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Sonothrombolysis in ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention

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for the MRUSMI Investigators

ABSTRACT

BACKGROUND Preclinical studies have demonstrated that high mechanical index (MI) impulses from a diagnostic ultrasound transducer during an intravenous microbubble infusion (sonothrombolysis) can restore epicardial and microvascular flow in acute ST-segment elevation myocardial infarction (STEMI).

OBJECTIVES This study tested the clinical effectiveness of sonothrombolysis in patients with STEMI.

METHODS Patients with their first STEMI were prospectively randomized to either diagnostic ultrasound-guided high MI impulses during an intravenous Definity (Lantheus Medical Imaging, North Billerica, Massachusetts) infusion before, and following, emergent percutaneous coronary intervention (PCI), or to a control group that received PCI only ($n = 50$ in each group). A reference first STEMI group ($n = 203$) who arrived outside the randomization window was also analyzed. Angiographic recanalization before PCI, ST-segment resolution, infarct size by magnetic resonance imaging, and systolic function (LVEF) at 6 months were compared.

RESULTS ST-segment resolution occurred in 16 (32%) high MI PCI versus 2 (4%) PCI-only patients before PCI, and angiographic recanalization was 48% in high MI/PCI versus 20% in PCI only and 21% in the reference group ($p < 0.001$). Infarct size was reduced (29 ± 22 g high MI/PCI vs. 40 ± 20 g PCI only; $p = 0.026$). LVEF was not different between groups before treatment ($44 \pm 11\%$ vs. $43 \pm 10\%$), but increased immediately after PCI in the high MI/PCI group ($p = 0.03$), and remained higher at 6 months ($p = 0.015$). Need for implantable defibrillator (LVEF ≤30%) was reduced in the high MI/PCI group (5% vs. 18% PCI only; $p = 0.045$).

CONCLUSIONS Sonothrombolysis added to PCI improves recanalization rates and reduces infarct size, resulting in sustained improvements in systolic function after STEMI. (Therapeutic Use of Ultrasound in Acute Coronary Artery Disease; NCT02410330). (J Am Coll Cardiol 2019;73:2832–42) © 2019 by the American College of Cardiology Foundation.

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Thrombolysis and emergent percutaneous coronary interventions (PCIs) have improved the prognosis of patients with acute ST-segment elevation myocardial infarction (STEMI) (1,2). Despite these advances, 2 major clinical problems remain. First, the ability of patients to achieve early PCI is hampered by patient factors and delays in transport to appropriate hospitals, especially in developing countries (3). Secondly, even with timely epicardial revascularization, significant microvascular obstruction (MVO) may still exist in over 50% of patients after successful early epicardial recanalization, resulting in higher necrotic areas, adverse left ventricular remodeling, and a worse prognosis (4–6).

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Transthoracic high mechanical index (MI) impulses from a diagnostic ultrasound (DUS) transducer are currently used to analyze regional wall motion, left ventricular systolic function, and myocardial perfusion during a continuous microbubble infusion or small bolus injection of microbubbles (7–9). The microbubble cavitation induced by the high MI impulses also creates shear forces (10), which are capable of dissolving coronary artery and microvascular thrombi (11–14). The cavitation-induced shear also induces endothelial and red blood cell nitric oxide release in small animal models of acute limb ischemia (15,16), which may further augment microvascular flow. Initial safety and feasibility studies suggested that intermittent high MI impulses, aimed at the myocardial microcirculation could improve capillary blood flow within the risk area and epicardial recanalization rates (14). Although a beneficial effect of DUS-guided high MI impulses on microvascular function has been suggested in small studies, a prospective randomized human study examining the utility of high MI impulses during a microbubble infusion has never been performed. We hypothesized that such an approach, when applied to the contemporary management of STEMI, would improve angiographic and microvascular reflow, leading to a reduction in infarct size and improved systolic function at follow-up. We tested this in patients presenting with their first STEMI.

METHODS

STUDY PROTOCOL. The MRUSMI (Microvascular Recovery with Ultrasound in Acute Myocardial Infarction) trial was designed to investigate whether applying high MI impulses from a DUS transducer during a commercially available microbubble infusion in patients with their first STEMI would improve early epicardial coronary patency rates, reduce myocardial infarct size, improve microvascular flow, and improve long-term left ventricular systolic function (15). This study was a single-center study approved by the Clinics Hospital of the University of Sao Paulo Medical School Ethics Committee (CAPPesq) and the Brazilian Government Agency CONEP (National Committee on Research Ethics, National Council of Health). Exclusion criteria were history of prior myocardial infarction, known cardiomyopathy, severe valvular heart disease, fibrinolytic therapy before arrival in the emergency department, allergy to perflutren, chest pain onset >12 h from arrival, or reduced life expectancy (<6 months) from any other comorbidity.

From May 2014 to July 2018, a total of 1,857 STEMI patients arrived at the Heart Institute University of São Paulo Emergency Department; of these, 303 met inclusion criteria for the study protocol, and 100 arrived within the time window (7 AM to 7 PM weekdays) for which emergent DUS could be applied before and after PCI (**Figure 1**). The remaining 203 patients did not get randomized, but served as a registry for determining angiographic recanalization rates immediately before PCI.

