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Ultrasound and Microbubbles for Coronary Artery Recanalization in Acute Myocardial Infarction

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Summary

Background: Intravenous microbubbles (MB) and transthoracic ultrasound (US) have been utilized to recanalize epicardial vessels in animal models of ST segment elevation myocardial infarction (STEMI). The feasibility of such an ultrasound-guided approach in humans with STEMI have not been studied.

Objective: Pilot study with the aim to evaluate the efficacy of MB plus US on coronary artery recanalization rate in patients with STEMI.

Methods: Twenty-four patients (18 men, mean age 58 ± 9 years) admitted to the emergency room with STEMI were randomized into 3 groups. Patients either received MB plus custom designed high mechanical index (MI) impulses at 4-20 usec pulse duration (n = 7), MB plus diagnostic high MI (MI = 1.0) with multiple impulses < 2 usec pulse duration (n = 8) or MB plus limited diagnostic high MI impulses (< 5) just to analyze myocardial perfusion, control group (n = 9). MB utilized in the study consisted of a solution of Definity 3%. All randomized groups underwent emergent PCI.

Results: The mean door-to-balloon time were 76 ± 35 minutes in group US 4-20 usec, 70 ± 20 minutes in group US multiple impulses and 81 ± 13 minutes in control group (p = NS). Angiographic recanalization before PCI was observed in 75% of patients treated with US multiple impulses, in 43% for US 4-20 usec and 11% in control (p = <0.05).

Conclusion: Utilization of MB and diagnostic US with multiple impulses may be a method of achieving early recanalization in acute STEMI. (Arq Bras Cardiol: Imagem cardiovasc. 2016;29(3):92-98)

Keywords: Myocardial Infarction; Ultrasonography; Microbubbles; Thrombolytic Therapy.

Introduction

Microbubbles are small gas-filled microspheres with acoustic properties that make them very useful as ultrasound contrast agents for diagnostic imaging. Diagnostic contrast echocardiography, supported by ultrasound and microbubbles, has been used to improve endocardial borders and analyze myocardial perfusion.[1,2] The application of high mechanical index (MI) pulses through diagnostic transducers may result in cavitation of microbubbles and allow the analysis of backfilling of myocardial perfusion contrast, facilitating the assessment of myocardial perfusion.[3-6] Additionally, the destruction of microbubbles by ultrasound may have therapeutic applications, such as drug delivery to specific locations or to accelerate the dissolution of thrombi, also known as sonothrombolysis.

Current recanalization therapies in patients with acute myocardial infarction with ST-segment elevation myocardial infarction (STEMI) include pharmacological thrombolysis and percutaneous coronary intervention (PCI), both with proven improvement of prognosis in patients with STEMI.[7,8] But each of these therapies have significant limitations in clinical practice. Delay in time between the admission and arterial dilatation still exists in developed countries, during which myocardial necrosis can occur. This issue is even greater in developing countries, where access to primary PCI or even lytic therapy is jeopardized. In this context, the application of ultrasound and microbubbles in patients with STEMI can be a very promising treatment. Pre-clinical studies with pigs have shown that during a continuous intravenous infusion of perfluorocarbons-filled microbubbles, the ultrasonic energy issued by a diagnostic ultrasound transducer was able to restore the flow of microcirculation and improve the recanalization rates in experimental models of coronary arteries with acute thrombotic occlusion.[9,10]

The purpose of this pilot study was to evaluate the effectiveness of microbubbles (MB) and ultrasound (US) on initial recanalization rates of the coronary artery in patients with STEMI.

