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**Case Study**

# Cardiac Ultrasound-thrombolysis: Case Series

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## Abstract

**Introduction and objectives:** The authors present a series of 3 cases in which thoracic insonation was used during the percutaneous coronary intervention procedure in patients with acute coronary syndrome with ST-segment elevation and 100% thrombotic obstruction, showing that its application alone influences coronary thrombi recovering distal flow.

**Methods:** The patients admitted to the emergency department with chest pain in whom ST-segment elevation acute coronary syndrome was diagnosed, the infarction code was activated, and were admitted to the hemodynamic room, diagnostic angiography was performed, followed by thoracic insonation with a 4mHz sector transducer for 15 minutes in patients with 100% thrombus obstruction and a second angiography was performed to evaluate the effect. The lesions were repaired as the case called for and a final contrast shot was made to verify results, all patients were discharged to the coronary care unit.

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**Results:** In the 3 patients presented, there was recovery of distal coronary flow after the use of conventional ultrasound waves for 15 minutes, regardless of the medical treatment used.

**Conclusions:** This first case series suggests that the use of ultrasound-thrombolysis improves the efficacy of standard treatment in ST-segment elevation or OMI-type acute coronary syndrome, regardless of the vessel to be treated or baseline characteristics of the patients.

**Keywords:** Ultrasound; Myocardial infarction; Thrombolysis; Coronary reperfusion; Acute coronary syndrome; Thrombosis.

**Abbreviations:** OMI: Obstructive Myocardial Infarction; MHZ: Mega Hertz; rt-PA: Tissue Plasminogen Activator; DD: D-dimer; LVEF: Left Ventricular Ejection Fraction; Hrs: Hours; Mg: Milligrams; U/kg: units/kilogram; SICACEST: ST-segment Elevation Acute Coronary Syndrome; Mcg: Microgram.