All randomized patients received immediate aspirin (300 mg), clopidogrel (600 mg), heparin, atorvastatin (40 mg), and emergent PCI protocols as outlined in the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of STEMI (2). Beta-blockers were administered during the hospital stay to all patients unless contraindicated. The patients were randomized to 1 of 2 available DUS algorithms: 1) a control group (PCI only) undergoing low MI (<0.2) imaging only with limited (no more than 3) diagnostic high MI impulses to assess regional wall motion and microvascular perfusion before and after PCI; and 2) a DUS therapeutic group (high MI PCI) that received frequent image-guided diagnostic high MI (1.8 MHz; 1.1 to 1.3 MI; <5-μs pulse duration) impulses applied to the myocardial contrast-enhanced areas in the apical 4-, 2-, and 3-chamber views before and following PCI. Patients who were randomized to high MI/PCI or PCI only in the pilot study (14) were also included in this prospective study.

The probe was rotated between the different views after each high MI impulse with time to replenishment analyzed (in seconds) in each affected segment (17-segment model). The catheterization laboratory

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging

CST = cardiac-specific troponin

DUS = diagnostic ultrasound

ECG = electrocardiogram/electrocardiographic

IS = infarct size

LVEF = left ventricular ejection fraction

MI = mechanical index

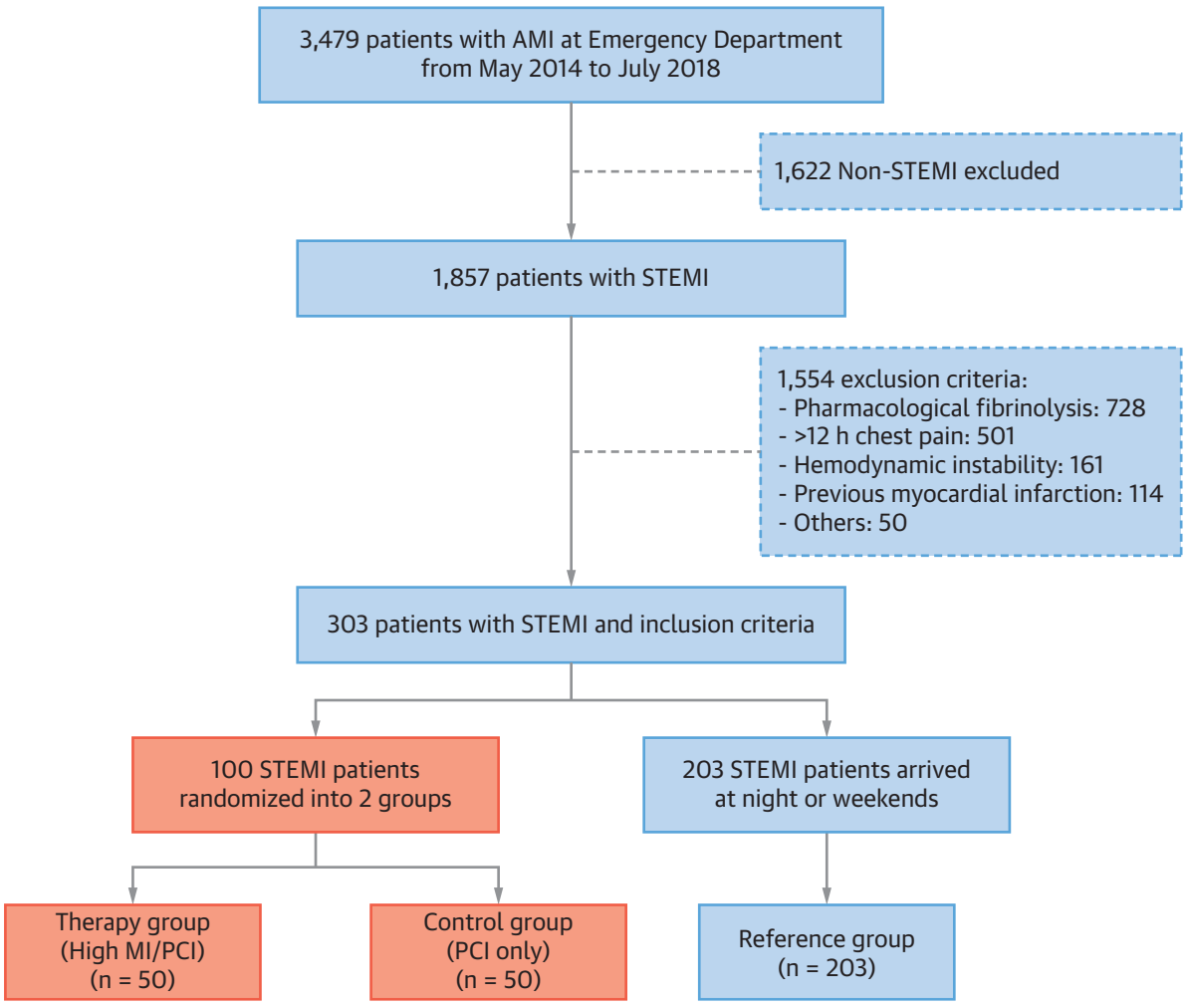
MVO = microvascular obstruction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

