Empagliflozin reduces cardiac pro-inflammatory cytokines, improves global longitudinal strain and exerts cardioprotective properties during treatment with Doxorubicin

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PURPOSE

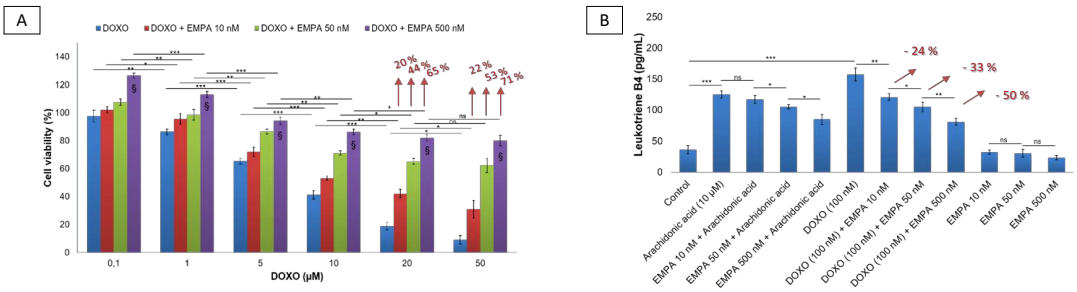
Doxorubicin is a highly effective antineoplastic drug belonging to the anthracycline class, however it is associated with relevant dose-dependent cardiotoxicity. Empagliflozin (EMPA), a selective inhibitor of the sodium glucose co-transporter 2, reduced the risk of hospitalization for heart failure and cardiovascular death in type 2 diabetic patients, in the EMPA-REG OUTCOME trial. In line with this finding, preclinical studies demonstrated that EMPA exerts anti-oxidant and cardioprotective effects. The aim of the present preclinical study was to evaluate whether EMPA exerts cardioprotective and anti-inflammatory effects in doxorubicin-induced cardiotoxicity.

METHODS

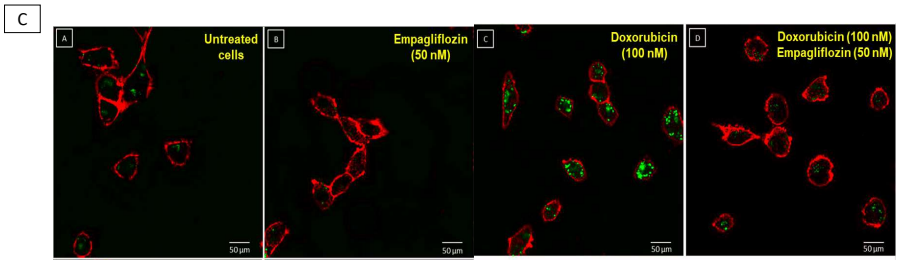
For this purpose, we tested the effects of EMPA (10, 50 or 500 nM) alone or in combination with DOXO in HL-1 adult cardiomyocytes evaluating: mitochondrial viability, Leukotriene-B4 expression and p65-NF-κB activation. Preclinical studies were also performed in C57BL6 mice, dividing them in 4 groups (n=6) : Sham (untreated mice), EMPA (mice treated with EMPA at 10 mg/kg/day, administrated orally for 7 days) ; DOXO (mice treated with DOXO at 2.25 mg/kg/day, intraperitoneally administered for 7 days); EMPA-DOXO (pre-treatment with EMPA for 3 days and 7 days of co-administration EMPA and DOXO). As predictor of cardiotoxicity, the Global Longitudinal Strain (GLS) was measured using 2D speckle tracking echocardiography. Heart, liver and kidney lysates were processed for analysis of pro-inflammatory interleukins involved in the anthracyclines-induced cardiotoxicity (Interleukin 1-β, 6 and 8).

RESULTS

(A) Empagliflozin increases the viability of cardiomyocytes during exposure to Doxorubicin in a concentration dependent manner and decreases significantly the expression of Leukotrienes B4, indicating its anti-inflammatory properties (B) *** P<0.001 ; **P<0.01 ; *P<0.05 ; ns: not significant

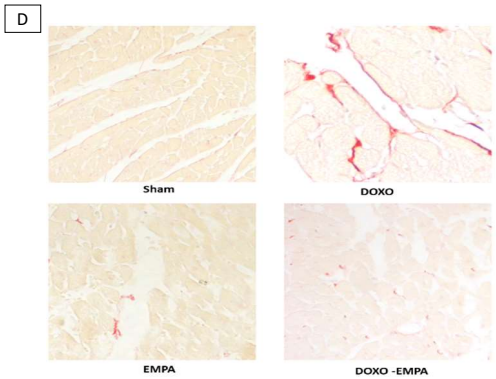


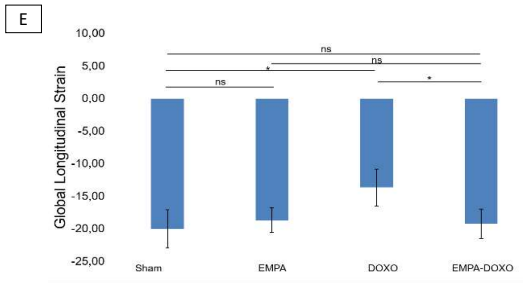
Empagliflozin inhibits the expression of p65/NF-kB* in cardiomyocytes during exposure to Doxorubicin (C)

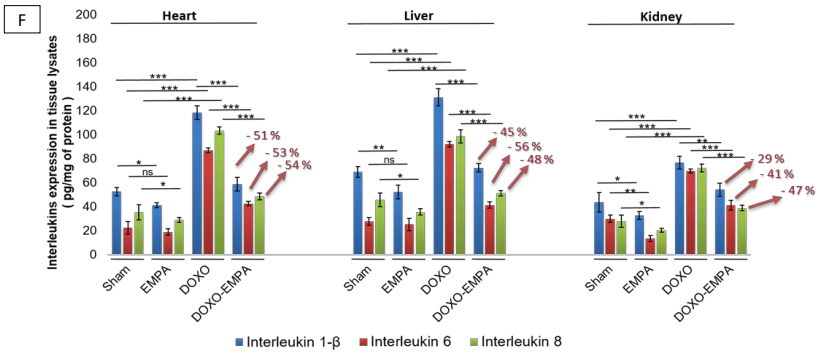


*nuclear factor kappa-light-chain-enhancer of activated B cells"

Empagliflozin reduces the cardiac fibrosis (D) (collagen expression), improves the Global Longitudinal Strain (E) and inhibits the expression of Interleukin 1-β, 8 and 6 (F) in heart, liver and kidney of mice treated with Doxorubicin. *** P<0.001 ; **P<0.01 ; *P<0.05 ; ns: not significant







CONCLUSIONS

EMPA has strong anti-inflammatory and cardioprotective effects in DOXO-Induced cardiotoxicity and these effects are mainly mediated by a reduction of the lipid peroxidation, Leukotriene-B4 and NF-κB activation bringing to a strong inhibition of the Interleukin 1β, 8 and 6 production.

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The authors declare no conflicts of interest