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Method

Study population

Patients admitted to the emergency room with chest pain and evidence of STEMI to the 12-lead electrocardiogram (ECG) were invited to take part in the study. Inclusion criteria: Age ≥ 18 years; eligible for emergency percutaneous coronary angioplasty; suitable apical and/or parasternal echocardiographic image; no known or suspected contraindication to the ultrasound contrast agent used in the study. Exclusion criteria: cardiogenic shock; life expectancy of less than two months or terminally ill patients history of previous myocardial infarction or severe heart disease, such as heart failure with ejection fraction <40% in previous evaluation; severe valvar lesions with significant hemodynamic repercussions; known hemorrhagic diathesis or contraindication to inhibitors of glycoprotein 2b/3a, anticoagulants or aspirin; known right/left shunt or severe pulmonary hypertension; women of childbearing age. The project was approved by the Commission of Ethics in Institutional Research (CAPPesq 342.799), and all the patients or their relatives signed the informed consent form.

Study protocol

Patients were randomized into 3 groups (Figure 1):

- Microbubbles group + high mechanical index (MI) impulses at 4 - 20 μseg: patients received ultrasound customized for this protocol through a 1.7 MHz-S5/1 Philips transducer, MI image > 1.0 and 4 - 20 μseg pulse duration, applied inside the risk area during continuous infusion of microbubbles (Definity® 3%, Lantheus Medical Imaging);

- Microbubbles group + high MI multiple impulses: patients received diagnostic ultrasound with high MI (> 1.0) multiple impulses, 15 frames each, at short duration (2 μseg), applied inside and outside the risk area during continuous infusion of microbubbles (Definity® 3%);

Echocardiographies were performed with IE 33 – Philips Medical Systems. Both groups used real-time perfusion imaging with low MI to evaluate microbubbles in the microvasculature. All patients were treated before and immediately after PCI for 50 to 60 minutes. The sonothrombolysis was performed while the patient waited to be taken to the hemodynamics room, without delay in the door-to-balloon time in view of the study protocol.

- Control group: the patients received microbubbles (Definity 3%) and real-time perfusion imaging with low MI was taken only to evaluate perfusion within the risk area at certain intervals. All patients in control group also underwent PCI.

A software specific for real-time myocardial perfusion imaging took echocardiographic images of longitudinal apical four-chamber and two-chamber views. The images were adjusted to minimize artifacts due to cardiac mobility and included: low MI (usually 0,2), pulse repetition frequency around 25 Hz, and maximum line density selected to achieve a clear myocardial opacification. A sequence of ultrasonic pulses of MI greater than 1.0 A (impulse) was manually triggered at the peak contrast intensity to destroy microbubbles within the myocardium. Then, low MI images were taken of at least 15 consecutive cardiac cycles to allow subsequent myocardial backfill.

Echocardiographic and angiographic analysis

The ejection fraction and the left ventricular end-diastolic and end-systolic volumes were calculated using Simpson's rule. The segmental wall motion score index was calculated by the sum of motility scores for every left ventricular segment (1 = normal, 2 = hypokinesis, 3 = akinesis and 4 = dyskinesis) divided by the number of segments evaluated. The myocardial perfusion index was calculated by the sum of myocardial perfusion scores for every left ventricular segment (1 = normal, 2 = hypokinesis, 3 = akinesis and 3 = dyskinesis) divided by the number of segments evaluated.

Coronary angiography was performed following standard protocol, and arterial patency was determined by analysis of the flow in the infarct-related vessel, before angioplasty. TIMI 0 or TIMI 1 cases were defined as occluded artery, and TIMI 2 or 3 were considered to represent an open artery.

Angiographic and echocardiographic analyzes were performed by interventional cardiologists and experienced echocardiographers who were not aware of the study's randomization.

Statistical analysis

Data are reported as mean ± standard deviation for normally distributed variables and as a percentage for qualitative variables. The method ANOVA was applied to compare door-to-balloon time, duration of chest pain, and recanalization rates obtained immediately after angioplasty, between the three study groups. P values <0.05 were considered significant.