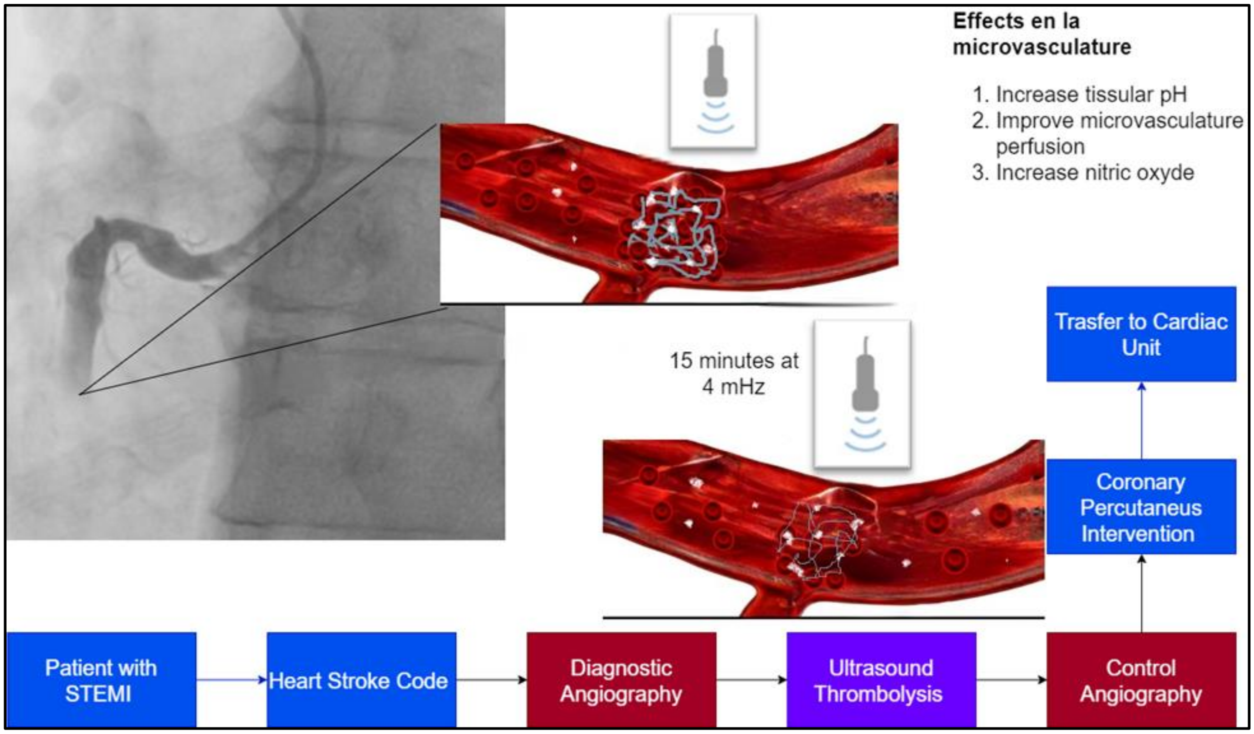


**Figure 1:** Article summary.

## Introduction

Reperfusion is the treatment that has most improved survival in patients with acute myocardial infarction, improving the prognosis in patients with ST-segment elevation acute coronary syndrome (STEMI), there are still different obstacles to the survival and long-term prognosis of these patients, among which the delay in seeking the first medical care stands out. As well as the resolution capacity of second-level centres to perform percutaneous coronary intervention, intravenous thrombolysis or transfer to specialized units [1,2]. In addition, up to 50% of patients will develop microvascular damage despite successful revascularization, implying long-term sequelae [3].

Thrombolysis is not a definitive treatment, but it provides time for admission to a unit with hemodynamic ability, adding the help of ultrasound looks to improve results and provide better results. In the case of intra-arterial thrombolysis, the aim is also to improve the result, especially at the microvascular level, although there is evidence that microbubble contrast may play a relevant role [4].

The theory behind sound-induced coagulation processes is based on the premise that particles exposed to mechanical waves (sound or ultrasound) generate changes in the distance between components, which can then favor or hinder their structural interactions, these changes are due to variations in the conditions of the Oseen flow


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due to the forces of attraction or repulsion by the relative position with respect to the acoustic field.

Therefore, different particles or molecules interact and respond differently at different frequencies. In general, these changes if applied to the same structure's present reproducible changes, for example, fibrin molecules will respond the same to 1MHz in all conditions and to 10MHz they will respond differently compared to exposure to 1MHz, but always in the same way to the stimulus of 10MHz [5].

These behaviors have already been applied to current medicine, for example, there are devices that help coagulation, such as high-frequency devices that generate local heat and help coagulate deep wounds [6], techniques used in rehabilitation.

These forces are also used in neurosurgery to apply energy to deep tissues without the need for an incision and minimizing the involvement of circulating tissues with the technique known as focused ultrasound guided by magnetic resonance imaging (MRgFUS) [7].

On the other hand, the use of ultrasound to alter coagulation has also been studied, perhaps one of the most representative studies is published by Braaten JV, et al. [8], where it showed that the application of ultrasound waves at 1MHz produced visible changes in the electron microscope in the ultrastructure of fibrin gels but only in the non-cross-links of the smallest fibers.

Therefore, in theory, it would generate an increase in binding sites for fibrinolytic components and therefore joint use could improve the prognosis [8].

Ultrasound has effects on the endogenous fibrinolytic system, demonstrating its efficacy in vitro; where it has been observed that it alters the distribution of plasminogen and tissue plasminogen activating factor (rt-PA); where it has been observed that the treatment of clots with rt-PA and combined with ultrasound, the levels of D-dimers (DD) were higher in the group treated with the combination (14895 ± 2513ng/ml vs. 2364 ± 725ng/ml). Thus, the thrombus showed a decrease in weight of 35.2% ± 6.9%, being statistically significant ($p<0.0001$) [9].

In addition to in vitro studies, ultrasound has shown promising results in animals. In a study with 14 animals (9 dogs and 5 pigs) that had a diagonal branch of the left anterior descending artery occluded and were administered low-frequency ultrasound (27kHz) for 60 minutes, which improved the coronary perfusion units by 19.7%, as well as the coronary pH to normal, the most relevant finding being that the histomorphology analysis showed an increase in the capillary area in the myocardium in patients with ultrasound exposure (16.2 ± 7.9 vs. 8.2 ± 2.1, $p <0.02$) [10].

