SUBNORMOTHERMIC MACHINE PERFUSION REDUCES NECROSIS AND APOPTOSIS AND IMPROVES ENERGY STATUS DURING PRESERVATION OF STEATOTIC RAT LIVERS: IMPLICATIONS FOR TRANSPLANTATION

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Machine perfusion (MP) preservation may enhance donor pool by reclaiming marginal livers including steatotic organs. We compared the efficacy of MP versus conventional cold storage both in control (Wistar rats) and fatty liver (Zucker rats). MP: livers perfused for 6 hrs with oxygenated Krebs-Henseleit solution (KH) containing 5mM N-acetylcysteine (NAC) pH 7.4 at 20°C. Cold storage: livers perfused *in situ* and preserved with Celsior solution at 4°C for 6 hrs. Reperfusion with KH (2 hrs at 37°C) was performed in the same condition either with the MP or cold storage preserved livers. The addition of NAC to the perfusate reduced the enzyme release during both MP and reperfusion period in livers of control rats. When fatty livers were perfused with KH containing NAC, very low release of enzyme was observed during MP and a significant lower hepatic damage was present at the end of reperfusion period compared with cold storage (AST U/l: 35.5±3 vs. 82.7±9, $p<0.02$; ALT U/l: 3.3±0.7 vs. 19,2±4, $p<0.02$). ATP levels, energy charge and ATP/ADP ratio were higher and a reduction of oxidative stress were observed in steatotic livers preserved by MP compared with cold storage. Bile production was higher and biliary enzyme release lower in fatty livers preserved by MP. In livers preserved by cold storage a 2-fold increase of TNF-alpha levels was observed as compared with organ preserved by MP (210±15 vs. 104±8 pmol/ml, $p<0.02$). In obese rats caspase-3 activity was largely increased during cold storage whereas during MP the increase was marked reduced (63.5±17.9 vs. 30.5±11.3 pmol/h/mg protein, $p<0.02$), evidencing that MP preservation method gives better results in terms of apoptosis activation, even if we did not observe DNA fragmentation in any sample. These data are substantiated by a better morphology, higher glycogen content and lower reactive oxygen species (ROS) production especially by sinusoidal cells in liver submitted to MP, respect to cold storage. In conclusion, MP at 20°C, improving cell survival, results in a better-quality hepatic preservation of steatotic livers compared with simple cold storage. MP under a moderate hypothermia might provide a new method for a successful utilization of marginal livers.