Results

For one year, a total of 24 patients (mean age 58 ± 9 years) admitted to the emergency room with STEMI were evaluated. Of these, 75% were male, 62% were smokers, 50% had a history of dyslipidemia, 50% were hypertensive, and 38% were diabetic. Patients were randomized into the following groups: 7 patients in the 4-20 μseg high MI group, 8 patients in the high MI group with multiple impulses, and 9 patients in the control group. There was no difference in duration of chest pain time of the three groups, and any delay in door-to-balloon time was observed in the three groups (Table 1).

The echocardiographic evaluation data of the patients under study are described in Table 2.

The recanalization angiographic rate at the beginning of angiography (before performing PCI) was 6 to 8 patients (75%) in the group that received MB and US with high MI and multiple pulses; 3 in 7 patients (43%) in the group that received MB and US with high MI and 4-20 μseg pulse duration, and 1 in 9 patients (11%) in the control group (p < 0.05), as shown in Figure 2.

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Table 1 – Duration of chest pain and door-to-balloon time in the 3 groups

	Door-to-balloon time (minutes)	Duration of chest pain (hours)
High MI 4-20 µseg (n = 7)	76 ± 35	3:28
High MI multiple impulses (n = 8)	70 ± 20	3:30
Control (n = 9)	81 ± 13	3:25
p	ns	ns

Table 2 – Echocardiographic characteristics of left ventricular function

Group	LVEF (%)	LV-EDV (mL)	LV-ESV (mL)	WMSI	MPI	Number of segments with perfusion defect
Control	49	93	47.5	2	2	9
Control	48	125	65	2.23	2.29	15
Control	34	180	118	2.7	2.56	16
Control	42	71	41	2.05	2	11
Control	25	142	107	2.35	2.29	14
Control	49	65	33	1.64	1.41	7
Control	32	144	108	2.47	2.29	15
Control	39	80	49	2.11	2	12
Control	41	83	49	1.94	1.93	9
High MI 4-20 µseg	36	135	87	2.17	2.05	11
High MI 4-20 µseg	47	74	39.5	2.05	1.88	9
High MI 4-20 µseg	55	84	38	1.76	1.12	2
High MI 4-20 µseg	57	80	34.5	1.7	1.41	6
High MI 4-20 µseg	54	87	40	1.41	1.41	7
High MI 4-20 µseg	46	48	26	2.05	1.82	9
High MI 4-20 µseg	64	106	38	1.17	1.23	4
High MI multiple impulses	41	113	67	1.76	2.17	12
High MI multiple impulses	41	92	54	2.05	1.86	7
High MI multiple impulses	35	156	141	2.35	2.23	14
High MI multiple impulses	35	103	67	2.05	2.16	12
High MI multiple impulses	43	120	68	2.41	2.37	13
High MI multiple impulses	57	90	39	1.23	1.47	5
High MI multiple impulses	63	46	17	1.23	1.17	3
High MI multiple impulses	62	60	23	1.17	1.17	3

LVEF: left ventricular ejection fraction; LV-EDV: left ventricular end-diastolic volume; LV-ESV: left ventricular end-systolic volume; WMSI: segmental wall motion score index; MPI: myocardial perfusion index.