Mathias W Jr, et al. [4], clinical trial with 50 patients with STEMI in whom echocardiography with contrast was performed prior to coronary intervention, demonstrated a reduction in infarction size compared to patients with standard management 32% vs 4%; also showing improvement in ejection fraction 6 months after the event with an LVEF of 47 ± 12 in the control group vs 41 ± 10 in treatment group [4].

Currently there is abundant evidence regarding the use of low-frequency


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ultrasound in conjunction with thrombolytics for the treatment of pulmonary thromboembolism, its use has decreased the use of thrombolytic doses and therefore reduced the risk of bleeding, adding few risks to the therapy, although with the need for an intra-arterial procedure, this type of treatment seems to provide significant advantages over conventional treatment. However, now it is a treatment that significantly increases treatment costs [11-13]. The use of transthoracic echocardiography provides a low-cost source of exposure to low-frequency ultrasound waves at a low cost, without the need for special facilities or special equipment, if administered during intravenous thrombolysis in cases of acute myocardial infarction, especially with the infusion of Tenecteplase, has the potential to increase thrombolysis success by increasing binding sites for the drug. During the infusion, which will usually last a couple of minutes, it can additionally provide important information about the patient's ventricular function and does not delay other critical areas of patient care.

## Methods

The procedure was performed in 3 patients selected for convenience, in whom STEMI was diagnosed in the emergency department with less than 12 hours of evolution time. Following the algorithm in diagram 1:

- A heart attack code is activated, which includes:
  1. Oral medication administration in the emergency room:
     - i. Acetylsalicylic acid 300mg
     - ii. Clopidogrel 600mg
     - iii. Atorvastatin 80mg
  2. Immediate admission to the hemodynamic room in less than 60 minutes (average time 23.5 minutes with a range of 5 to 45 minutes).
     - i. Radial access in the 3 patients with parenteral drug administration:
       - a. Heparin in fractionated bolus 100U/kg intravenously.
       - b. Radial intra-arterial nitro-glycerine 200mcg.
     - ii. Cardiac catheterization was performed, with a diagnosis of 100% obstruction of the guilty artery due to thrombus (grade 5 thrombus).
     - iii. Thoracic insonation (ultrasound-thrombolysis) was performed with a Phillips Epiq 7 ultrasound machine for 15 minutes with a 4mHz xMATRIX (X5-1) sector transducer (phase array) (without delaying at any time the other interventions considered the standard of care).
     - iv. A new shot was fired with contrast prior to the guideline or therapeutic step of coronary intervention.
     - v. Coronary intervention is performed according to the patient's requirements.
  3. The patient is admitted to the coronary care unit.


