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● *Original Contribution*

UNEXPECTED HIGH INCIDENCE OF CORONARY VASOCONSTRICTION IN THE REDUCTION OF MICROVASCULAR INJURY USING SONOLYSIS (ROMIUS) TRIAL

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Abstract—High-mechanical-index ultrasound and intravenous microbubbles might prove beneficial in treating microvascular obstruction caused by microthrombi after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI). Experiments in animals have revealed that longer-pulse-duration ultrasound is associated with an improvement in microvascular recovery. This trial tested long-pulse-duration, high-mechanical-index ultrasound in STEMI patients. Non-randomly assigned, non-blinded patients were included in this phase 2 trial. The primary endpoint was any side effect possibly related to the ultrasound treatment. The study was aborted after six patients were included; three patients experienced coronary vasoconstriction of the culprit artery, unresponsive to nitroglycerin. Therefore, coronary artery diameter was measured in five pigs. Coronary artery diameters distal to the injury site decreased after application of ultrasound, after balloon injury plus thrombus injection (from 1.89 ± 0.24 mm before to 1.78 ± 0.17 after ultrasound, $p = 0.05$). Long-pulse-duration ultrasound might cause coronary vasoconstriction distal to the culprit vessel location. (E-mail: sebastiaanroos@gmail.com)

Key Words: **Sonothrombolysis, Ultrasound contrast agents, Microvascular obstruction, Myocardial infarction, Theragnostic ultrasound.**

INTRODUCTION

Acute occlusion of a coronary artery causes elevation of the ST segment on the electrocardiogram, resulting in ST-segment elevation myocardial infarction (STEMI). Current therapy is focused on immediate restoration of flow of the obstructed epicardial coronary artery. This can be achieved with either thrombolytic therapy or primary percutaneous coronary intervention (PCI), the latter being favored in situations where trained personnel and specialized equipment are available (Windecker et al. 2015). Unfortunately, despite successful epicardial reperfusion, myocardial perfusion of the microvasculature is not restored in 5%–50% of cases, resulting in adverse clinical outcomes (Niccoli et al. 2009; Wu et al. 1998; Yellon and Hausenloy 2007). This phenomenon, known as no-reflow or microvascular occlusion (MVO), is of multifactorial origin and is possibly initiated by microvascular thromboembolization (Henriques et al. 2002; Niccoli et al. 2009), as well as intra-myocardial hemorrhage (Kloner et al. 1974; Robbers et al. 2013), but platelet and leukocyte aggregation, inflammation, edema and vasoconstriction all play an important role (Ibáñez et al. 2015). The relatively sudden reperfusion caused by PCI can also lead to cellular lethal reperfusion injury (Betgem et al. 2014). This is most likely caused by a combination of factors including high oxidative stress, intracellular calcium overload, (micro)vascular thrombi and inflammation, but the exact mechanism remains unknown (Fröhlich et al. 2013; Yellon and Hausenloy 2007). Detection and treatment of MVO are currently a focus of scientific research, which has led to mixed results in efficacy (Jaffe et al. 2010; Roos et al. 2014).

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One potential technique used an attempts to support PCI in the treatment of patients with acute STEMI is called sonolysis and consists of high-mechanical-index (MI) therapeutic ultrasound (US) directed at epicardial and microvascular thrombi to disrupt them and increase microvascular perfusion (Unger et al. 2004). Diagnostic ultrasound has already proven to be a useful tool in clinical cardiology, but normally uses low-mechanical-index US that allows function assessment and myocardial perfusion imaging. Therapeutic US usually consists of high-intensity US, which by itself causes cavitation in fluids and is therefore not suitable for diagnostic imaging. Combining therapeutic US with intravenous microbubbles significantly increases the amount of cavitation (Stride 2009). By using inertial cavitation, a large proportion of cavitating microbubbles release large amounts of energy, resulting in microjetting, among other effects, capable of destroying thrombi (Roos et al. 2014). However, the amount of microbubbles that undergo inertial cavitation is strongly dependent not only on the amplitude of the US, but also on the US frequency and the mechanical properties of the microbubble used (Radhakrishnan et al. 2013).

