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Pharmacological preconditioning with the guanylate cyclase activator cinaciguat (BAY 58-2667) protects against reperfusion injury after cardiopulmonary bypass

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Background

Activation of the nitric oxide – soluble guanylate cyclase – cyclic guanosine monophosphate (NO-sGC-cGMP) pathway can induce potent cardioprotection-like effects against ischemia-reperfusion injury. We investigated the effects of pharmacological preconditioning with cinaciguat (BAY 58-2667), a novel sGC-activator on myocardial and coronary vascular function during reperfusion in a canine model of cardioplegic arrest and extracorporal circulation.

Materials and methods

Vehicle- (control group, n = 6) and cinaciguat-pretreated (8.33 μg/h iv. for 30 min; n = 7 low-dose treatment group and 25 μg/h iv. for 30 min; n = 6 high-dose treatment group) anesthetized dogs underwent cardiopulmonary bypass with 60 min of hypothermic cardiac arrest. Left and right ventricular end-systolic pressure volume relationship (ESPVR) was measured by a combined pressure-volume conductance catheter at baseline and after 60 min of reperfusion. Left anterior descending coronary blood flow, vasodilatation to acetylcholine and myocardial level of adenosine triphosphate were determined.

Results

Compared to control, pharmacological preconditioning with cinaciguat (25 μg/h) led to significantly higher myocardial adenosine triphosphate content, to a better recovery of left and right ventricular contractility (Δ slope of left ventricular ESPVR given as percent of baseline: 102.4 ± 19.1 vs. 56.0 ± 7.1%, $p < 0.05$) and to a higher coronary blood flow (49.6 ± 3.5 vs. 28.0 ± 3.9 ml/min, $p < 0.05$). Endothelium-dependent vasodilatory responses to acetylcholine were improved in the treatment groups.

Conclusion

Preconditioning with cinaciguat improves myocardial and endothelial function after cardiopulmonary bypass with hypothermic cardiac arrest. The observed protective effects imply that pharmacological sGC-activation could be a novel therapeutic option in the protection against ischemia-reperfusion injury in cardiac surgery.