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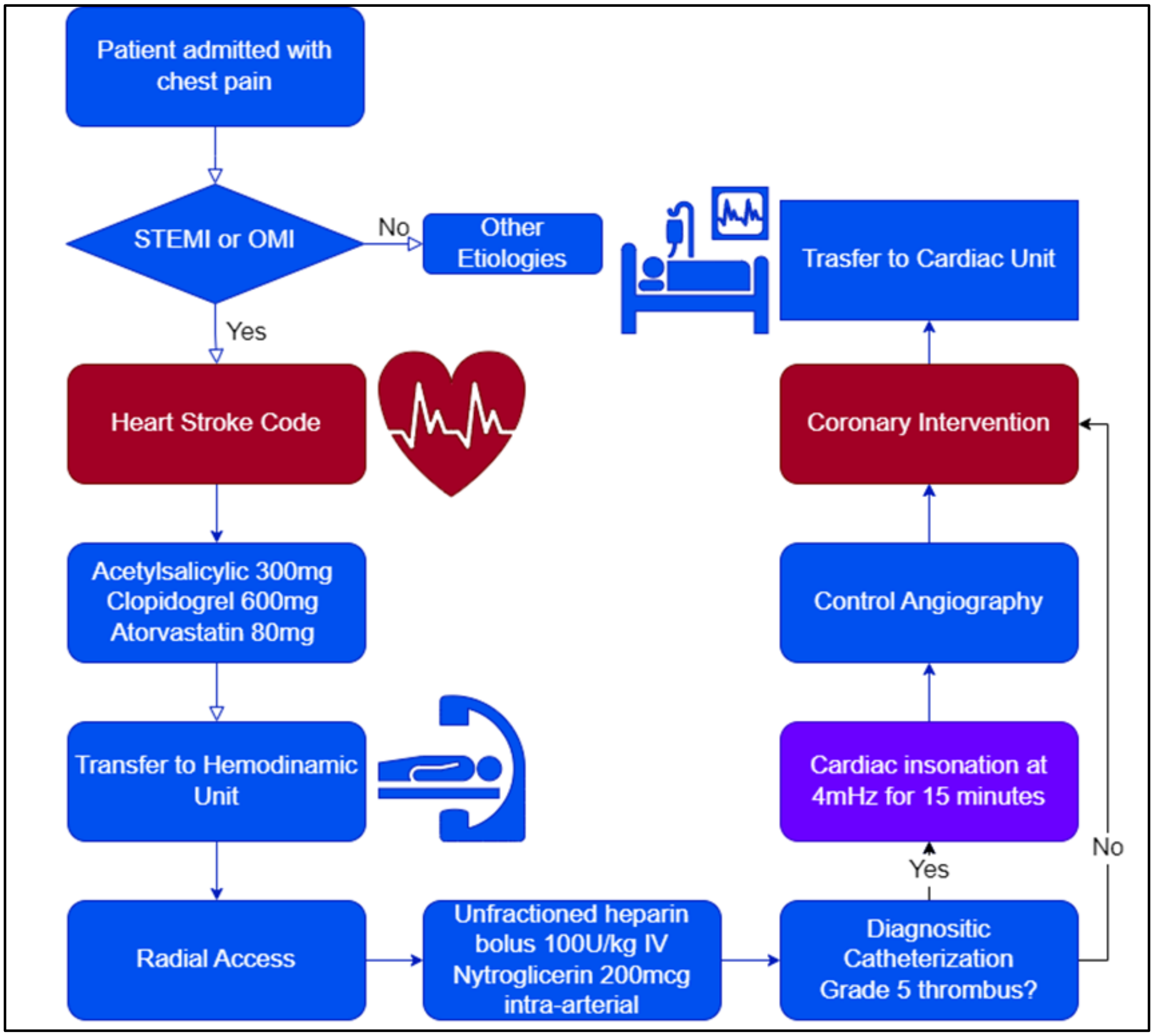


**Figure 2:** Treatment algorithm.

## Results

The authors present 3 cases of patients admitted with a diagnosis of ST-segment elevation acute coronary syndrome (Table 1).

## Case 1

A 75-year-old male with a history of type 2 diabetes was diagnosed with metformin 850mg every 8 hours and glimepiride 2 mg every 12 hours, systemic arterial hypertension diagnosed 17 years ago and was treated with losartan 100mg every 24 hours. The patient denies a history of cardiovascular disease. The symptoms began when the patient was at rest, presenting oppressive chest pain of 10/10 intensity accompanied by nausea, diaphoresis and dyspnoea, which is why the patient went to the emergency room 5 hours after the onset of symptoms.

On admission, an electrocardiogram was taken, showing complete right bundle branch block of the bundle and ST-segment elevation in V1-V6 of the patient. The infarction code is activated, and the patient is transferred to the hemodynamic room. A right radial approach was performed with a 6Fr introducer, a


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diagnosis was made with a 5Fr TIG catheter and the anterior descending artery was shown in the middle segment as the artery responsible for infarction, finding grade 5 thrombus, final flow TIMI 0. Ultrasound-thrombolysis was performed for 15 minutes, cannulation was performed with a 6Fr VL 3.5 guide catheter, next injection of contrast was performed, recovering TIMI 2 with grade 4 thrombus and mid-segment lesion at the end of the flow. Angioplasty was performed with a 2.0 × 20mm semi-compliant balloon and a 3.0 × 38mm medicated stent was implanted, optimizing with a 3.5 × 12mm non-compliant balloon on the proximal segment of the stent, obtaining adequate procedural results, without residual thrombus and adequate final flow TIMI 3 and TMP 3. The patient was admitted to the coronary unit and discharged home 3 days later without complications.

| Age | Gender | Dear Infato | Ischemia Time | Guilty Artery | Diabetes | Hipertension | Cardiopatia Isquemica Previa |
|---|---|---|---|---|---|---|---|
| 75 | Male | AnteroseptaL | 6hrs | Anterior Descendant | Yes | Yes | No |
| 63 | Male | Inferior | 5hrs | Right Coronary Artery | No | Yes | No |
| 85 | Female | Inferolateral | 7hrs | Circumflex | No | No | No |