FIGURE 1 Patient Selection

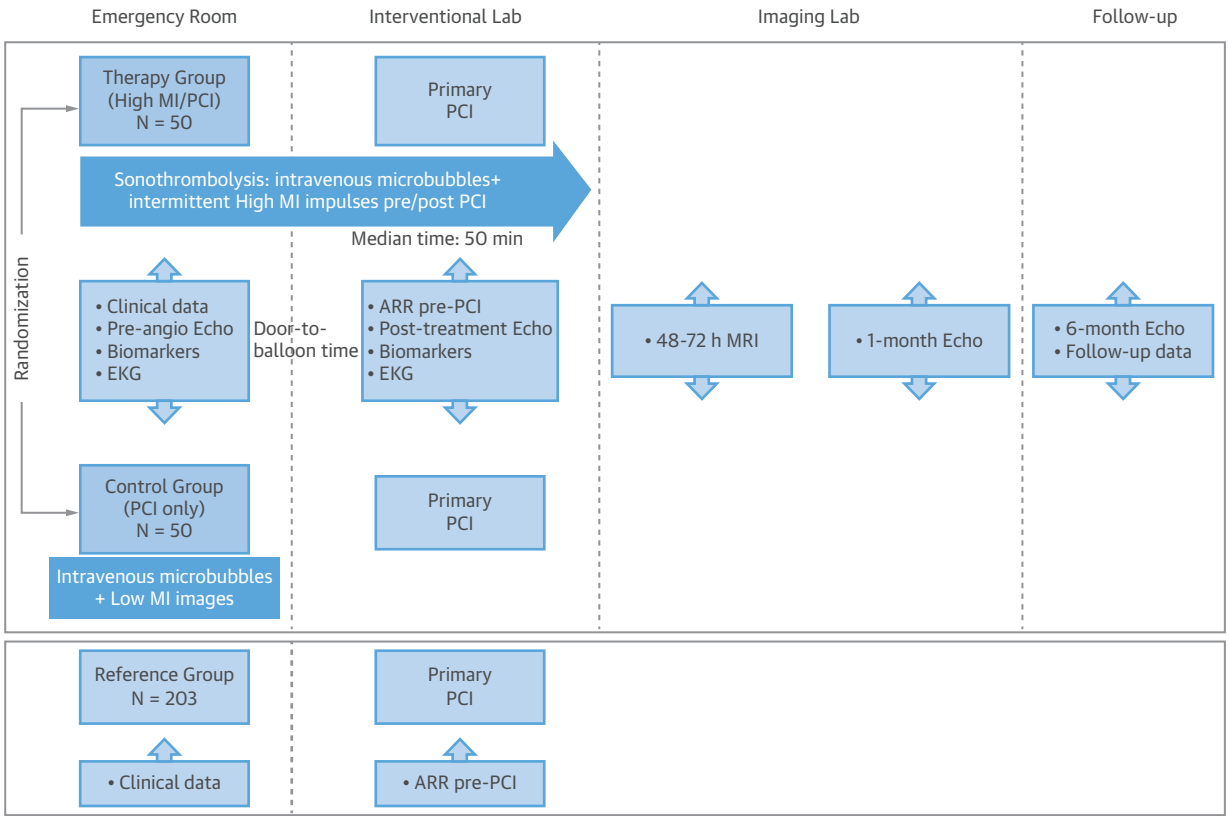


Patients that arrived in the emergency department with STEMI were selected for reference group or randomized between ultrasound-mediated thrombus dissolution and control groups. AMI = acute myocardial infarction; MI = mechanical index; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

was blinded to treatment assignment. There were 2 time periods in the acute setting that the high MI impulses were applied (Figure 2). A total of 2 vials of perflutren (3.0 ml) (Definity, Lantheus Medical Imaging, North Billerica, Massachusetts) were administered as a 5% dilution. The first treatment was for a variable time period before emergent PCI, which varied depending on catheterization lab availability. The second treatment period was immediately post-PCI and included the remainder of what was left after the pre-PCI treatment. The infusion ranged from 1 to 2 ml/min and was adjusted to maintain myocardial opacification without cavity shadowing. During the continuous infusion of microbubbles, the high MI impulses were applied for 10 frames repeatedly after very low MI imaging detected replenishment of microbubbles within the myocardial segments. Each apical window received approximately 20 to 30 high MI impulses (total of 60 to 90 high MI impulses) over the pre- and post-PCI treatment period.

Therapeutic and diagnostic echocardiographic imaging was performed using commercially available equipment, an IE33 ultrasound (Philips Medical Systems, Bothell, Washington). Very low MI imaging during the microbubble infusion was used in both groups to compute biplane-derived measurements of left ventricular ejection fraction (LVEF) before randomized treatment and immediately after the second

FIGURE 2 Study Protocol



Complete protocol at emergency room, interventional lab, imaging lab and follow-up for randomized patients and reference group. ARR = angiographic recanalization rate; EKG = electrocardiogram; MRI = magnetic resonance imaging; other abbreviations as in Figure 1.

ultrasound treatment post-PCI. Biplane measurements of LVEF with microbubbles and very low MI imaging were repeated at 1 and 6 months post-hospital discharge. The biplane method with ultrasound contrast has a high reproducibility and correlates the closest with cardiac magnetic resonance imaging measurements (9). All biplane LVEF and volume assessments were made by an independent experienced echocardiographic reviewer (W.M.) using American Society of Echocardiography guidelines (17), who was blinded to treatment assignment. The number of segments exhibiting perfusion defects (a plateau defect persistent at 10 s post-high MI impulse and/or a delay in replenishment at >4 s after the high MI impulse) was assessed in each group by a blinded reviewer (W.M.). A score of 1 was given to normal perfusion, 2 for a >4-s delay in replenishment, and 3 for absent replenishment at up to 10 s post-high MI impulse. A perfusion defect score using a 17-segment model was computed as described previously (14). An intraclass correlation coefficient was used to compute intraobserver variability in volume and ejection fraction measurements in 20 randomly selected patients. The complete study protocol timetable is displayed in Figure 2.

ANGIOGRAPHIC, ELECTROCARDIOGRAPHIC, AND BIOMARKER ASSESSMENTS. All coronary angiograms were analyzed offline by an independent interventional cardiologist, blinded to clinical characteristics or randomized treatment. The initial pre-PCI and post-PCI angiograms were examined for Thrombolysis In Myocardial Infarction (TIMI) flow grading within the infarct vessel (18). Angiographic recanalization was defined as the presence of TIMI flow grade 2 or 3 in the infarct vessel.

