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High versus Low Mechanical Index Imaging Diagnostic Ultrasound in Patients with Myocardial Infarction: A Therapeutic Application Study

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Data Interpretation D
Manuscript Preparation E
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Background: High mechanical index impulse of ultrasound is used for diagnosis of microvascular coronary obstruction and the necrotic area, but an experimental model study suggested that it can restore microvascular and epicardial coronary flow. The purposes of the study were to test the safety and therapeutic efficacy of high acoustic energy diagnostic ultrasound in patients with ST-segment elevation myocardial infarction.

Material/Methods: Patients with ST-segment elevation myocardial infarction subjected to a low (n=199) or high (n=251) mechanical index ultrasound before and after percutaneous coronary interventions and echocardiographic parameters were evaluated. Coronary angiographies were performed for the assessment of culprit vessels. Thrombolysis in myocardial infarction flow grade 1 or 2 were considered as culprit vessels.

Results: Patients diagnosed through low acoustic energy ultrasound reported 235 infarct vessels and patients diagnosed through high acoustic energy ultrasound reported 300 infarct vessels. With respect to low acoustic energy, high acoustic energy reduced the number of culprit vessels at post-percutaneous coronary interventions at 48 hours before hospital discharge (P=0.015) and post-percutaneous coronary interventions at 1-month from the baseline interventions (P=0.043). Also, the maximum% ST-segment resolution and an ejection fraction of the left ventricle was increased and microvascular coronary obstruction in infarct vessels was decreased for both evaluation points. High acoustic energy could not affect heart rate (P=0.133) and oxygen saturation (P=0.079).

Conclusions: High acoustic energy ultrasound is a safe method for diagnosis of ST-segment elevation myocardial infarction and may have therapeutic applications.

MeSH Keywords: **High-Intensity Focused Ultrasound Ablation • Myocardial Infarction • Percutaneous Coronary Intervention • Stroke Volume • Ultrasonography**

Abbreviations: **STROBE** – strengthening the reporting of observational studies in epidemiology; **TIMI** – thrombolysis in myocardial infarction

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Background

Acute myocardial infarction remains a primary health concern all over the world [1] and is the main cause of morbidity and death in China [2]. Current treatment for myocardial infarction is thrombolysis [3] and percutaneous coronary intervention [2]. These treatments lead to microvascular coronary obstruction and a higher necrotic area [4]. Intravascular ultrasound is mainly used to show different aspects of coronary disease [5] because it has high tissue penetration and evaluates plaque vulnerability [6].

Transthoracic high mechanical index impulse of ultrasound is used for diagnosis of microvascular coronary obstruction and the necrotic area [3] but an experimental model study suggests that high mechanical index impulse of ultrasound can restore microvascular and epicardial coronary flow [7]. Also, a study reported that ultrasound waves might dissolve intravascular thrombi [8]. The combination of intravenous tissue plasminogen activator with ultrasound might achieve effective thrombolysis [9]. In short, contrast-enhanced ultrasonography is used for diagnosis of microvascular obstruction, wall motion abnormalities, or ejection fraction [10] and has therapeutic action [11].

The primary objective of the study was to investigate the safety and therapeutic efficacy of the high mechanical index impulse diagnostic ultrasound on microvascular coronary flow and left ventricular systolic functions in patients with ST-segment elevation myocardial infarction. The secondary objective of the study was to access the effect of the high mechanical index impulse diagnostic ultrasound at 30-days post percutaneous coronary interventions.

Material and Methods

Ethics approval and consent to participate

The designed protocol (FHB/CL/23/19 dated 21 September 2019) of the established study was approved by the First Central Hospital of Baoding review board and Medical Council of China. The study reporting adheres to the law of China, strengthening the reporting of observational studies in epidemiology (STROBE) statement, and the Declaration of Helsinki (v2008).