**Table 1:** In which the characteristics of the patients treated in this series are shown.

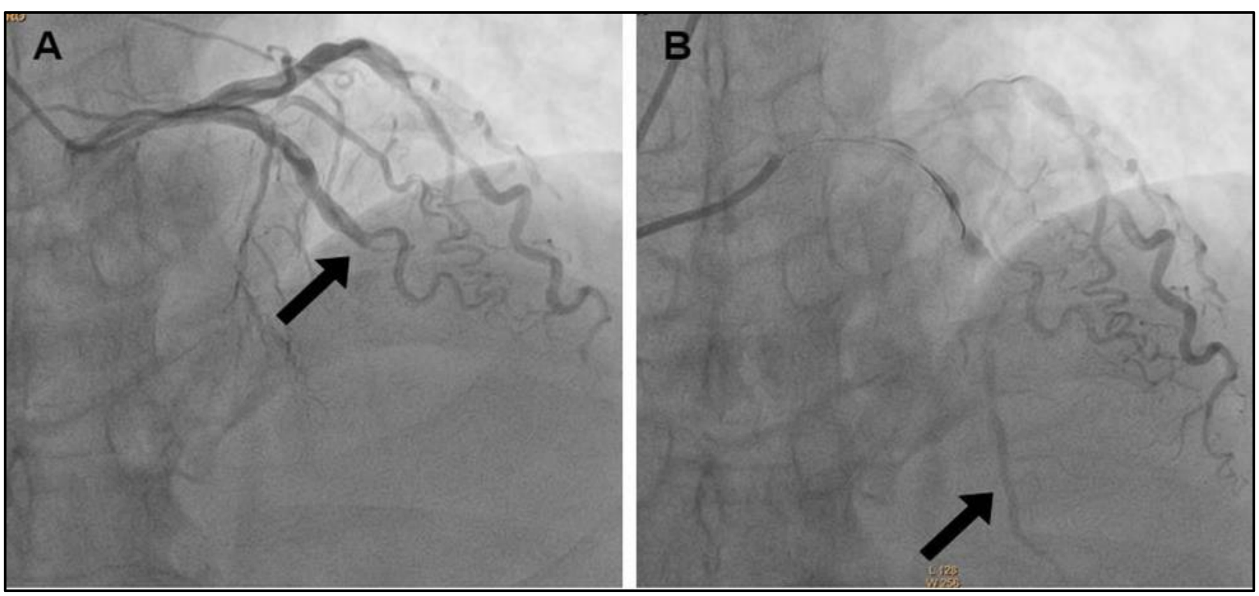


**Figure 3:** SICACEST type IMO anteroseptal-anterior descending culprit artery. A) diagnostic angiography with 100% anterior descending mid-segment obstruction (arrow); B) recovery of distal flow after ultrasound-thrombolysis (arrow), final flow TIMI 1.


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**Case 2**

Male patient, 63 years old, with a history of systemic arterial hypertension of 15 years of diagnosis, treated with losartan 50mg every 24 hours and chlorthalidone 25mg every 24 hours, adenocarcinoma of the pancreas IIB (T2N1M1) treated with Whipple surgery on 30-09-2022, currently palliative treatment with Gemcitabine=Capecitabine, both considered cardiotoxic and have been associated with acute coronary events [14-18].

The patient began with oppressive chest pain of 10/10 intensity, accompanied by diaphoresis and lipothymia, so went to the emergency room 6 hours after the onset of the pain and with persistence of the pain. On admission, an electrocardiogram was taken, showing ST-segment elevation of the face DII, DIII and aVF with negative ST elevation in DI, aVL, V1-V4 with electrical extension to the right ventricle. The infarction code was activated, and the patient was transferred to the hemodynamic room with a radial approach with a 6Fr catheter, performing diagnostic catheterization with a 5Fr TIG catheter, showing evidence of right coronary ectasia, with grade 5 thrombus in the middle segment, with final flow TIMI 0.