Example description: 57-year male patient with a history of smoking (40 cigarettes/day) and dyslipidemia; he was admitted to the emergency room with chest pain frame intensity 9 (0 -10), radiating to the left arm, lasting 1h30. His ECG at admission showed ST-segment elevation on the side wall (Figure 3A). The patient signed the informed consent form, underwent echocardiography with perfusion that showed akinesia of the inferior and septal wall associated with myocardial perfusion defect (Figure 4A). The patient was treated with Definity® through peripheral intravenous access and US with high MI with multiple impulses for 15 minutes while waiting for the PCI. In the hemodynamics room, prior to coronary angiography, the patient showed improvement of chest pain and a slight reduction of ST-segment elevation on ECG (Figure 3B). Angiography showed right coronary artery with subocclusive lesion with thrombus, rechanneled (TIMI 3 flow, Figure 5A). The patient underwent implantation of intracoronary stent
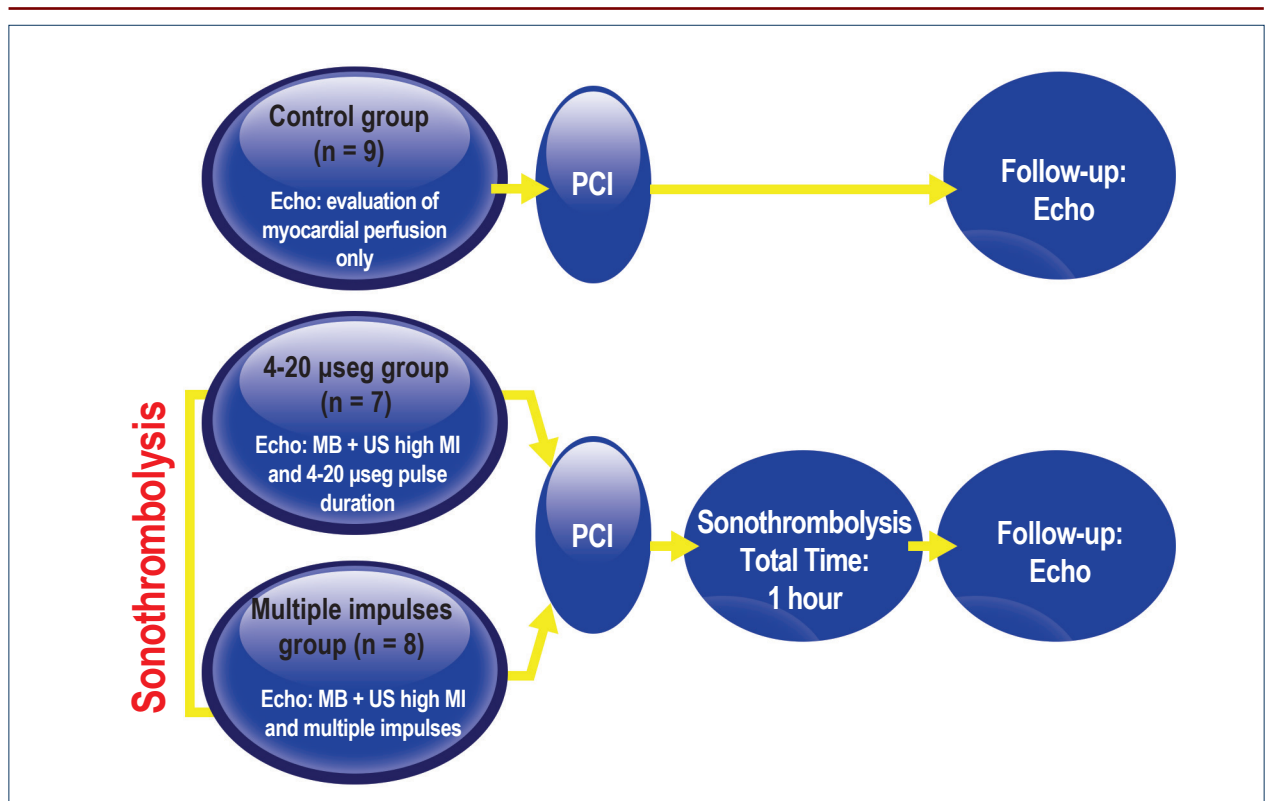
Figure 1 – *Flowchart of randomization of the 3 groups. MB: microbubbles; US: ultrasound; MI: mechanical index; PCI: percutaneous coronary intervention.*
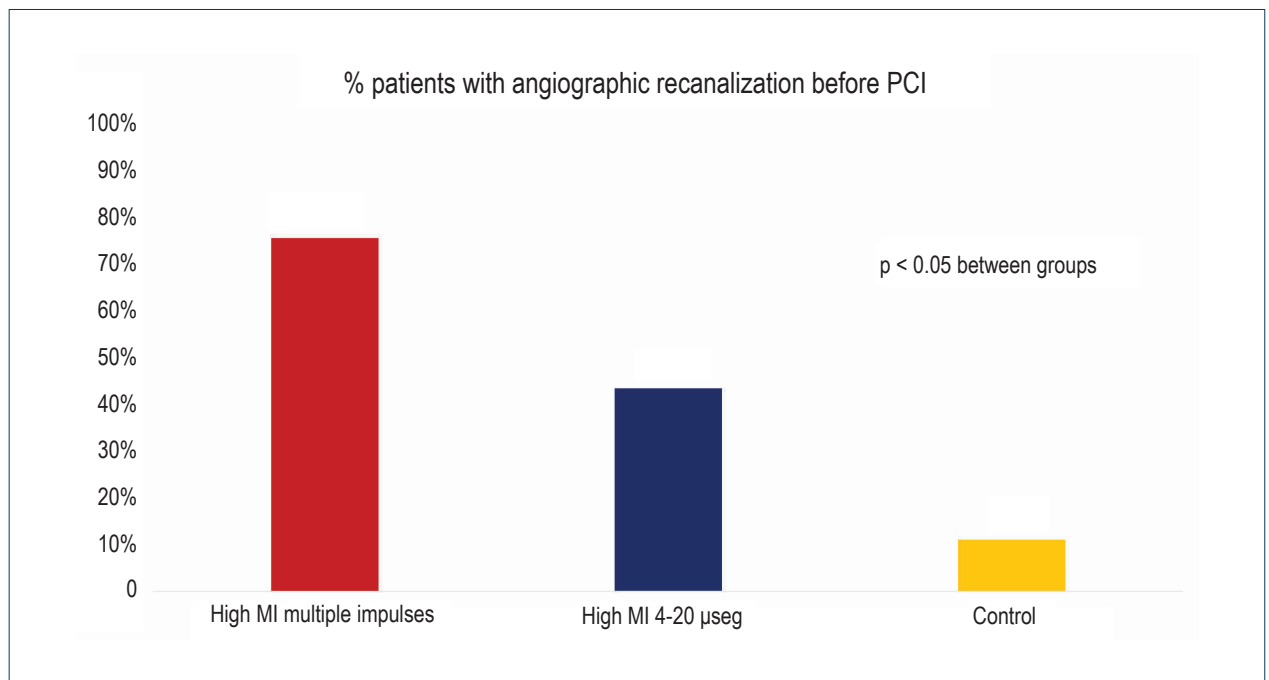