Electrocardiographic (ECG) ST-segment resolution was computed by another cardiologist (M.O.D.A.) blinded to treatment assignment in the lead with maximum ST-segment deviation on the initial ECG. The % change in this lead immediately before PCI (after the first ultrasound treatment) and again after

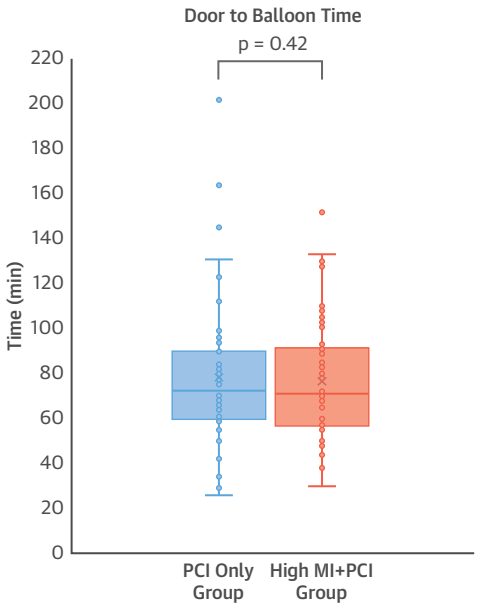
TABLE 1 Demographic Variables Among the 3 Groups

	Control Group (PCI Only) (n = 50)	Therapy Group (High MI/PCI) (n = 50)	Reference Group (n = 203)	p Value
Age, yrs	59 ± 11	59 ± 10	59 ± 11	0.96*
Sex	40 (80)	32 (64)	148 (73)	0.20†
Weight, kg	77 ± 16	74 ± 16	76 ± 13	0.65*
BSA, m^2	1.86 ± 0.22	1.82 ± 0.22	1.82 ± 0.19	0.41*
Diabetes	11 (22)	21 (42)	67 (33)	0.10†
Hypertension	28 (56)	28 (56)	118 (58)	0.95†
Hyperlipidemia	15 (30)	20 (40)	55 (27)	0.20†
Smoking	20 (40)	24 (48)	70 (34)	0.20†
Medication in use				
Statin	14 (28)	19 (38)	21 (10)	<0.001†
Beta-blocker	5 (10)	14 (28)	27 (13)	0.019†
Aspirin	50 (100)	48 (96)	202 (99)	0.14‡
Nitrate	25 (50)	27 (54)	95 (47)	0.64†
Calcium-channel blocker	4 (8)	5 (10)	14 (7)	0.72‡
STEMI arterial territory				
LAD	26 (52)	26 (52)	90 (44)	0.83†
RCA	14 (28)	17 (34)	84 (41)	
LCx	10 (20)	7 (14)	29 (14)	

Values are mean ± SD or n (%). *Analysis of variance. †Chi-square test. ‡Fisher exact test.

BSA = body surface area; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = mechanical index; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

FIGURE 3 Distribution of Door-to-Balloon Times



The graphic demonstrates the range of door-to-balloon times observed in the High MI/PCI group versus PCI only. TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figure 1.

the second ultrasound treatment period following PCI were compared. Categorical comparisons of patients who had ≥50% ST-segment deviation were also analyzed (19).

Cardiac-specific troponin (CST) and creatine phosphokinase MB fraction were drawn every 3 h for 18 h following randomization. Peak values were compared between groups; values >50 for CST and 200 for CPK-MB could not be measured with the assay, and were assigned a value of 50 and 200, respectively.

CARDIAC MAGNETIC RESONANCE IMAGING. Between 48 and 72 h post-PCI, cardiac magnetic resonance imaging (CMR) was performed using a 1.5-T scanner (Philips Achieve, Philips Medical Systems, Best, the Netherlands). Steady-state free precession images (TR 3.0 ms, TE −1.5 ms; flip angle 60°) were used to compute left ventricular volumes, LVEF, and mass. Early (2 min post-injection) and late (10 min post-injection) gadolinium enhancement images were obtained in the same short-axis planes following injection of 0.2 mmol/kg gadolinium chelate (Dotarem, Guerbet, Paris, France) to compute microvascular obstruction (MVO) and infarct size (IS), using offline software (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Early gadolinium enhancement was performed at 2 min post-injection to compute the extent of MVO (mass of unenhanced zone from the same short-axis windows). Late gadolinium enhancement was performed with an inversion time ranging from 250 to 350 ms and gradient echo readout parameters (TR 6.0 ms; TE 3.0 ms; flip angle 25°). All measurements were obtained by a blinded reviewer outside of the institution (A.M.F.) who had no knowledge of treatment assignment.

STATISTICAL ANALYSIS PLAN. Two primary outcomes were tested: rate of ST-segment resolution and angiographic patency before PCI. Secondary outcomes were infarct size by delayed enhancement CMR and microvascular flow as assessed by contrast perfusion after PCI and CMR at 48 h, as well as LVEF at 6 months. The proportion of patients who meet current guidelines for automatic implantable cardioverter-defibrillator placement at follow-up was also assessed (20).

On the basis of pilot data (14), we anticipated randomizing 100 patients to achieve statistical significance ($p < 0.05$ using contingency tables for dichotomous variables and unpaired 1-tailed *t*-test for continuous variables) between treatment groups in the primary endpoint. Data were analyzed for possible confounders, including demographics, patient medications, and disease characteristics. We expected the high MI/PCI group to have >50%

ST-segment resolution in 80% of cases versus 50% of cases in the PCI-only group after all interventions were completed. On the basis of the pilot data, we also projected an expected early angiographic patency rate of at least 50% in the high MI/PCI group versus 20% in the PCI-only group. Secondary outcomes (IS and MVO by CMR at hospital discharge, and 6-month follow-up measures of LVEF) were not analyzed for power calculations because pilot data were not available on these variables.

