INTERMITTENT ANTAGONISM OF BK2-RECEPTOR TRIGGERS THE MOST EFFECTIVE KININ-DEPENDENT POSTCONDITIONING.

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The extent of heart damage is a major prognostic determinant for survival stratification risk in patients undergoing acute myocardial infarction (AMI). Ischemic post-conditioning (IPC) afforded by repetitive periods (3-10 cycles) of ischemia alternated with brief (10-30 s) periods of reperfusion may help to protect the heart against ischemia-reperfusion (I/R) injury by activating a complex cascade of interlinked signalings collectively termed the reperfusion injury salvage kinase (RISK pathway). Pharmacological post-conditioning may significantly reduce the extent of ischemic area as well, but administration of extracellular autacoids or drugs (adenosine, bradykinine, opioids, etc.) requires specific dosages and exact algorhythms (Bice et al., 2014). For example, it has been shown that exogenous bradykinin (BK) may be protective when intermittently administered during the early reperfusion, whereas it does not enhance myocardial tolerance if continuously infused (Penna et al., 2007). Accordingly, continuous infusion of HOE140, a specific BK2 receptor (BK2R) antagonist, abolishes IPC cardioprotection (Sgarra et al. 2014). These observations suggest that the BK system confers myocardial protection only if modulated in a pulsatile manner. Based on this, it is plausible that therapeutic strategies variating endogenous BK levels may result as effective as the iatrogenic administration of BK, with the advantage of limiting the potential risks of supraphysiological BK levels. Thus, the aim of this study was to evaluate whether intermittent administration of HOE140 may represent an effective post-conditioning strategy, alternative to exogenous BK administration.

Hearts isolated from male Sprague-Dawley rats were mounted on a Langendorff system and exposed to I/R injury (30/120 min). Bradykinin (100 nM) and HOE-140 (1 □M) were administered post-ischemically during the first 3 min of reperfusion, under continuous or intermittent infusion (10 s/each). Rat hearts were randomly assigned to 4 groups and subjected to: 1) I/R alone (n=5); 2) continuous HOE140 (CHOE n=5); 3) intermittent HOE140 (IHOE n=5); 4) continuous bradykinin (CBK n=5); 5) intermittent bradykinin (IBK n=5). End-diastolic left ventricular pressure (LVEDP), developed left ventricular pressure (dLVP) and coronary flow (CF) were monitored throughout the experiments. For each heart, left ventricular infarct mass (IM) was quantified together with the activation status of RISK kinases Akt and GSK3β at the end of the reperfusion.

Consistent with previous results, infarct area extent was not significantly reduced in CBK or CHOE groups (vs. I/R). Conversely, hearts in the IBK and IHOE groups both showed a significant limitation in infarct mass, with the best recovery effect observed in the IHOE group (vs. I/R, $p<0.05$, $p<0.01$ respectively). Concomitantly, Akt phosphorylation levels were found higher in hearts of both IBK and IHOE groups (vs. I/R, $p <0.05$). Interestingly, when functional recovery of left ventriculum was evaluated, LVEDP values were significantly worsened in CHOE groups (vs. all groups, $p<0.05$), whereas dLVP values significantly improved only in the IHOE groups (vs. all groups: $p<0.01$). No significant differences in both LVEDP and CF values were observed among all groups.

These results suggest that, in isolated rat hearts, intermittent modulation of endogenous kallikrein-kinin system with a specific BK2R antagonist represents the most effective post-conditioning algorithm triggering endogenous BK-dependent RISK pathway activation.

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Penna et al. (2007) Cardiovascular Res 75,168-77

Sgarra et al (2014) Plos One 9, e88542