Patient population

Data of patients admitted at the Emergency Department with chest pain who required admission diagnosis and follow-up from January 15, 2019 to September 3, 2019 (n=505) of the Affiliated Hospital of Hebei University, Baoding, Hebei, China, the Handan Shengji Tumor Hospital, Handan, Hebei, China, and the First Central Hospital of Baoding, Baoding, Hebei, China were included for review after written permission from competing authorities. Among them, 5 patients had been put on fibrinolytic therapy, 3 patients had a history of myocardial infarction, 6 patients had been receiving percutaneous coronary interventions, and 41 patients had acute non-ST-segment elevation (transient ST elevation, ST depression, or new T wave inversions) myocardial infarction. Therefore, these patients were excluded from the study. A total of 450 patients with first time ever chest pain with ST-segment elevation myocardial infarction (2 mm of ST elevation in V2 and V3 in male patients (Figure 1A) and 1.5 mm of ST elevation in V2 and V3 in female patients (Figure 1B), age ≥40 years old) and required admission diagnosis were included in the study (Figure 2).

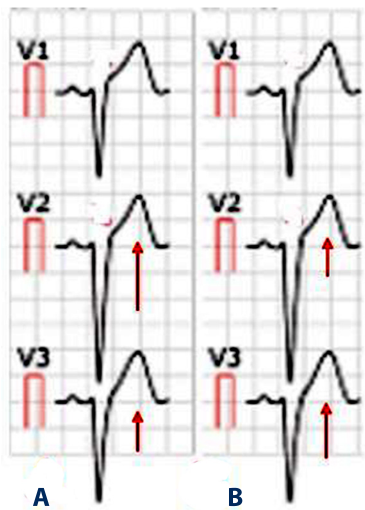

Figure 1. Electrocardiogram. (**A**) Electrocardiogram of male patient aged 45 years. (**B**) Electrocardiogram of female patient aged 44 years. The red arrow indicates elevation in ST-segment.

Stratification

The patients were subjected to diagnostic ultrasound either a low mechanical index (n=199): only 1.8 MHz diagnostic ultrasound consisting 0.18 low mechanical index imaging at 25 Hz frame rate with not more than 3 high mechanical index for diagnosis of heart wall motion and microvascular coronary circulation before and after percutaneous coronary interventions or high mechanical index (n=251): received 1.8 MHz, 1.1–1.3 mechanical index at 3 µS pulse duration in 2, 3, and 4 apex chamber for diagnosis of heart wall motion and microvascular coronary circulation before and after percutaneous coronary interventions by XG3 (Philips Healthcare System, Andover, MA, USA) based on the decision of physician(s). The intervals between the high mechanical index varied from 10–20 seconds. Transmit line spacings were 2°. We used 132 lines/frame for low

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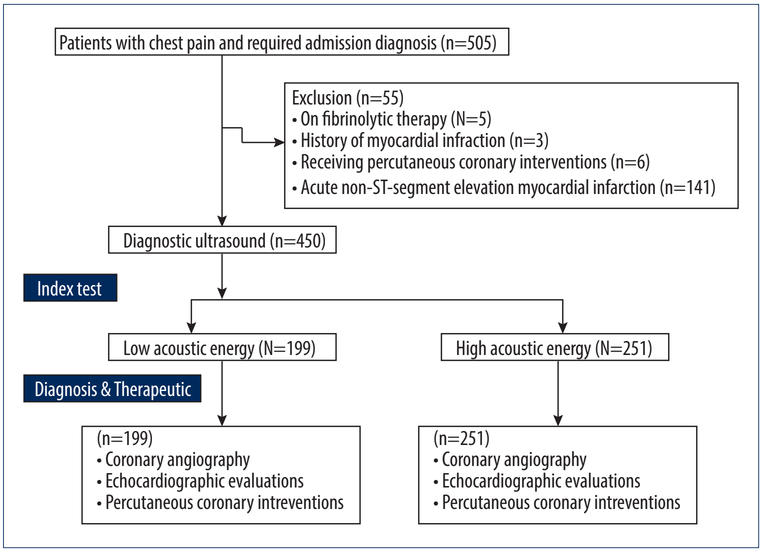

Figure 2. Flowchart of the diagnosis and treatment.

mechanical index and 120 lines/frame for the high mechanical index; 0.5 mL Optison™ (perflutren protein-type A microspheres, GE Healthcare Inc., Princeton, NJ, USA) was used as a contrasting age (injected into a peripheral vein). All patients were subjected to study mitral valve movement (as a routine diagnostic practice) [3]. All diagnosis was performed by ultrasound technologists (a minimum of 3-years of experiences) of institutes.