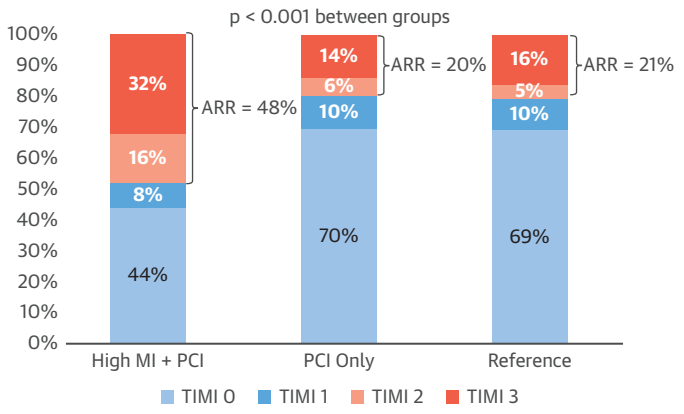
Although the hypothesis being tested was that DUS-guided high MI impulses would reduce MVO and improve systolic function when added to PCI, a 2-sided unpaired *t*-test was used to compare treatment outcomes to ensure no detrimental effect was seen with high MI impulses. ST-segment resolution was compared between treatment groups as both a continuous variable (% change from maximum ST-segment elevation) and also as a dichotomous variable using ≥50% ST-segment resolution as a cutoff. Angiographic recanalization rate was defined as TIMI flow grade 2 or 3 in the infarct vessel and was analyzed both pre- and post-PCI. Proportional differences in primary and secondary outcomes were compared using contingency tables (chi square testing 2 × 2 contingency tables or Fisher's exact test).

Contingency tables were also used to compare for differences in any demographic variables, here using 3 × 2 tables that also included the reference group.

RESULTS

Mean age in the randomized patients and reference groups was 59 years, and there were no differences in body size or sex (Table 1). There were also no differences in the proportion of patients with a history of hypertension, hyperlipidemia, diabetes, or smoking (Table 1). The high MI/PCI group had more patients with on beta-blockers at the time of arrival. Total sonothrombolysis time (pre- and post-PCI) was a median 50 min. Pre-PCI sonothrombolysis times ranged from 0 to 66 min (median 18 min). Assuming a 1.5 ml/min infusion rate, the averaged dose of Definity before PCI was 25 ml of the 5% dilution. A total of 8 patients did not get post-PCI sonothrombolysis because the entire dose of Definity (2 vials) was given pre-PCI in 6 patients, or because of death or hemodynamic instability during PCI in 2 patients. Door-to-balloon times were not different between treatment groups (78 ± 32 min PCI only vs. 77 ± 26 min high MI/PCI; p = 0.42), but were longer in the reference group getting PCI outside of the 7 AM to 7 PM weekday window (96 ± 49 min; p < 0.001 compared with treatment groups). The distribution of door-to-balloon times in the high MI/PCI and PCI-only groups is displayed in Figure 3.

FIGURE 4 ARR Pre-PCI



Percentage of patients with TIMI flow grade 0, 1, 2, and 3 by angiography pre-PCI for the 3 studied groups. Abbreviations as in Figures 1, 2, and 3.

ANGIOGRAPHIC FINDINGS. Recanalization of the infarct vessel on the first angiogram before PCI was seen in 24 of 50 high MI/PCI patients (48%) compared with 10 of 50 PCI-only patients (20%) (p < 0.001) (Figure 4). The reference group had a recanalization rate similar to the PCI-only group (43 of 203; 21%). Similarly, TIMI flow grade 3 rates were higher in the high MI/PCI group (32% vs. 14% in the PCI-only and 16% reference group; p = 0.02). Ten patients (10%) did not get culprit vessel recanalization with a stent due to either an open infarct vessel without significant stenosis at the time of angiography in 3 patients (2 in PCI only, 1 in high MI/PCI), failed attempt to open the infarct vessel (4 PCI-only patients), 3-vessel disease requiring bypass surgery in 1 patient (PCI-only group), thrombus aspiration without stent in 1 (PCI only), and in 1 patient, the infarct vessel was

TABLE 2 ST-Segment Resolution and Peak Troponin/CPK-MB Values

	Control Group (PCI Only) (n = 50)	Therapy Group (High MI/PCI) (n = 50)	p Value
≥50% ST-segment resolution before PCI	2 (4)	16 (32)	<0.001*
ST-segment resolution post-PCI, %	50 (0–75)	67 (33–100)	0.011*
Peak troponin, ng/ml	47 ± 8	40 ± 17	0.011†
Peak CPK-MB, ng/ml	204 ± 105	165 ± 120	0.093†

Values are n (%), median (interquartile range), or mean ± SD. *Mann-Whitney test. †Student *t*-test.
CPK-MB = creatine phosphokinase MB fraction; other abbreviations as in Table 1.

TABLE 3 CMRI Parameters at 48 to 72 h Post-PCI

	Control Group (PCI Only)	Therapy Group (High MI/PCI)	p Value*
LVEF, %	47 ± 10	52 ± 11	0.031
IS, g	40 ± 20	29 ± 22	0.026
MVO, g	8.5 ± 11.0	4.4 ± 5.6	0.095
MVO, g†	12.1 ± 13.3	5.0 ± 6.3	0.05

Values are mean ± SD. *Mann Whitney test. †MVO in patients with infarctions in the left anterior descending coronary artery territory.

