

Targeting Advanced Glycation End Products in Cardiac Surgery: The Unexplored Alternative

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Dear Editor,

In the previous issue of “Research in Cardiovascular Medicine”, our group presented a review of pharmacologic approaches against advanced glycation end products (AGEs) in diabetic cardiovascular disease (1). Over the last years, clinicians' viewpoint about diabetes moved from “glycaemia” to “glycaemia, glycated haemoglobin and glycation pathway”, and the recognized pivotal role of AGEs in genesis and progression of cardiovascular disease led to the development of new anti-AGEs compounds, with alagebrium, statins and thiazolidinediones being the most promising. These pharmacological studies were always performed in cardiology settings, but evidence-based medicine states that diabetic patients are more likely to have long-term benefits with surgical than percutaneous procedures (2). So, what is the state-of-the-art about AGEs awareness and anti-AGEs treatment in cardiac surgery?

AGEs levels and its pathways are closely related to post-operative outcomes and length of hospital stay. In fact, higher pre-operative plasma soluble receptor for AGEs (sRAGE) values are associated with prolonged duration of care (3), and higher carboxy-methyl-lysine (CML) values correlate with prolonged ventilation time after cardiac surgery (4). Also, sRAGE are a sensitive and early marker of post-operative lung distress, and this represents the most attractive field of investigation in both paediatric and adult procedures (5-7). sRAGE level was also reported to be lower in patients scheduled for surgical aortic valve replacement compared to healthy subjects, and its role in the pathogenesis of aortic valve stenosis is being currently investigated (8). As for diastolic dysfunction, plasma CML values are associated with mitral E/A ratio in pa-

tients undergoing coronary artery bypass graft surgery (9). The prognostic implication of AGEs appears also in orthotopic heart transplantation, as AGEs deposition in diabetic patients was related to acute rejection episodes (10). However, despite its potential interest, there is no unanimous consensus in the literature regarding the optimal technique for AGEs measurements. Plasma essays, skin autofluorescence and immunochemical methods have been differently reported throughout the literature and this complicates the possibility of a clear comparisons among the clinical studies (11). In the next years, the standardization of AGEs measurement would improve the actual understanding of the mechanisms underlying AGEs biological pathways and the effects of anti-AGEs treatments.

As far as pharmacologic approaches against AGEs are concerned, despite the flourishing production of literature in the field of cardiology on this topic, there are no current or terminated clinical trials investigating anti-AGEs role in cardiac surgery. This may be because newer drugs, such as alagebrium and aminoguanidine, are associated with side effects that seem to outnumber the potential benefits in AGEs modification. On the other hand, statins and thiazolidinediones are well-known drugs exerting significant anti-AGEs effect, but targeted clinical trials are still lacking. Thus the under-use of anti-AGEs compounds may be due to the under-comprehension of their potential benefits, which can be evaluated only during a long-term time span. In fact, notwithstanding the general lack of clinical trial on anti-AGEs treatments, the available studies only focus on short-term follow up which might elucidate side effects

of anti-AGEs compounds, but cannot reveal their actual long-term benefits in the progression of diabetic cardiovascular disease.

Alexis Carrel, French surgeon, Nobel laureate in 1912, wrote that “A few observation and much reasoning lead to error; many observations and a little reasoning to truth”. Studies on anti-AGEs compounds showed benefits in arterial compliance, ventricular stiffening and slowed progression of diabetic vascular disease. Spurred by the wave of optimism regarding the potential of anti-AGEs compounds, it seems to be right moment to introduce anti-AGEs drugs also into cardiac surgery study protocols, using newer safe compounds such as alagebrium and assessing the modification in the glycation pathway caused by known compounds such as statins and thiazolidinediones. As mentioned above, some investigators introduced interesting associations between AGEs and cardiac outcomes in cardiac surgery, but more structured approach are needed in this context. Also, considering the role of AGEs as marker of disease progression in the complex scenario of diabetes, measurement of AGEs levels should become part of the routine evaluation of the diabetic patient, not only to monitor blood glucose effects, but also to predict potential cardiac complications and provide prompt treatment. We hope that our considerations might shed light on this shaded topic in cardiac surgery and foster the scientific debate on this argument.

Footnotes

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