Figure 2 – *Angiographic recanalization rate observed before the first angiography, before percutaneous coronary intervention (PCI) in the 3 study groups.*
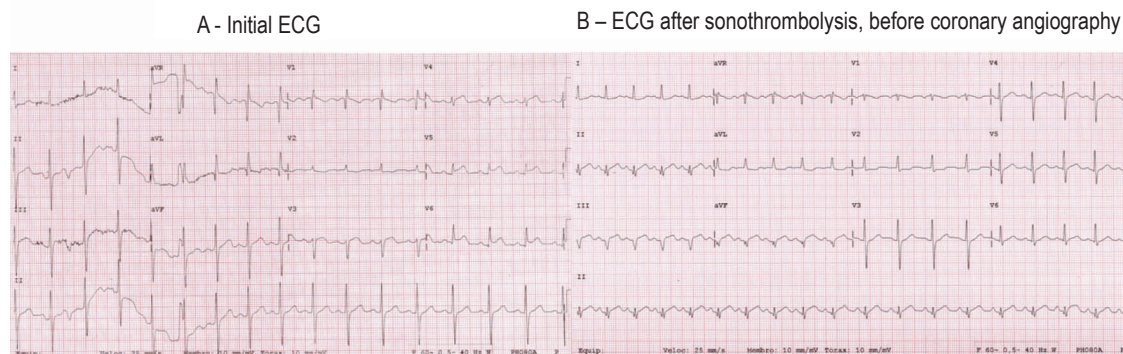
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Figure 3 – *12-lead electrocardiogram (ECG) traces at admission to the emergency room (A) showing ST-segment elevation on the side wall, and after 15 minutes of sonothrombolysis, before coronary angiography, with a slight reduction in ST-segment elevation (B).*
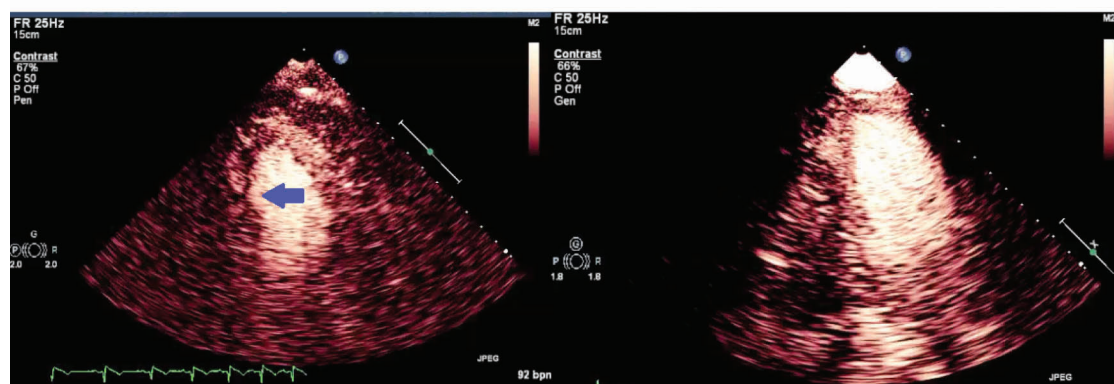

