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Editorial

Paving the way for improving no-reflow phenomenon

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Following ST elevation myocardial infraction (STEMI) early reperfusion therapy has been consistently shown to improve outcome [1]. This has been shown both with thrombolytic therapy and with percutaneous intervention (PCI).The latter technique was found to be superior to thrombolytic therapy and is now the treatment of choice in STEMI. However, thrombolytics are widely used in developing countries because of lack of PCI centres. Despite, early reperfusion therapy it has been reported that 20–30% of patients failed to improve the function of the jeopardised myocardium in spite of patent coronary artery. Persistent dysfunctional myocardium leads to adverse cardiac remodelling, heart failure and thromboembolic phenomenon -all leading to adverse survival. The persistent myocardial dysfunction despite patent coronaries is because the microcirculation remains affected mainly because of microembolic phenomenon following reperfusion therapy that prevents microcirculatory flow leading to infarcted myocardium [2]. This is known as no-reflow phenomenon and today remains an elusive therapeutic target [2].

The study by Hu et al. from China in this journal sought to address this issue in an experimental model of vascular thrombus [3]. The group showed that liquid nanoparticles may be made to phase change to gas filled microbubbles using ultrasound at the site of interest. The transformation to microbubbles under repeated ultrasound irradiation then leads to cavitation of the microbubbles which leads to liberation of thermal energy resulting in thrombolysis- a phenomenon called sonothrombolysis. The phenomenon of sonothrombolysis has been utilised clinically to dissolve thrombus both in the large coronary artery and in the microcirculation by Mathias et al. using commercially available microbubbles and commercially available ultrasound system [4]. They used diagnostic ultrasound power to affect sonothrombolyis. Previously, sonothrombolyis was utilised clinically in patients with Transient Ischemic attack. The CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and systemic TPA) trial showed that continuous transcranial Doppler ultrasound augments t-PA–induced middle cerebral arterial recanalization [5].

However, the uniqueness of the technique by Hu et al. is that the liquid nanoparticles can permeate the surfaces of thrombus at a high concentration at which point when it is irradiated with ultrasound the rapid transformation of the liquid to gas -filled microbubbles and subsequent cavitation will affect a larger surface area of the thrombus and the effect will be sustained for a longer period of time compared to microbubble technique as applied clinically. The cavitation effect of the microbubble is less intense and more transient than the phase changing nanoparticles from the liquid to gaseous form. Furthermore, administration of microbubbles in the circulation will not allow the whole concentration of the microbubbles to be delivered at the site of interest as some of it will be destroyed by the stress of the circulation itself-shear forces within the circulation. In this experiment they have shown clearly that the weight loss of thrombus was significantly less with microbubble administration compared to liquid nanoparticle administration. What is not clear in the study is how the ultrasound power used to ensure phase change the nanoparticle will be applicable in humans. The authors used a power of 6 W for 20 min but its equivalence in clinical systems is not clear. In this study safety in terms of collateral damage to the surrounding structure using this power for this time was the least.

The clinical application of this technique will in the first instance require testing in suitable animal models. The complexity of circulatory environment in-vivo, the distance between the transducer and heart in close-chest experiment that will require considerable higher ultrasound power and therefore the efficiency with which the nanoparticle will phase change to gaseous form and subsequent cavitation intensity will ultimately decide how optimally this technique can dissolve the clots in the microcirculation. Though a significant part of clot dissolution may be mechanical at the microvascular level, other ultrasound-induced bioeffects may also contribute to clot dissolution. The ultrasound power may provoke nitric oxide release that is known to improve microvascular perfusion and at the same time augments the thrombus-dissolving effects of cavitation. Its previously shown that in animal models low-frequency ultrasound improved downstream perfusion beyond the ligated vessel. This effect was counteracted after the administration of NO synthase inhibitor [6].

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Thus, the world of ultrasound and nanoparticle technology awaits these exciting developments in therapy. The authors must be congratulated for this study.

Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] P.T. O'Gara, F.G. Kushner, D.D. Ascheim, et al., 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, J. Am. Coll. Cardiol. 61 (2013) e78–140.

[2] H. Ito, T. Tomooka, N. Sakai, et al., Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction, Circulation 85 (1992) 1699–1705.

[3] Bo Hu, Nan Jiang, Qing Zhou, Sheng Cao, Shunji Gao, Binghong Zhang, Jinling Chen, Ruiqiang Guo, Stable cavitation using acoustic phase-change dodecafluoropentane nanoparticles for coronary micro-circulation thrombolysis, 2018.

[4] W. Mathias, J.M. Tsutsui, G.B. Tavares, et al., Diagnostic ultrasound impulses improve microvascular flow in patients with STEMI receiving intravenous microbubbles, J. Am. Coll. Cardiol. 67 (2016) 2506–2515.

[5] A.V. Alexandrov, C.A. Molina, J.C. Grotta, Z. Garami, S.R. Ford, J. Alvarez-Sabin, J. Montaner, M. Saqqur, A.M. Demchuk, L.A. Moyé, M.D. Hill, A.W. Wojner, for the CLOTBUST Investigators, Ultrasound-enhanced thrombolysis for acute ischemic stroke, N. Engl. J. Med. 351 (2004) 2170–2178.

[6] R.J. Siegel, V.N. Suchkova, T. Miyamoto, et al., Ultrasound energy improves myocardial perfusion in the presence of coronary occlusion, J. Am. Coll. Cardiol. 44 (2004) 1454–1458.