CMRI = cardiac magnetic resonance imaging; IS = infarct size; LVEF = left ventricular ejection fraction; MVO = microvascular obstruction; other abbreviations as in Table 1.

considered too small to attempt PCI (PCI-only group). Following emergent PCI, TIMI flow grade 3 in the infarct vessel was observed in 37 of 50 high MI/PCI patients (74%) and 30 of 50 PCI-only patients (60%).

ST-SEGMENT AND CST VALUES. ST-segment resolution≥50% before angiography occurred in 16 high MI/PCI patients (32%) versus 2 PCI-only patients (4%) ($p < 0.001$). Quantitatively, % ST-segment decrease was greater in the high MI/PCI group after the first therapy before PCI, as well as after PCI and the second therapy period (Table 2). The peak values for CST were lower in the high MI/PCI group ($p = 0.011$) (Table 2).

CARDIAC MAGNETIC RESONANCE IMAGING. Six patients (12%) in the high MI/PCI and 13 (26%) in the PCI-only group could not complete the CMR protocol due to either claustrophobia ($n = 11$), renal failure ($n = 1$), metal clips ($n = 2$), death before CMR ($n = 2$), or hemodynamic instability ($n = 3$). In the remaining patients, the IS was smaller ($p = 0.026$) in the high MI/PCI group (Table 3), but the extent of MVO was not significantly different. In the patients with a left anterior descending coronary artery STEMI, there was a tendency to lower degrees of MVO in the high MI/PCI group ($p = 0.05$). IS was not different between high MI/PCI patients with angiographic recanalization (23 ± 11%) versus those without recanalization before PCI (23 ± 15%). Despite similar LVEF by biplane contrast echocardiography before randomized treatment (44 ± 11% high MI/PCI and 43 ± 10% PCI only; $p = 0.39$), LVEF at CMR was significantly higher in the high MI/PCI group at 72 h (51 ± 11% vs. 43 ± 10% PCI only; $p = 0.01$). The Central Illustration and Figure 5 are examples of ECG, angiographic, and microvascular perfusion changes during the treatment period when randomized to high MI/PCI versus PCI only.

ECHOCARDIOGRAPHIC AND CLINICAL FOLLOW-UP. Baseline ejection fraction before randomized therapy was not different between groups (Table 4), and the number of segments exhibiting perfusion defects before randomized treatment (risk area) was not different (7.4 ± 3.2 segments PCI only vs. 7.5 ± 3.3 segments high MI/PCI; $p = 0.85$), and perfusion defect scores were similar (Table 4). However, there was a significantly higher LVEF in the high MI-treated group immediately following the second ultrasound treatment ($p < 0.032$ compared with PCI only). Perfusion defect score after PCI was also significantly lower in the high MI/PCI group (Table 4). Follow-up contrast echo measurements at 1 and 6 months were obtained for 44 patients in each group. The improvement in LVEF observed immediately after randomized treatment in the high MI/PCI group remained significant at 1 month ($p = 0.018$) and 6 months ($p = 0.015$) of follow-up. Intraclass correlation coefficients on repeated measurements of contrast-enhanced end-diastolic volume, end-systolic volume, and LVEF were 0.95, 0.98, and 0.75, respectively (all $p < 0.001$).

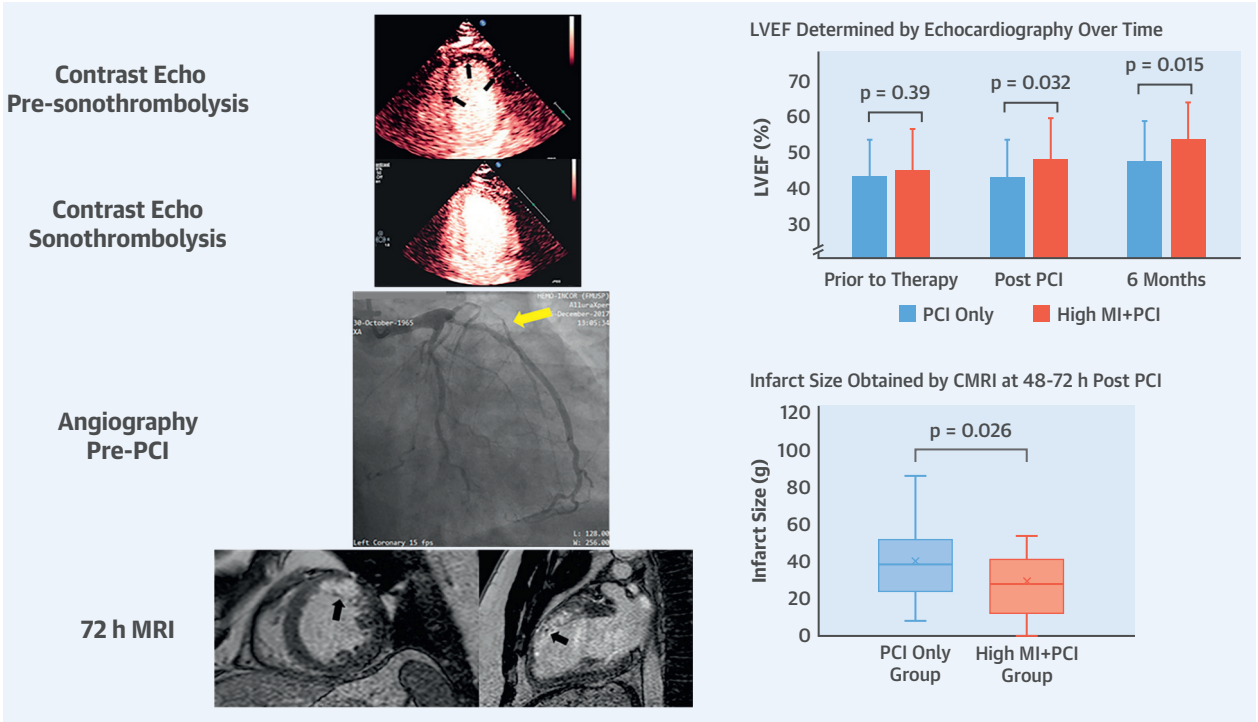
An indication for defibrillator placement for primary prevention (LVEF ≤30% at 6 months follow-up) was present in 2 of 44 high MI/PCI patients (5%) compared with 8 of 44 PCI-only patients (18%) ($p = 0.045$). At a median follow-up of 17 months, 8 patients (16%) had died in both the high MI/PCI and PCI-only groups.