Figure 4 – *Real-time perfusion ECG imaging of apical two-chambers view, showing akinesia of the inferior wall associated with perfusion defect (A, arrow). After 15 minutes of sonothrombolysis, prior to coronary angiography, the echocardiographic evaluation showed that the inferior akinesia remained, but the myocardial perfusion defect on this wall improved (B).*

(Figure 5B). After the angioplasty, the patient remained under sonothrombolysis therapy until the end of the treatment. The post-treatment ECG shows improvement in myocardial perfusion in the infarcted area, and maintenance of the change in segmental contractility (Figure 4B), with a slight decrease in left ventricular global function (ejection fraction 55%)

Discussion

Today, epicardial recanalization is the main therapy for STEMI. Although PCI remains the first-line treatment for STEMI patients, in Brazil, only a small number of people have access to this therapy. Nevertheless, in patients in whom epicardial recanalization is successful through emergency PCI, the distal microvasculature to the occluded vessel remains closed, leading to significant myocardial necrosis in up to 65% of patients.[11,12]

The high-energy transthoracic ultrasound has been studied both as a supporting therapy for fibrinolytic drugs in the treatment of arterial thrombi, and a single method for the treatment of vascular thrombi.[13-17] A proposed mechanism of how the ultrasound dissolves the thrombus is by inducing cavitation.[18,19] Cavitation is the ultrasonic generation of gas bodies that expand and retract. This leads to shear forces, which disturb the environment and have the potential to break thrombus.