Coronary angiography

Pre-percutaneous coronary interventions and post-percutaneous coronary interventions (at 48 hours before discharge from the hospital and at 1-month from baseline interventions) coronary angiographies were performed by interventional cardiologists (a minimum of 3-years of experiences) of institutes. Angiograms were analyzed according to thrombolysis in myocardial infarction (TIMI) flow grading [12] by interventional cardiologists (a minimum of 3-years of experiences) of institutes. TIMI flow grade 1 or 2 was considered as culprit vessels (Figure 3). The coronary angiography was performed immediately after echocardiography.

Echocardiographic evaluations

All echocardiographic data were evaluated at pre-percutaneous coronary interventions and post-percutaneous coronary interventions (at 48 hours before discharge from the hospital and at 1-month from baseline interventions) by ultrasound technologists (a minimum of 3-years of experiences) of institutes.

Maximum ST-segment resolution

It was calculated as per Eq. 1 [13]:

$$\text{Maximum \% ST} - \text{segment resolution} = \frac{\text{The initial ST} - \text{segment elevation} - \text{ST segment elevation on the second ECG)}}{\text{The initial ST} - \text{segment elevation}} \quad (1)$$

Wall motion score index

It was assessed from wall thickening of contrast-enhanced apical windows through a 17-segment model [14].

Ejection fraction

Contrast-enhanced images were used for the evaluation of left ventricular ejection fraction as per Eq. 2 [14]:

$$\text{Ejection fraction} = \frac{\text{(End-diastolic volume)} - \text{(end-systolic volume)}}{\text{End} - \text{diastolic volume}} \quad (2)$$

Microvascular coronary obstruction

The microvascular coronary perfusion score index was used for the assessment of microvascular coronary obstruction. Score 1: the replenishment of myocardial contrast within 4 s of the applied high mechanical index impulse. Score 2: complete myocardial contrast replenishment of the assessed area but delayed (more than 4 seconds of the applied high mechanical index impulse). Score 3: virtually myocardial contrast non-replenishment (not after 10 seconds of the applied high mechanical index impulse) (Figures 4, 5). The score of 3 was considered as microvascular coronary obstruction. The scoring index was calculated as per Eq. 3. Attenuated basal segments (due to shadowing) were excluded from evaluation [3].

$$\text{Score index} = \frac{\text{Total score}}{\text{Total numbers of segments evaluated}} \quad (3)$$

Statistical analyses

InStat 3.01, GraphPad, San Diego, CA, USA was used to perform statistical analyses. the Mann-Whitney U test (between groups) and paired *t*-test (within a group) [3] were performed for numerical data and the Fischer's exact test (between groups) or

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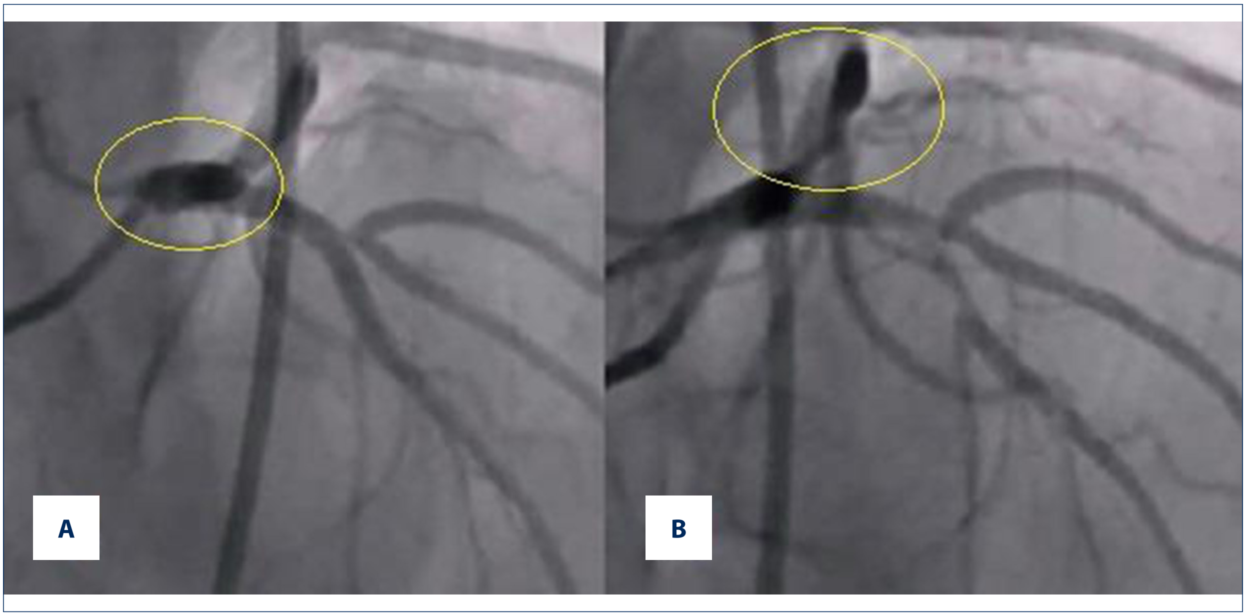

