# Therapeutic Application of Ultrasound and Microbubbles (Sonothrombolysis) in Patients with Acute Myocardial Infarction

***Aplicação Terapêutica de Ultrassom e Microbolhas (Sonotrombólise) em Pacientes com Infarto Agudo do Miocárdio***

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Despite recent advances in understanding and treatment of acute coronary syndromes, their mortality and morbidity rates remain high. Acute myocardial infarction patients with ST-segment elevation (STEMI) usually have a coronary artery obstructed by a thrombus for which the restoration of vessel patency, as soon as possible, is crucial for short- and long-term survival and reduced morbidity. Pharmacological thrombolysis and percutaneous coronary intervention (PCI), the current recanalization therapies available for STEMI, improve patient prognosis[1]. However, some limitations persist regarding the use of these treatments in patients with STEMI, such as the success rate in coronary recanalization with the available pharmacological thrombolytics and their administration rate for the general population, the limited number of hospitals with an appropriate structure to perform primary angioplasty, and the difficulty performing the procedure early due to delayed patient transport, especially in developing countries[2]. It is also necessary to consider that, even with epicardial recanalization of the culprit artery, significant microvascular obstruction can still occur in up to 50% of patients with STEMI, resulting in areas of myocardial necrosis, ventricular remodeling, and worsening patient prognosis[3-5]. In this context, therapeutic alternatives have the potential to add value to the management of patients with STEMI.

## Keywords

Sonothrombolysis; Acute Myocardial Infarction; Microbubbles.

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High-energy transthoracic ultrasound has been studied as an adjuvant to fibrinolytic drugs in the treatment of arterial thrombi as well as an isolated method to treat vascular thrombi. Cavitation induction is a proposed mechanism of how the ultrasound dissolves the thrombus. Pre-clinical studies of acute coronary artery disease indicate that a continuous intravenous infusion of microbubbles containing a perfluorocarbon gas, associated with the energy emitted by a transthoracic diagnostic ultrasound transducer, can restore the coronary microcirculation, improve the rates of epicardial recanalization obtained with conventional therapy, and reduce the no-reflow degree[6-8]. Thus, the use of ultrasound associated with the intravenous infusion of microbubbles, called sonothrombolysis, has been assessed as a new treatment option for clinical situations associated with acute arterial obstructions. This study pioneered the role of sonothrombolysis in patients with STEMI[9,10]. The pilot study included 30 patients and randomized another 100 patients into a control group (undergoing conventional treatment with primary angioplasty) and a therapy group (undergoing sonothrombolysis before and after conventional treatment with primary angioplasty) (Figure 1). The results showed that sonothrombolysis is a safe therapy that increases angiographic recanalization (48% pre-angioplasty recanalization in the sonothrombolysis group versus 20% angiographic recanalization in the control group), decreases infarct size on magnetic resonance imaging and improves coronary microcirculation[10].

Sonothrombolysis was performed with an IE 33 echocardiograph machine (Philips Medical Systems) equipped with a broadband transthoracic transducer. The solution was prepared with commercially available microbubbles (Definity®, Lantheus Medical Imaging Inc., North Billerica, MA, USA) and intravenously infused. The recommended preparation is to dilute 1.5 mL of the activated Definity® suspension in 48.5 mL of 0.9% saline and infuse it at a rate of 1.5 mL/min.

# Editorial

Sonothrombolysis is the intravenous infusion of microbubbles associated with the application of diagnostic ultrasound using multiple high-energy pulses (1.8 MHz; mechanical index, 1.1–1.3; pulse duration, 3 μsec) guided by low-energy echocardiographic imaging (mechanical index, 0.18–0.20). This low mechanical index imaging allows the visualization of the contrast in the myocardium and, when the image is saturated with contrast and high-energy impulses are applied, successively alternating the position of the transducer in the apical planes of 2, 3, and 4 chambers. The intervals between flashes vary from 5 to 15 seconds depending on the time required for myocardial refilling by the microbubble contrast agent, which is verified by real-time perfusion images (Figure 2). Thus, this time interval allows the microbubbles to enter small canaliculi existing in the arterial thrombus. When high mechanical energy pulses are applied, the microbubbles break, improving thrombus dissolution. High-energy pulses are applied in two steps. The first stage of sonothrombolysis is conducted for as long as possible before primary PCI. The second stage is applied after primary PCI,

