Can the degree of cardiac I/R damage determined in animal models be translated to the damage in humans with myocardial infarction or cardiac surgery?

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Introduction

A wealth of preclinical knowledge about cardioprotective agents has been gained over the past decennia. However, the translation of the laboratory data of ischemia-reperfusion (I/R) injury experiments into clinical application has been largely unsuccessful. In this literature review we compared the degree of I/R damage in animal studies to the degree of I/R damage in patients with acute myocardial infarction (AMI) and patients subjected to coronary artery bypass grafting (CABG) surgery.

Methods

Peak blood concentration values of commonly used biomarkers in the diagnosis of ischemic heart injury (Troponin T (TnT), Troponin I (TnI), creatine kinase (CK) and MB isoenzymes of creatine kinase (CK-MB)) were extracted from animal I/R studies and human AMI and CABG studies. The preferred animals in I/R injury studies were used, namely dogs, rabbits, mice, rats and pigs. PubMed database was screened until January 2016 by two authors. To compare the separate animals- versus human AMI, CABG and OPCAB groups a Mann Whitney U test was used since data were not normally distributed.

Results

In total, 243 animal and 151 human studies were included. Only animal groups with >5 studies per cardiac marker were used for further analysis. Figure 1A-F show the average value per cardiac marker for the animal and human AMI, CABG and OPCAB groups (1A-B) and the values for the specific animal groups compared with the respective human groups (1C-F). Mann-Whitney Tests showed there was no significant difference between the animal and human AMI group for the cardiac markers TnI, TnT and CK. The animal CK-MB group with AMI showed higher values than CK-MB measurements in the human AMI group. All four cardiac markers in the animal group were significantly higher than the values found in the human CABG and OPCAB groups. There was a large variability in test results.

F. 1A

F. 1C

F. 1E

F. 1B

F. 1D

F. 1F

Figure 1 A-F: Biomarkers indicative of cardiac ischemie-reperfusion damage compared between animal research models and the human condition of cardiac surgery and acute myocardial infarction. Values are reported as median and interquartile (25%-75%) range per cardiac marker per study group

Discussion & Conclusion

This review found that the degree of cardiac I/R damage examined in most animal AMI models is comparable to AMI damage in human studies using TnI, TnT and CK as biomarkers. However, the damage in animal research models is more severe than the damage occurring in the human conditions of CABG and OPCAB surgery. The cardiac marker CK-MB in animal studies (only rat studies were included) was significantly higher than in both human AMI and CABG groups. This might be explained by the CK-MB immunoassays used in animal research, which are most likely to be human-antigen based and often are non-specific for the respective animals. There was a very large variability in test results, making it difficult to directly compare studies from different species including human tissue. We conclude that pre-clinical models of cardiac I/R mimic AMI in humans, but largely overestimates the cardiac injury present during cardiac surgery.