Ultrasound-thrombolysis was performed for 15 minutes, and a right femoral temporary pacemaker was placed due to the presence of third-degree AV block; A right coronary cannula was obtained with a JR 3.56Fr guide catheter and contrast injection was performed, observing recovery of flow with grade 4 thrombus residual final flow TIMI 3, not requiring another intervention. The procedure was ended and intracoronary thyrofiban was administered in bolus plus 16 hours infusion, then it remained with anticoagulation with enoxaparin 1mg/kg every 12 hours for a second time 5 days later. The patient stayed stable and later recovery to sinus rhythm and the temporary pacemaker was removed. Catheterization was performed at 5 days as a second stage with patent coronary vessel and thrombus decrease, without requiring any further intervention. Graduated without complications.

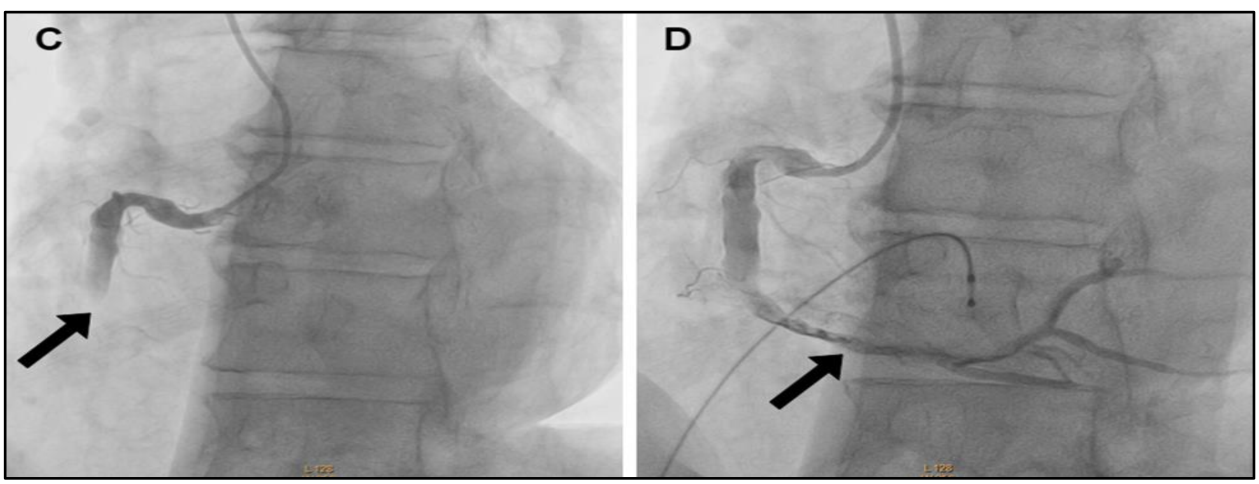


**Figure 4:** SICACEST type lower OMI, right coronary culprit artery. A) diagnostic angiography with 100% right coronary proximal segment (arrow) obstruction; B) recovery of distal flow after ultrasound-thrombolysis (arrow), final flow TIMI 3.


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**Case 2**

An 85-year-old female patient with no known medical history. The current condition began in the early hours of the morning when the patient woke up with chest pain of intensity 6/10 accompanied by diaphoresis that increased after two hours to intensity 10/10 with dyspnoea at rest, so went to the emergency room 4 hours after the onset of symptoms.

An ST-segment elevation electrocardiogram was taken in DII, DIII, aVF, DI, V5 and V6. The infarction code was activated, the patient was admitted to the hemodynamic room, and the patient was approached radially with a 6Fr introducer and a 5Fr TIG diagnostic catheter. Circumflex dominance with grade 5 thrombus, final flow TIMI 0 is seen. Ultrasound thrombolysis was performed for 10 minutes, then injection with a guide catheter was seen, observing improvement in flow to TIMI grade 2, achieving satisfactory intervention performing angioplasty with a semi-accommodating balloon 2.5 × 12mm and implantation of a medicated stent 3.0 × 24mm. With adequate result, no residual thrombus, final flow TIMI 3 TMP 3.

The patient progressed satisfactorily and was discharged 4 days after the intervention.