Figure 3. Thrombolysis in myocardial infarction flow grading. (**A**) Thrombolysis in myocardial infarction flow 2. (**B**) Thrombolysis in myocardial infarction flow 1.

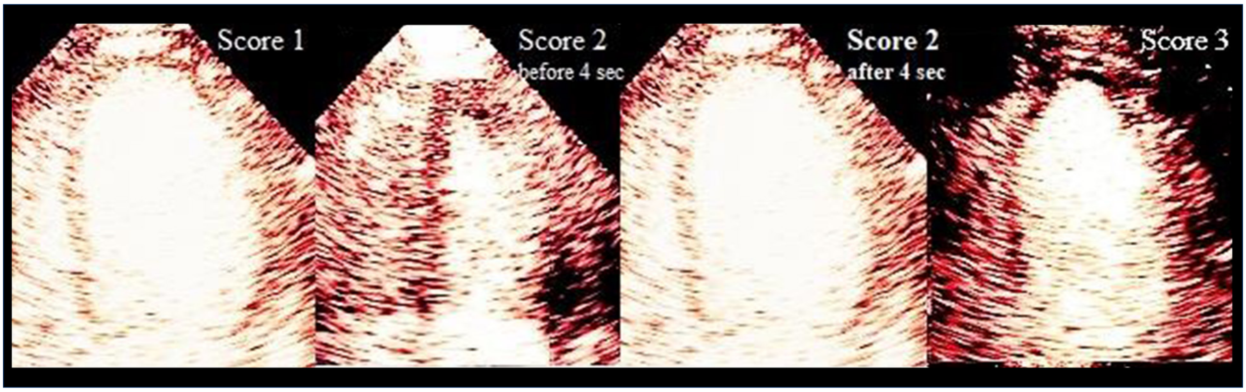

Figure 4. The assessment of microvascular coronary obstruction for low acoustic energy.

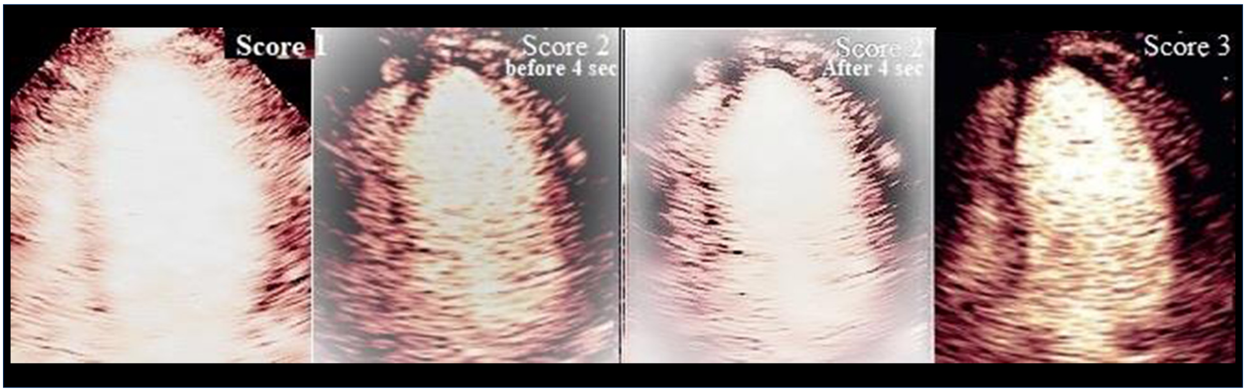

Figure 5. The assessment of microvascular coronary obstruction for high acoustic energy.

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Table 1. Demographical, clinical, and pre-percutaneous coronary interventions characteristics.

