( $+6 \pm 4\%$ ).
- ⇒ Positive inotropic effect of combined drugs improved by pre-treatment with DEX 100  $\mu$ M ( $+20 \pm 8\%$ ).

### QTc



- ⇒ No variation in control conditions ( $+1 \pm 0\%$  in 45 min).
- ⇒ Increase of QTc by DOX 30  $\mu$ M ( $+12 \pm 1\%$ ).
- ⇒ Moderate decrease with DEX 100  $\mu$ M ( $-5 \pm 1\%$ ).
- ⇒ DOX-induced QTc increase partially inhibited by DEX 100  $\mu$ M ( $+3 \pm 1\%$ ).
- ⇒ Protection of DEX 100  $\mu$ M against DOX-induced QTc increase anticipated by the pre-treatment with DEX 100  $\mu$ M ( $+1 \pm 2\%$ ) and sustained during recovery by the post-treatment with DEX 100  $\mu$ M.

### APD<sub>90</sub>



- ⇒ Slight increase in control conditions ( $+4 \pm 2\%$  in 45 min).
- ⇒ Increase of APD<sub>90</sub> by DOX 30  $\mu$ M ( $+12 \pm 1\%$ ).
- ⇒ Moderate decrease with DEX 100  $\mu$ M ( $-5 \pm 1\%$ ).
- ⇒ DOX-induced APD<sub>90</sub> increase partially inhibited by DEX 100  $\mu$ M ( $+3 \pm 1\%$ ).
- ⇒ Protection of DEX 100  $\mu$ M against DOX-induced APD<sub>90</sub> increase anticipated by the pre-treatment with DEX 100  $\mu$ M ( $+1 \pm 2\%$ ) and sustained during recovery by the post-treatment with DEX 100  $\mu$ M.

## CONCLUSION:

DEX exhibited beneficial effects during acute DOX administration as DEX prevented DOX-induced QTc prolongation and DOX+DEX showed synergic vasodilatation with positive inotropic effect.