Increasing the mechanical index (Leeman et al. 2012) and increasing pulse duration (Wu et al. 2014) result in increased thrombus destruction in most but not all studies. Holland et al. (2008) reported that the largest thrombolytic enhancement at 1 MHz was achieved using a 1.0-MPa peak-to-peak pressure amplitude; however, with 120-kHz probes, a frequency that is not used in echocardiography in humans, pressures beyond 0.48 MPa did not result in increased sonothrombolysis (Datta et al. 2006; Holland et al. 2008). The increase in mechanical index and pulse duration might be the reason for the reduction in the amount of tissue plasminogen activator treatment needed to achieve thrombolysis in remote areas (Wu et al. 2015). A recent *in vivo* study in rats revealed that high-MI, long-pulse-tone therapeutic ultrasound is capable of achieving a reduction in microemboli in the biceps femoris muscle in a thrombotic vascular occlusion model (Pacella et al. 2015). The aim of the present study was to incorporate these pre-clinical results in a clinical scenario and to test the tolerability and feasibility of longer-pulse-duration (20 μs), high-MI (1.3) US with intravenous microbubble infusion for treatment of microvascular disease in acute STEMI patients using novel software that alternates therapeutic high-intensity US and diagnostic low-intensity US. This allows myocardial perfusion imaging to be used as a guide for therapy (theragnostic imaging).

METHODS

Patient population

Consecutive adult patients with acute STEMI were enrolled in the study. Exclusion criteria were cardiogenic shock, known allergy to ultrasound contrast agents, contraindications to magnetic resonance imaging (MRI) and any other reason judged by the investigators to hamper inclusion. After inclusion, patients were treated up to a maximum of 15 min with theragnostic ultrasound during preparation for PCI. US treatment was discontinued immediately on insertion of the wire through the arterial sheet or after completion of therapy (15 min). During PCI all patients received bivalirudin. Stent placement was performed based on the judgment of the interventional cardiologist. After PCI, all patients received an additional 30 min of sonolysis therapy (Fig. 1). The study was approved by the local ethics committee; a Data Safety Monitoring Board (DSMB) was created, and the trial was registered at http://trialregister.nl, identifier: NTR4791.

Theragnostic ultrasound

After giving consent, all patients received an intravenous infusion of Definity (Lantheus Medical Imaging, North Billerica, MA, USA) microspheres at 1.3 mL/min. The dosing protocol and instructions for continuous intravenous infusion as specified in the packaging instructions were used to administer Definity to our patients. A Philips S5-1 (Philips Healthcare, Best, Netherlands) probe on the IE33 system (Philips Healthcare), placed in the left fourth intercostal space, was used to alternate between diagnostic (contrast imaging only mode, MI = 0.18, 1.6-MHz center frequency, 50-Hz frame rate) and therapeutic ultrasound (pre-defined imaging area similar to the color Doppler box, superimposed on anatomic imaging, MI = 1.3, pulse duration = 20 μs, 1.6-MHz center frequency, 50-Hz frame rate) using myocardial perfusion defects as a guide for therapeutic high-MI ultrasound delivery. Diagnostic US and therapeutic US were manually alternated at the rate of 15 s per imaging mode, both to allow optimal microbubble replenishment and to treat the entire left ventricle, as the 2-D probe was manually rotated at 8 rotations/min, continuously alternating between 0° and 90° during treatment to contain as much of the risk area as possible.

Clinical and imaging data

Extensive blood analysis was performed regularly starting from initial hospital admission, and cardiac enzymatic markers were measured every 6 h until creatine phosphokinase MB (CKMB) had peaked.

Magnetic resonance imaging was performed 3–7 d after STEMI and at the 4-mo follow-up. The MRI protocol consisted of multiple imaging modalities including delayed contrast-enhanced (DCE) imaging to evaluate left ventricular function and infarct size, including area at risk and percentage of MVO. The primary endpoint was the myocardial salvage index. Area at