Characteristics		Cohorts		Comparisons between cohorts
Ultrasound diagnosis		Low acoustic energy	High acoustic energy	
Numbers of patients		199	251	*P*-value
Age	Minimum	40	40	0.059
	Maximum	70	70	
	Mean±SD	54.12±3.45	54.71±3.15	
Ethnicity	Han Chinese	180 (90)	223 (89)	0.791
	Mongolian	17 (9)	26 (10)	
	Tibetan	2 (1)	2 (1)	
Gender	Male	175 (88)	209 (83)	0.181
	Female	24 (12)	42 (17)	
Smoking	Non-smoker	133 (67)	149 (59)	0.266
	Current smoker	42 (21)	65 (26)	
	Smoker	24 (12)	37 (15)	
Diabetes		33 (17)	53 (21)	0.231
Hyperlipidemia		35 (18)	57 (23)	0.197
Blood pressure (mmHg)	Systolic pressure	135±4	134±7	0.073
	Diastolic pressure	84±5	85±6	0.060
Heart rate (bpm)		76±7	77±7	0.133
% Oxygen saturation		96±2	95.7±1.5	0.070
* The culprit vessel (thrombolysis in myocardial Infarction flow grade 1 or 2)		181 (77)	239 (80)	0.461
Maximum% ST segment resolution		3.11±0.15	3.14±0.22	0.101
Wall motion score index		1.81±0.52	1.78±0.49	0.531
% Ejection fraction		37±6	38±7	0.101
* Microvascular obstruction		83 (35)	109 (36)	0.856

Ordinal and constant data are shown as frequency (percentage) and numerical data are shown as mean±standard deviation (SD). The Fischer's exact test was performed for ordinal data and the Mann-Whitney U test was performed for numerical data. $P<0.05$ was considered significant. * Frequency with respect to the total number of infarct vessels.

the chi-square (within a group) test were performed for ordinal data. The results were considered significant at a 95% confidence level.

Results

Pre-percutaneous coronary interventions characteristics

Majorities of patients were between the ages range of 45–55 years and 85% of patients were male. All patients reported high blood pressure of stage I. All patients received Aspirin (Ecosprin 325 mg, US Vitamins Limited, Mumbai, India) and clopidogrel (Plavix 600 mg, Sanofi-Aventi, Paris, France) in the Emergency Department. There was no significant difference for characteristics between the 2 cohorts at pre-percutaneous coronary interventions ($P>0.05$ for all). The other demographical and clinical parameters at the pre-percutaneous coronary intervention stage are reported in Table 1.

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Table 2. Coronary angiography characteristics.

Characteristics		Cohorts		Comparisons between cohorts
Ultrasound diagnosis		Low acoustic energy	High acoustic energy	
Numbers of patients		199	251	
Total number of infarct vessels		235	300	*P*-value
Type of infarct vessel(s)/ patient	Single vessel	168 (84)	209 (83)	0.945
	Two vessels	26 (13)	35 (14)	
	Three vessels	5 (3)	7 (3)	
Infarct locations	Left anterior descending	88 (38)	114 (38)	0.594
	Right coronary artery	78 (33)	109 (36)	
	Left circumflex territories	69 (29)	77 (26)	

Data are represented as the frequency (percentage). The Fischer's exact test was performed for statistical analyses. $P<0.05$ was considered significant.

Coronary angiography

Patients diagnosed with low acoustic energy reported 235 infarct vessels and patients diagnosed with high acoustic energy reported 300 infarct vessels. There was no statistical difference for the location of the infarct vessel between both groups ($P=0.594$, Table 2).

With respect to low acoustic energy, high acoustic energy reduced the number of obstructed culprit vessels at post-percutaneous coronary interventions at 48 hours before hospital discharge (101(43) versus 98(33), $P=0.015$) and post-percutaneous coronary interventions at 1-month from baseline interventions (41(17) versus 33(11), $P=0.043$, Figure 6).

