Timely reperfusion is known as the best therapeutic strategy for limiting the extent of myocardial damage during an ST-segment–elevation myocardial infarction (STEMI). The concept of reperfusion as a means to limit necrosis during an STEMI was established in an experimental large animal (dog) model 4 decades ago. Noteworthy, the translation of the reperfusion concept in STEMI is one of the most successful stories of therapies ever. This example highlights the critical relevance of using preclinical models similar to humans for efficient translational research. Further research in the field identified that reperfusion is not a free lunch, and it can come at the price of inducing additional damage to the myocardium, a phenomenon known as reperfusion injury. The final extent of myocardial necrosis after a STEMI, resulting from both ischemic and reperfusion injuries, is a major determinant of mortality and morbidity after infarction. Therefore, huge efforts have been dedicated for exploring cardioprotective therapies that might limit ischemia/reperfusion injury beyond timely reperfusion. Opposed to what occurred with the reperfusion concept, the translation of therapies aiming to ameliorate reperfusion injury has been more disappointing than the former. With the exception of a few therapies succeeding in translating experimental results into positive proof of concept clinical trials demonstrating reduction in infarct size and increase in myocardial salvage, most promising cardioprotective agents/interventions have failed to replicate the positive results in experimental models in the clinical arena over the last decades. It is important to note that failure in translation is not restricted to the cardioprotection field, and similar frustrating findings have been observed in other areas.

What are the reasons responsible for this loss in translation? Inadequate experimental data and overoptimistic erroneous conclusions resulting from methodological flaws in animal studies might be one of the main reasons accounting for this scientific inconsistency. Like in any formal clinical trial, animal studies testing the efficacy of a given (cardioprotective) therapy/intervention should be based on a well-designed prespecified protocol paying rigorous attention to design (including expected effect size), conduct, statistical, and reporting-style aspects. Unfortunately, critical methodological elements such as blinding, randomization, or a priori sample size calculation are too frequently neglected in the experimental setting, increasing the chances of biased and hyped positive results. In the case of cardioprotective therapies, specific aspects directly related to the ultimate myocardial damage, such as animal species, strain differences, anesthetic agents, duration of ischemia, drug administration, manner and duration of reperfusion, and methodology and timing of end point (myocardial damage/salvage) evaluation may be decisive in the outcome of the study as well. Having all these variables as potential sources of variability, it is not so surprising that the replication and reproducibility of experimental results among different laboratories are alarmingly low. Several Working Groups of experts have deeply discussed the reasons for the failure to effectively translate potential therapies for protecting the heart from ischemia/reperfusion, making recommendations to try solving this unmet research need. The US initiative further included the creation of a network of research laboratories with expertise in small and large animal models of ischemia/reperfusion injury to systematically test a particular cardioprotective therapy using a multicenter randomized controlled study approach as a check-point before jumping into the clinical setting: the CAESAR (Consortium for preclinical Assessment of cardioprotective therapies) Cardioprotection Consortium (http://www.nhcaesar.org/). Recently, the European Society of Cardiology Group in Cellular Biology of the Heart have proposed the establishment of a European network of research centers to test cardioprotective interventions in an attempt to mimic the pioneer endeavor of the CAESAR’s enterprise.

Two highly relevant papers on the topic of translating preclinical results into clinics in the field of cardioprotection during STEMI appear in this issue of the Journal. Jones et al report the initial validation of the CAESAR initiative by testing the protection afforded by preconditioning, and Prof Heusch presents an outstanding comprehensive review of the mechanisms and signal transduction pathways in ischemic conditioning. The landmark CAESAR validation is based on the principles of detailed conduct of experimental protocols, randomization, researcher blinding, a priori sample size calculation and exclusion criteria, appropriate statistical analyses, and assessment of reproducibility. For such proof of concept validation, authors decided to test ischemic (local) preconditioning as the intervention to reduce infarct size in 3 species...
times animal studies yielding neutral results are never reported. CAESAR is certainly an endeavor of such relevance that a room for the report of negative preclinical studies should be identified. In this regard, it is noteworthy that Jones et al. acknowledge in their paper that 2 other agents have been tested by CAESAR, sodium nitrite and sildenafil citrate, and both failed to limit infarct size despite prior experimental studies reporting beneficial effects with these therapies. The best venue for reporting these negative findings in CAESAR is to be decided by the implicated institutions.

What is the ultimate translational relevance of the CAESAR initiative? This enterprise will certainly help in the better identification of therapies/interventions with chances to be tested in pilot clinical trials. Early identification of therapies with no (or limited) benefits will be of massive help for the scientific and pharmaceutical communities. The personal and economical costs associated with clinical trials is humongous and the proper early identification of potential failures is capital. There are some interventions that have already shown positive results in pilot clinical trials (for more details, we refer to the accompanying review paper by G. Heusch). It is noteworthy that these positive experiences were always preceded by thorough preclinical studies.

Emulating Julius Caesar and his legionsary, who built the first 2 bridges across the Rhine River to defeat Germanic tribes during the Gallic War in 53 BC, the CAESAR initiative has built a new bridge that will help the translation expansion in the field of cardioprotection during STEMI.

Disclosures

None.

References


   


   


   


   


   


   


Kw Words: Editorials ■ animal experimentation ■ infarction ■ ischemic preconditioning ■ random allocation ■ reperfusion ■ reproducibility of results
CAESAR: One Step Beyond in the Construction of a Translational Bridge for Cardioprotection
Rodrigo Fernández-Jiménez and Borja Ibanez

Circ Res. 2015;116:554-556
doi: 10.1161/CIRCRESAHA.115.305841

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/116/4/554

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/