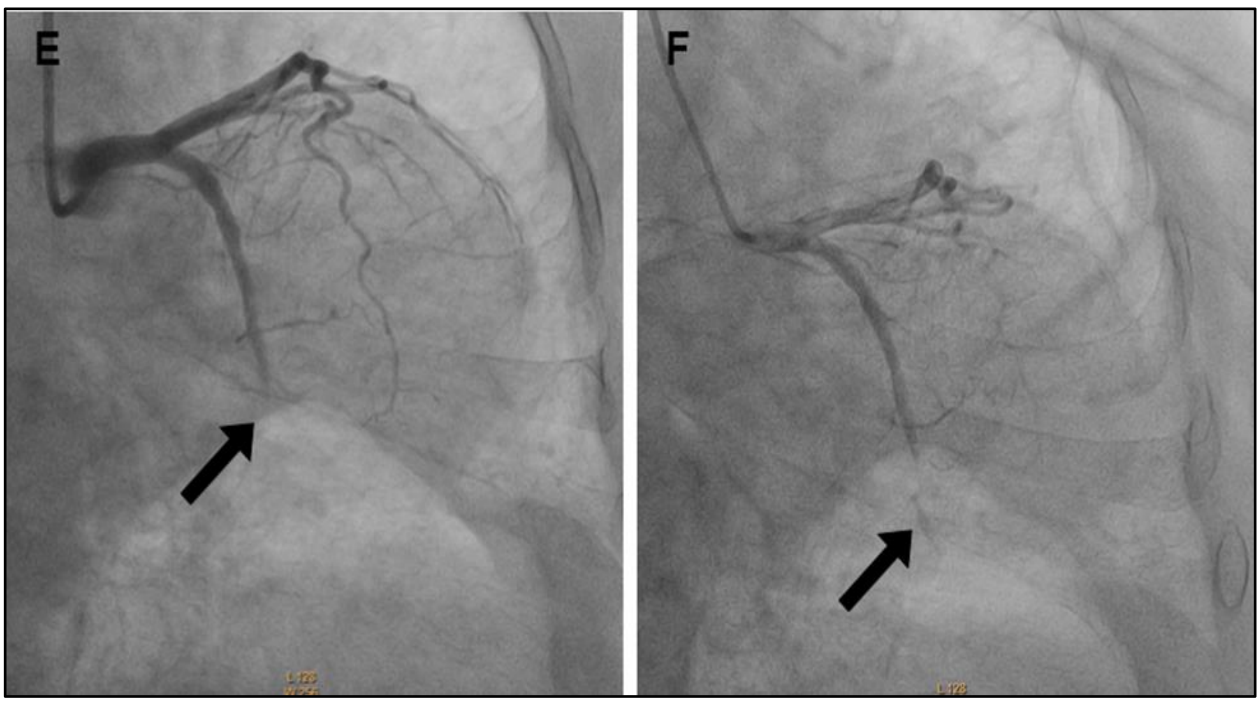


**Figure 5:** STEMI type OMI inferolateral with circumflex culprit artery. A) diagnostic angiography with 100% circumflex distal segment obstruction (arrow); B) recovery of distal flow after ultrasound-thrombolysis (arrow), TIMI flow 1.

In this series of cases, the authors found that after insonation for 15 minutes, the image perceived in the diagnostic and control angiography showed a change in the flows, with improvement in all 3 cases (Table 2).


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| | Initial flow | Post-intonation flow | Post-intervention flow |
|---|---|---|---|
| **Case 1** | TIMI 0 | TIMI 1 | TIMI 3 |
| **Case 2** | TIMI 0 | TIMI 3 | Not applicable |
| **Case 3** | TIMI 0 | TIMI 1 | TIMI 3 |

**Table 2:** Initial, post-insonation, and post-intervention coronary flow. TIMI 0: Complete occlusion of the artery related to the infarction; TIMI 1: Contrast medium flows beyond the area of occlusion without perfusing distal coronary artery and distal coronary bed; TIMI 2: The contrast dye flows through the entire artery, but at a delayed rate compared to a normal flow; TIMI 3: Normal flow from the artery.

## Discussion

Currently, one of the major problems in the treatment of ST-segment elevation or OMI-type acute coronary syndrome (obstructive myocardial infarction) is adequate reperfusion.

