Postconditioning and Debio-025 improve functional recovery and reduce mortality following acute myocardial infarction in mice

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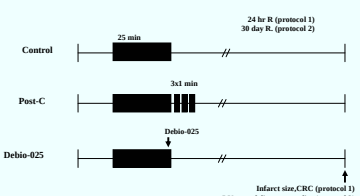
Background:

Major critical events following acute myocardial infarction include LV remodeling, heart failure and death. Ischemic postconditioning (Post-C) has been shown to reduce infarct size, possibly via the inhibition of the opening of the mitochondrial permeability transition pore (mPTP).

We sought to determine whether Post-C or pharmacological inhibition of the mPTP (Debio-025) at the time of reperfusion might reduce infarct size, improve LV functional recovery, and ameliorate survival.

Methods:

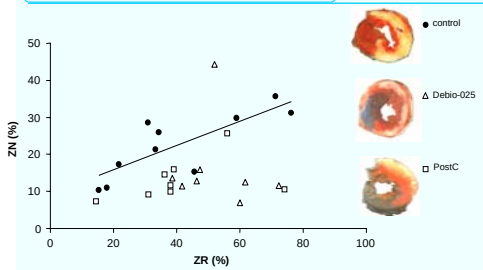


Anesthetized open-chest mice were subjected to two protocols: mice underwent 25 minutes of coronary artery occlusion followed by 24 hours of reperfusion (Protocol 1) or 30 days of reperfusion (Protocol 2).

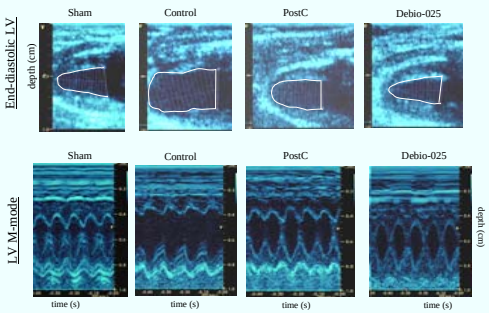
Mice underwent either no other intervention (control; C, n=10), an IV injection of 10mg/kg of Debio-25 (Debio-25, n=14), or postconditioning (Post-C; n=12) by 3 episodes of 1 minute ischemia each followed by 1 minute of reperfusion, starting 1 minute after reflow.

At 24 hours of reperfusion, mitochondria were isolated from the area at risk myocardium for assessment of the calcium retention capacity (CRC: fluorimetric technique, Calcium Green-5N), and infarct size was measured by TTC staining. At 30 days of reperfusion, mortality and recovery of LV contractile function (echocardiography) were evaluated.

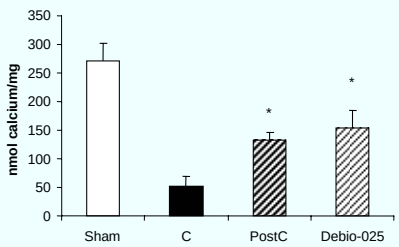
Results:



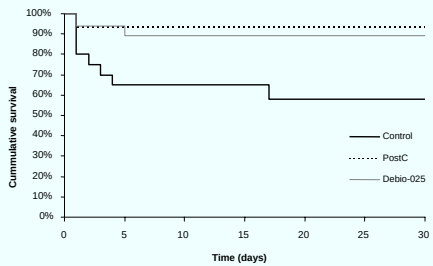
Infarct size (ZN) plotted as function of area at risk (ZR). For any size of area at risk, Post-C and Debio-25 treated hearts displayed smaller infarcts than control.



Typical examples of 2D and M-mode echocardiography in mice at day 30. Mettre valeurs de SF and EF ici! Ou bar graph que j'ai mis dans le papier!!



Calcium Retention Capacity (CRC): In the control group, CRC was significantly reduced versus Sham. Mitochondria isolated from Post-C and Debio-25 treated groups had increased CRC (i.e. resistance to Ca^{2+} overload) * $p<0.05$ versus control



Post-infarction mortality. During the 30 day follow up period, survival was significantly improved from 58% in control to 92 and 89% in Post-C and Debio025 groups, respectively.

Conclusion:

These data suggest that, beyond infarct size reduction, postconditioning and pharmacological inhibition of the mitochondrial permeability transition pore may have a potential interest to improve patient's prognostic after acute myocardial infarction.