A – Coronary angiography showing lesion in right coronary (RC)

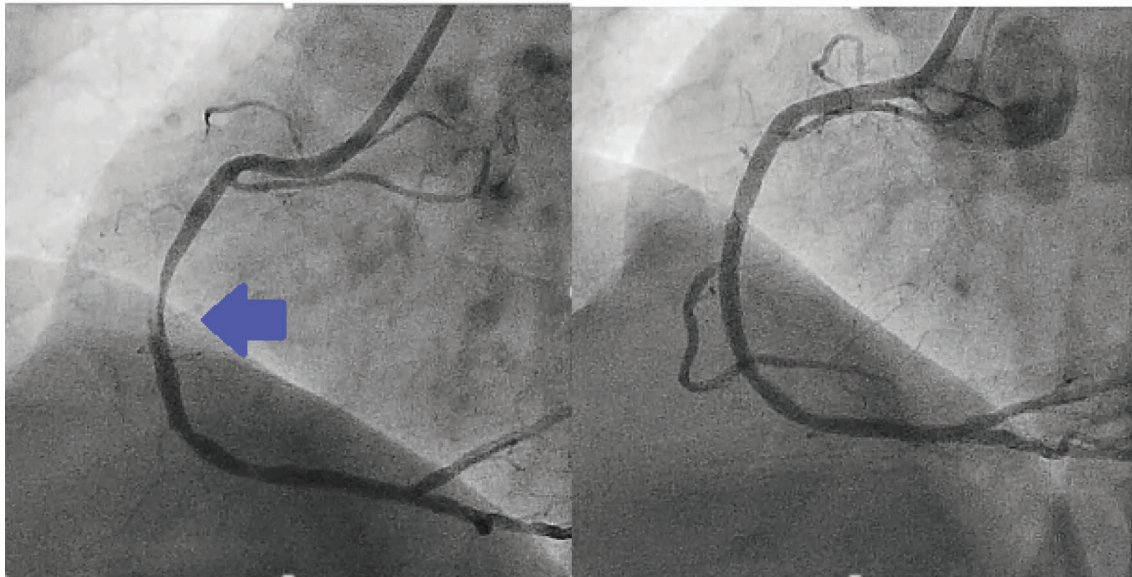B – Coronary angiography showing implantation of stent in right coronary (RC)

Figure 5 – *Coronary angiographic images after 15 minutes of sonothrombolysis showing subocclusion with thrombus in the middle third of the right coronary artery (A, arrow), with the presence TIMI 3 filling flow. The patient underwent implantation of intracoronary stent (B).*

Future application

The demonstration that the use of microbubbles, originally applied for diagnostic ultrasound, also has effect on the restoration of the affected epicardial coronary flow and microcirculation in STEMI will drastically impact how patients are handled in the initial phase of treatment. In view of the widespread availability and safety of ultrasound and microbubbles, the therapy to restore blood flow could be started in primary care units and in ambulances by skilled technicians as soon as the diagnosis of STEMI was defined. This would lead to a significant decrease in cardiac muscle losses, which occur while waiting for the safe performance of emergency primary angioplasty, besides reducing future complications to the patient, such as development of heart failure and complex arrhythmias.

Limitations

This is a pilot study, therefore, results in a greater number of patients, and the analysis of other myocardial perfusion parameters to define the impact on the microvasculature are still required.

Conclusion

This pilot study proved that it is possible to treat STEMI patients with microbubbles and ultrasound in the emergency room. The acoustic radiation forces generated by multiple impulses of diagnostic US of high MI applied on the myocardium can be a method of early recanalization of epicardial arteries in STEMI patients.

Authors' contributions

Research conception and design: Tsutsui JM, Kalil-Filho R, Porter TR, Mathias-Jr W; Data collection: Tavares BG, Aguiar MO, Garcia DR, Soeiro A; Data analysis and interpretation: Tavares BG, Aguiar MO, Garcia DR, Lemos-Neto PA; Statistical analysis: Tsutsui JM; Obtaining funding: Porter TR, Mathias-Jr W; Manuscript writing: Tavares BG, Soeiro A, Lemos-Neto PA; Critical revision of the manuscript's major intellectual content: Tsutsui JM, Kalil-Filho R, Porter TR, Mathias-Jr W; Clinical follow-up of patients with acute myocardial infarction: Oliveira MT.

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