DISCUSSION

This is the first prospective randomized human study to demonstrate a supplemental beneficial effect of DUS-guided microvascular-targeted cavitation of intravenously administered commercially available microbubbles during acute STEMI. Short durations of high MI impulses (median 18 min) before emergent PCI had no effect on door-to-dilation times, but resulted in higher proportions of ST-segment resolution and angiographic recanalization before PCI. Furthermore, we observed immediate, but sustained, improvements in systolic function at follow-up. The beneficial effects of high MI impulses were evident at hospital discharge, where a significant reduction in infarct size was observed by CMR. Systolic function was similar between groups before randomization, but sustained improvements in ejection fraction were observed following treatment with high MI/PCI, and there appeared to be no alteration in safety or door-to-dilation times, suggesting that adding this simple, safe diagnostic-based procedure before and after PCI may effectively reduce MVO and its complications.

The high MI impulses used in the current study are standard features on an ultrasound system and are, in essence, the same high MI impulses used to evaluate

CENTRAL ILLUSTRATION **Patient With ST-Segment Elevation Myocardial Infarction Treated With Sonothrombolysis**



Mathias, Jr., W. et al. J Am Coll Cardiol. 2019;73(22):2832–42.

An acute anterolateral STEMI treated with high MI impulses during an intravenous microbubble infusion. The **top panel** shows resting microvascular defect **(arrows)**. After 12 min of high MI impulses, there is ST-segment elevation resolution and microvascular flow **(black arrows, right panels)** within the distal septal and apical segments. Angiography performed before PCI demonstrated TIMI flow grade 3 in the left anterior descending coronary artery **(yellow arrow)** and 72-h magnetic resonance imaging (MRI) in the **bottom panel** demonstrated no microvascular obstruction and reduced infarct size (planimetered areas). MI = mechanical index; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

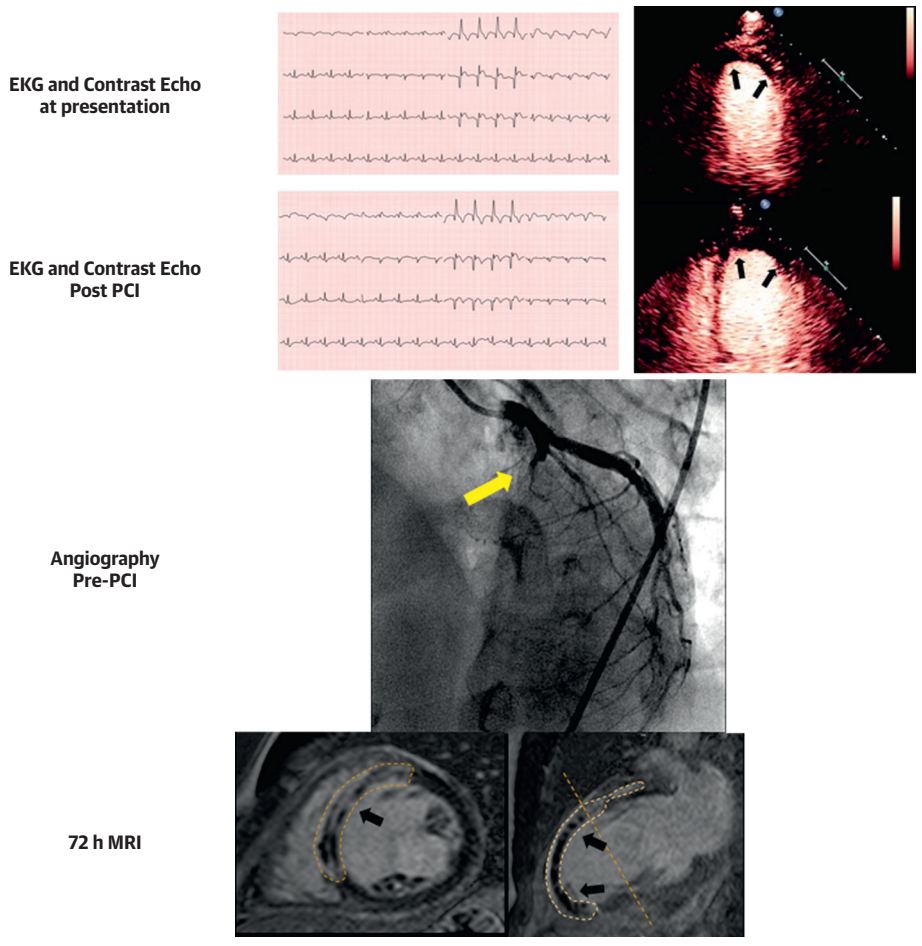
regional and global systolic function and perfusion during a commercially available microbubble infusion (21–23).