Ideally, a patient with this pathology should be able to be treated in the first hours of the event, however, the reality is that care is delayed due to different factors of the patient or the health system. This is mainly due to the absence of hemodynamic rooms in most hospitals, which implies the need to transfer a considerable number of patients to specialized centres, involving complex administrative and operational logistics, this delay is sometimes remedied with the use of systemic thrombolysis in candidate patients, and subsequently receive a rescue angioplasty or completing the pharmacoinvasive therapy.

Instead of receiving a primary angioplasty, leading to an increase in the incidence of poor final perfusion of the microvasculature or the phenomenon of non-reflux.

Exposure to low-frequency ultrasound waves under observation in the hemodynamic room showed an improvement in flow without any other type of intervention, this phenomenon is explained by the interactions that exist between the fibrin bonds that when excited by the ultrasound waves separate and thin creating flow recovery and binding sites for the thrombolytic.

The phenomenon may be particularly useful for the treatment of microvasculature and therefore with potential long-term functional improvement, being able to avoid the phenomenon of non-reflux and improving myocardial perfusion. It is important to note that in the cases reviewed, the result was obtained regardless of the baseline characteristics of the patients (time of ischemia, affected artery, comorbidities).

Ultrasound-thrombolysis has demonstrated its usefulness in the treatment of pulmonary thromboembolism as well as thrombotic ischemic cerebral event, its use in acute myocardial infarction type OMI has the potential to improve the outcome of reperfusion in conjunction with systemic thrombolysis and percutaneous coronary intervention, it has great advantages, such as that it does not involve the use of expensive or unavailable technologies such as those


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currently used in pulmonary thromboembolism.

In fact, it uses a widely available technology and expansion in emergency rooms and prehospital systems in the world [18], it does not require extensive experience or training, its use can be simplified to a very basic algorithm for implementation and it is a therapy that is combined with conventional therapy, such as double antiplatelet therapy that together with thrombolytic therapy has been shown to achieve TIMI 3 flows by 63% with TMP 3 55.8% with residual intracoronary thrombus in 44% of cases during diagnostic angiography [19].

It can be applied even from a prehospital system where intravenous thrombolysis has been performed during transfer and with subsequent percutaneous coronary intervention in an average of 8 hours, with TIMI 3 flow in 58.5% of patients and with urgent PCI requirement in 36.3% [20], in the TRANSFER AMI study, post-thrombolysis TIMI 3 flow was found in 52.2% of cases [21].

The potential impact of this simple and low-cost therapy is especially significant considering the limited access to hemodynamic rooms in the author's country and other Latin American nations.

The RENASICA II study, which included 8098 patients with acute coronary syndromes, found that 4555 patients had ST-segment elevation infarctions, highlighting the need for accessible treatment options. of which 37% received fibrinolytic therapy and 15% received primary angioplasty with a mortality of 10% in these patients.

The overall rate of revascularization was 39%; with only 4% for those who received fibrinolytic treatment, with thrombolysis being the main reperfusion treatment in the author's country [22].

## Conclusions

This first case series suggests that the use of ultrasound-thrombolysis improves the efficacy of standard treatment in ST-elevation or OMI-type acute myocardial infarction, regardless of the vessel to be treated or baseline characteristics of the patients.

The need to find alternatives in the face of the lack of opportunity for treatment with percutaneous coronary intervention in developing countries makes it necessary to find ancillary treatments to systemic thrombolysis.

Ultrasound-thrombolysis has the potential to be this treatment, as it increases the success rate in reperfusion measured by indirect criteria and with objective results such as TIMI flow and myocardial flow during percutaneous coronary intervention.

There is currently little evidence on its use, however, as it does not expose patients to radiation, invasive procedures, does not increase actual costs or delay treatment, it eases the development of large-scale clinical trials to corroborate its efficacy.

## Key points

### What do we know about ultrasound-thrombolysis?

It is a treatment based on in-vitro, in-vivo in animals and in-vivo studies in humans, in the latter microbubble contrast has been used regularly and a considerable part of the improvement in reperfusion has been attributed to it.

One of the strengths of the treatment is the improvement of microcirculation, for which currently great tools are not available.

**What does this study contribute?**

It is the first human study to prove improvement with the application of ultrasound waves alone without microbubble contrast, nor does it require the use of special equipment for the administration of ultrasound waves.

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