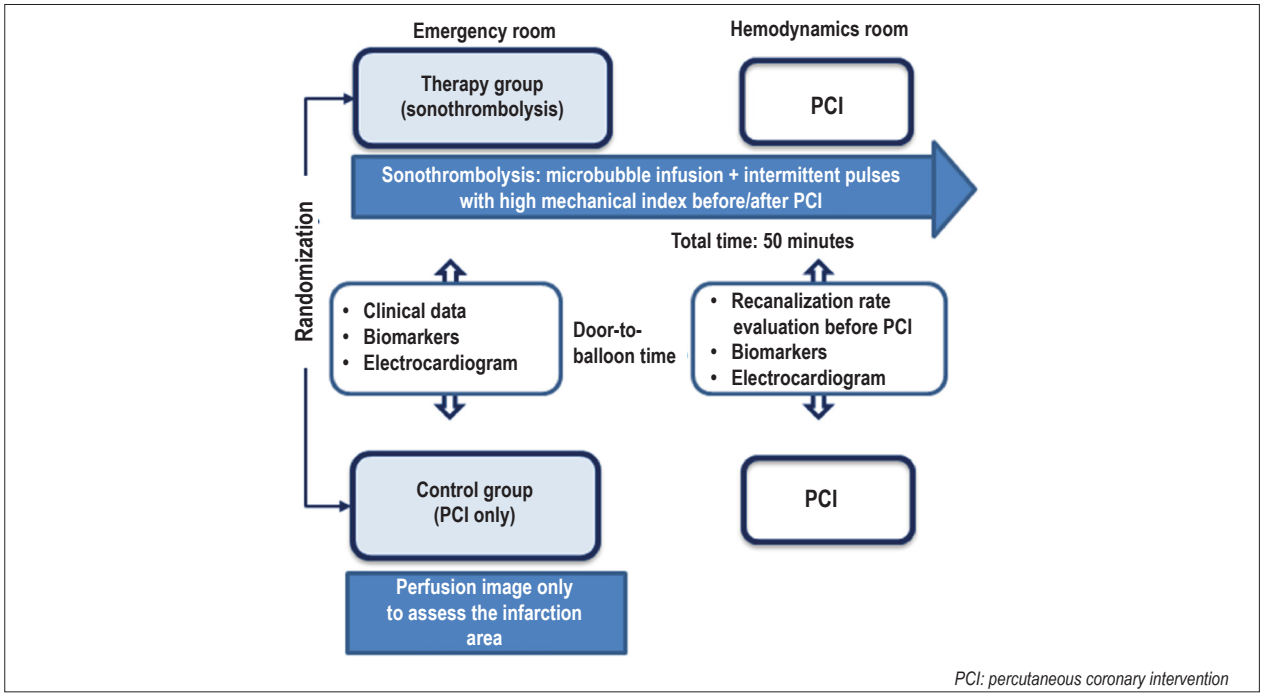


**Figure 1 –** *Study protocol for assessing sonothrombolysis in patients with acute myocardial infarction with ST-segment elevation. The patients meeting the inclusion criteria were randomized into a control group, in which participants underwent conventional treatment and percutaneous coronary intervention (PCI), and a therapy group, in which participants underwent sonothrombolysis. Sonothrombolysis (microbubble infusion and ultrasound with a high mechanical index) is applied for a total of 50 minutes.*

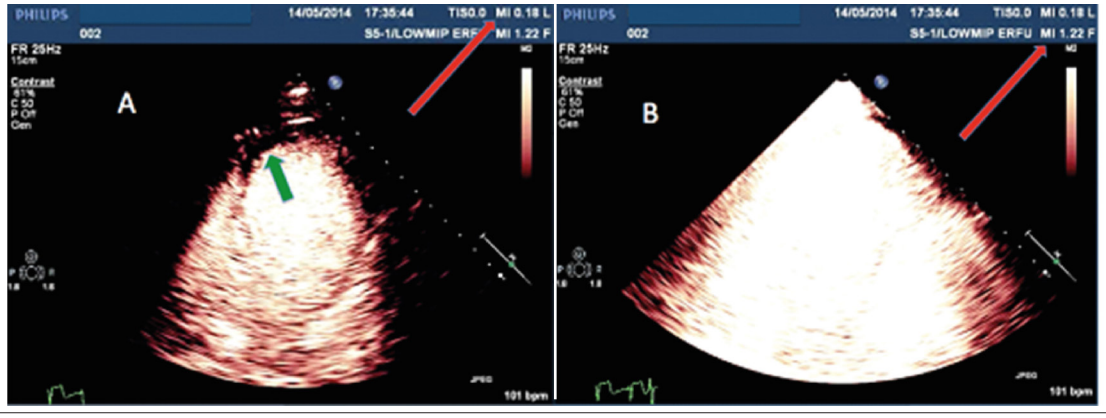


**Figure 2 –** *Example of sonothrombolysis application in a patient with acute myocardial infarction with ST-segment elevation. Image A shows the location of an apical perfusion defect in the left ventricle (green arrow) in a low mechanical index image (0.18) (red arrow). Image B shows the application of the flash, an impulse with a high mechanical index (1.22) (red arrow) that destroys the microbubbles inside the coronary microcirculation and results in cavitation and sonothrombolysis.*

in the hemodynamics room, for a total time of 50 minutes. The objective of this second stage is to exert sonothrombolysis effects on coronary microcirculation. In the control group, the patients underwent echocardiography with diagnostic imaging using a 1.8-MHz diagnostic ultrasound transducer with low-energy imaging (mechanical index, 0.18) and a frequency frame of 25 Hz limited to no more than three complete images in the standard apical planes of 2, 3, and 4 chambers to assess regional wall motility and microvascular perfusion before and after primary PCI.

The benefits of sonothrombolysis have yet to be proven with studies including a larger number of patients and can be assessed in other acute coronary syndromes. It is worth mentioning that it is an innovative therapy with great potential to assist the treatment of patients with STEMI.

## Conflict of interest

The authors have declared that they have no conflict of interest.

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