Timely reperfusion is known as the best therapeutic strategy for limiting the extent of myocardial damage during an ST-segment–elevation myocardial infarction (STEMI).1,2 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.3,4 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.5 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.6 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,7–11 most promising cardioprotective agents/interventions have failed to replicate the positive results in experimental models in the clinical arena over the last decades.8,12 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.13,14

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.15 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.16 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,17–19 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.20 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.17,19,21 The US initiative further included the creation of a national 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 checkpoint before jumping into the clinical setting: the CAESAR (Consortium for precliniCAI assESSment of cARdioprotective therapies) Cardioprotection Consortium22 (http://www.nihcaesar.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 interventions17 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 al23 report the initial validation of the CAESAR initiative by testing the protection afforded by preconditioning, and Prof Heusch24 presents an outstanding comprehensive review of the mechanisms and signal transduction pathways in ischemic conditioning. The landmark CAESAR validation25 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

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**CAESAR**

One Step Beyond in the Construction of a Translational Bridge for Cardioprotection

Rodrigo Fernández-Jiménez, Borja Ibanez

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(mouse, rabbit, and pig) at 3 different centers of the consortium (2 sites/species). Authors wisely chose ischemic preconditioning as a protective intervention because it is probably the most robust and reproducible cardioprotective intervention known to date. The mechanisms of protection during ischemic preconditioning are extensively presented in the review paper appearing in the same issue of the journal.24

The CAESAR authors and institutions involved in this work should be congratulated for their innovative and huge effort to achieve a rigorous experimental setting. Overall, this approach should result in a reduction of potential biases and consequently in an increase in the confidence of attributing the differences observed between groups of animals allocated to different interventions to the treatment under investigation rather than to confounding factors or to just random error. However, there are potential shortcomings in the implementation and universalization of the CAESAR methodology. Counterintuitively, the excessive protocol standardization to reduce data variance can come at a negative price in some cases. It has been postulated that highly environmental standardized conditions may reveal restricted conclusions to a concrete experimental setting with little external validity being a cause, rather than a cure, of poor study reproducibility25 something that has been previously referred to as the standardization fallacy.26 External validity of experimental studies can be also affected by inevitable species differences. Therefore, even with rigorous design and conduct of an experimental study, such as the one elegantly presented by CAESAR, the translation of animal results to the clinics may fail because of disparities between the model and the real-world patient. CAESAR tries to overcome this limitation by using >1 laboratory for each species, but in the end 2 laboratories closely associated and following the exact same methodology are virtually a single hyperspecialized unit. The adding of more laboratories, eventually using slight different approaches (eg, different strain of animals, different anesthetics, different methods for outcome assessment, etc.), can serve to further improve the salutary long-term benefits of CAESAR.

Even the best animal models are approximations to human physiology/pathophysiology, and it is fair to acknowledge that in most cases they are only partially resembling what is seen in a more complex human diseased system. As an example, aging and multiple comorbid conditions seen in patients included in regular clinical trials are barely present in the experimental setting. Obviously, the intrinsic limitations inherent to animal models do not invalidate the use of laboratory research. We are convinced that animal models are useful tools in biomedical research, but a call for rigor in experimental investigation as presented by CAESAR initiative is necessary to improve translation. In this regard, it is noteworthy that in the paper by Jones et al,23 there seems to be a species-related effect size gradient: infarct size reduction by the applied preconditioning intervention was largest in mice, intermediate in rabbits, and smallest in pigs. This anecdotical findings highlight that the extrapolation of animal results into clinics highly depends on the species evaluated.

Another relevant aspect close to the topic here discussed is the positive results publication bias. The report of negative preclinical studies is an extremely hard endeavor, and many 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 al23 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. Heusch26). It is noteworthy that these positive experiences were always preceded by thorough preclinical studies.9,11,27

Emulating Julius Caesar and his legionsaries, who built the first 2 bridges across the Rhine River to defeat Germanic tribes during the Gallic War in 53 BC, the CAESAR initiative23 has built a new bridge that will help the translation expansion in the field of cardioprotection during STEMI.

Disclosures

None.

References


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