INVITED COMMENTARY

The Strength of Reperfusion: The Dark Side of Ischaemia

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In their paper, "Single muscle fibre contractility testing in rats to quantify ischaemic muscle damage during reperfusion injury",[1] Gok et al. attempted to determine the early extent of reperfusion injury, with single muscle fibre contractility (SMFC) testing. Using a remarkable *ex vivo* functional assay, they were able to demonstrate, surprisingly, that the maximum isometric and specific force generated by rat single tibialis anterior muscle fibre increased six hours after reperfusion but was reduced thereafter at two and seven days of reperfusion. Of importance, these findings were corroborated with quantitative histological injury. While the evidence presented in this elegant and insightful work highlights the potential role of SMFC testing, the study has some limitations, on which we would like to comment.

As the reduction of contractile force at myofibrillar level seems to correlate with the overall extent of muscle injury, the question of functional outcome remained unresolved. Indeed, owing to the absence of validated animal models, muscle function such as walking or running capacity, which represent the most relevant clinical endpoint, could not be evaluated. In humans, only a clinical prospective study could identify the diagnostic and eventually prognostic value of SMFC testing. Moreover, it would be interesting to explore the mechanistic basis for the initial increase in muscle force. While curious, it could provide insight into therapies to enhance muscle resistance to stress. Finally, the majority of the methods presented to quantify the extent of muscle injury required a long preparation time, limiting their bedside use. As acknowledged by the authors, SMFC testing also requires highly specialised equipment and expertise, which could ultimately limit its routine use, but seems feasible within one day.

Vascular surgeons often inflict short-term organ (e.g., limb, kidney) ischaemia and reperfusion injuries during vessel revascularisation and aneurysm repair. In addition to acute (trauma, emergency tourniquet application, or compartment syndrome) and chronic limb ischaemia, other iatrogenic causes include organ transplantation and free tissue transfer. Understanding the mechanism of injury and optimizing outcomes have been the basis for investigation encompassing multiple fields of physiological and surgical research for decades. The current consensus is that a period of ischaemia primes the tissue for subsequent damage upon reperfusion. Ischaemic cells will eventually die if blood flow is not restored, but it is during reperfusion itself that most of the damage is initiated, as also shown by Gok et al. Reperfusion is characterised by the increased formation of reactive oxygen species (ROS), a decrease in adenosine triphosphate production, and cell death.[2] Importantly, mitochondrial ROS not only drive acute damage, but also initiate the pathology that develops over the minutes, days, and weeks after reperfusion.[3] Interestingly, in rodent skeletal muscle, oxidative fibres were protected against the deleterious effects of ischaemia—reperfusion (vs. glycolytic), thanks to their antioxidant pool,[4] and, logically, recovered faster.[5]

While clinically recognised ischaemia—reperfusion injury is relatively rare during vascular reconstruction for aneurysm repair or peripheral artery disease, we probably underestimate both the local and systemic effects of clamping and unclamping major arteries. There are still many questions that remain unanswered. In addition to these local effects, could a subclinical systemic ischaemia—reperfusion syndrome drive perioperative cardiac stress? What is the impact of pre-existing disease or, more specifically and of great importance nowadays, the role of ageing in the magnitude of local, and distant ischaemia—reperfusion injury? Could we predict muscle recovery following revascularisation in both acute and chronic limb ischaemia?

In conclusion, this promising study highlights the importance of early quantification of the extent of muscle injury following ischaemia and reperfusion by using minimally invasive testing. Identification of specific therapies that may facilitate the recovery upon muscle ischaemia—reperfusion injuries will ultimately be facilitated by methods that can detect and quantify the extent of injury, such as SMFC testing.

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DOI of original article: https://doi.org/10.1016/j.ejvs.2019.01.009
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https://doi.org/10.1016/j.ejvs.2019.02.007