Mechanistically, the high MI impulses have been shown to elicit asymmetric growth and collapse of the microbubbles, which then generate shear forces that can dissolve thrombi in vitro (24,25). Although longer pulse durations on nondiagnostic systems have been shown to improve the degree of thrombus dissolution (26,27), these longer pulse durations are not available for diagnostic use and could potentially contribute to unwanted bioeffects such as coronary vascular spasm (28) or endothelial disruption with capillary hemorrhage (29,30). An optimal pulse duration for thrombus dissolution has not been evaluated, but the current study confirmed that short diagnostic transthoracic ultrasound pulses (duration <5 μs) at a high MI are capable of achieving improved epicardial coronary flow rates and reduced IS in the acute STEMI setting.

Although we cannot separate the microvascular versus epicardial effects of the high MI impulse, we hypothesize that both the effects of improved microvascular flow and thrombus dissolution in the coronary artery played a role in the increased epicardial recanalization rates.

An improvement in systolic function occurred in the immediate post-PCI measurements of ejection fraction only in the high MI/PCI group (**Table 3**). Although a significant component of this improvement may be related to mechanical thrombus dissolution resulting in improved flow at the microvascular level, nitric oxide release from cavitation may also play a role. Following coronary artery ligation in animal models, directly applied low-frequency ultrasound applied distal to the obstruction improved

FIGURE 5 Patient With STEMI Treated With PCI Only



The EKG abnormalities and resting microvascular defect **(arrows)** are demonstrated at baseline **(top)** and after primary PCI. There was no resolution of ST-segment elevation, and perfusion defect remained unchanged **(bottom)** within the distal septal and apical segments. Angiography performed before percutaneous coronary intervention demonstrated TIMI flow grade 0 at the left anterior descending coronary artery **(yellow arrow)** and 72 h MRI demonstrated microvascular obstruction on first-pass perfusion and subsequent delayed enhancement images (planimetered areas). Abbreviations as in Figures 1, 2, and 3.

TABLE 4 Echocardiographic Assessments of Left Ventricular Systolic Function and Microvascular Perfusion

PD Score	Control Group (PCI Only)	Therapy Group (High MI/PCI)	p Value
LVEF before therapy, %	43 ± 10	44 ± 11	0.39*
PD score before therapy	1.76 ± 0.35	1.74 ± 0.39	0.830*
LVEF immediately post-PCI, %	43 ± 10	47 ± 11	0.032*
PD score immediately post PCI	1.72 ± 0.34	1.57 ± 0.35	0.032*
LVEF 1 month, %	46 ± 11	52 ± 10	0.018*
LVEF 6 months, %	47 ± 12	53 ± 10	0.015*
6 months, %†	48 ± 11	53 ± 10	0.048*

Values are mean ± SD. *Student's *t*-test. †After removing the patients who were on beta-blockers at presentation.

PD = perfusion defect; other abbreviations as in Table 1.

downstream tissue perfusion and function (31). This effect was reversed following nitric oxide synthase inhibition. Following iliac artery occlusion in a rodent model, diagnostic high MI impulses applied during an intravenous microbubble infusion have been shown to improve downstream microvascular flow (15). In these same animal models, the high MI impulses have been shown to induce endothelial and red blood cell release of ATP that result in sustained improvements in microvascular flow (16). In our study, we did not observe an overall reduction in MVO, but did demonstrate a trend toward this in the left anterior descending coronary artery infarctions. Nonetheless, there was a reduction in infarct size and an

immediate improvement in systolic function in the high MI/PCI group that was still evident before hospital discharge and at 6-month follow-up. Although this improvement in systolic function may lead to reductions in the indication for primary prevention defibrillator placement, larger studies will be required to determine what effect it will have on the incidence of congestive heart failure and mortality.

STUDY LIMITATIONS. There are no generally accepted methods to quantify risk area noninvasively in humans. T2-weighted assessments of edema have been shown to correlate more closely with infarct size than actual risk area (32) and therefore were not used for comparing groups in this study. There is a possibility, therefore, that our observations of decreased infarct size and MVO were due to smaller risk areas. This seems unlikely, based on our observations of similar ejection fractions before randomization, and similar demographics (**Table 1**).

Patients randomized to high MI/PCI were more frequently taking beta-blockers on admission than PCI-only patients (14 vs. 5 patients, respectively), which may affect risk area and recovery of function (33). All patients, though, received beta-blockers and high-intensity statins after study entry, and thus this difference at study entry should not have affected our outcome measures. Furthermore, 6-month ejection fraction was still higher in the high MI/PCI group after patients on beta-blockers at admission were removed from the analysis (**Table 4**).

CONCLUSIONS

Transthoracic high MI DUS impulses targeted to the myocardium during a commercially available microbubble infusion may play a critical supplemental role in restoring early epicardial flow and reducing myocardial IS in patients with acute myocardial infarction. The effects of sonothrombolysis were observed early in the treatment period before emergent PCI, but resulted in sustained improvements in systolic function and reduced need for defibrillators at 6-month follow-up. The limited time period in which ultrasound could be applied before PCI may have limited its effectiveness. Therefore, further study is needed to determine whether portable ultrasound and commercially available microbubbles could be provided in an ambulance setting, at the point of patient contact, to further reduce infarct size and improve patient outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Ultrasonic cavitation of intravenously administered microbubbles can increase early epicardial patency, reduce infarct size, and improve systolic function in patients with STEMI undergoing primary PCI.

COMPETENCY IN MEDICAL KNOWLEDGE: Further studies are needed to determine the optimal ultrasonic frequency and pulse duration for coronary thrombus disruption and understand the relative roles of microvascular and epicardial effects on clinical outcomes when this technology is employed.

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