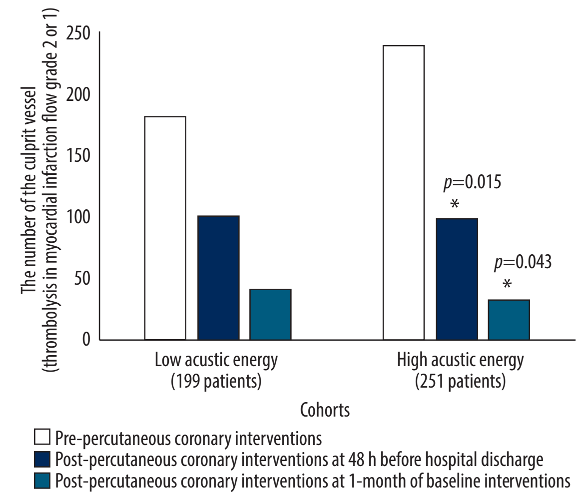

Figure 6. Culprit vessel evaluation by coronary angiography. Data are represented as a frequency. The Fischer's exact test was performed for statistical analyses. A $P<0.05$ was considered significant. * Significantly lower than low acoustic energy.

Echocardiographic evaluations

Low acoustic energy was successful to increase% ST-segment resolution ($P<0.0001$) and ejection fraction of left ventricle ($P<0.0001$) only at 1-month after percutaneous coronary interventions. While, high acoustic energy was successful to increase% ST-segment resolution ($P<0.0001$) and ejection fraction of left ventricle ($P<0.0001$). Also, it was decreased wall motion score index ($P=0.035$) and numbers of microvascular obstruction in infarct vessels ($P<0.0001$) at 1-month after percutaneous coronary interventions. With respect to low acoustic energy diagnostic ultrasound, maximum% ST-segment resolution was increased by high acoustic energy diagnostic ultrasound post-percutaneous coronary interventions at 48 hours before hospital discharge ($P<0.0001$) and post-percutaneous coronary interventions at 1-month from baseline interventions ($P<0.0001$). Wall motion score index was decreased by high acoustic energy diagnostic ultrasound post-percutaneous coronary interventions at 48 hours before hospital discharge ($P<0.0001$) and post-percutaneous coronary interventions at 1-month from baseline interventions ($P<0.0001$). However, ejection fraction of left ventricle was increased by high acoustic energy diagnostic ultrasound post-percutaneous coronary interventions at 48 hours before hospital discharge ($P=0.003$) and post-percutaneous coronary interventions at 1-month from baseline interventions ($P<0.0001$) and microvascular coronary obstruction in infarct vessels was decreased by high acoustic energy diagnostic ultrasound post-percutaneous coronary interventions at 48 hours before hospital discharge ($P=0.045$) and post-percutaneous coronary interventions at 1-month from baseline interventions ($P=0.049$). The detailed values of echocardiographic evaluations are presented in Table 3.

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Table 3. Echocardiographic evaluations.

Ultrasound diagnosis	Cohorts										Comparisons between cohorts	
	Low acoustic energy					High acoustic energy						
Numbers of patients	199					251						
Characteristics	BL	ML		EL		BL	ML		EL		ML	EL
Number of infarct vessels	235	235	*P-value	235	*P-value	300	300	*P-value	300	*P-value	P-value	P-value
Maximum% ST segment resolution	3.11±0.15	5.12±0.18	<0.0001	15.14±1.12	<0.0001	3.14±0.22	20.18±1.15	<0.0001	22.45±2.45	<0.0001	<0.0001	<0.0001
Wall motion score index	1.81±0.52	1.85±0.47	0.3821	1.79±0.41**	0.644	1.78±0.49	1.68±0.42	0.008	1.61±0.39	0.035	<0.0001	<0.0001
% Ejection fraction	37±6	41±7	<0.0001	45±6	<0.0001	38±7	43±7	<0.0001	48±8	<0.0001	0.003	<0.0001
Microvascular obstruction in infarct vessels	83 (35)	80 (34)**	0.846	64 (27)**	0.073	109 (36)	78 (26)	0.018	59 (20)	<0.0001	0.045	0.049

BL – pre-percutaneous coronary interventions; ML – post-percutaneous coronary interventions at 48 hours before hospital discharge; EL – post-percutaneous coronary interventions at 1-month of interventions. Ordinal data are shown as frequency (percentage) and numerical data are shown as mean±standard deviation (SD). The Fischer's exact test (between groups) and the chi-square test (within a group) were performed for ordinal data and the Mann-Whitney U test (between groups) or paired *t*-test (within a group) were performed for numerical data. *P*<0.05 was considered significant. * Comparison with respect to BL; ** insignificant difference with respect to BL.

Table 4. Safety study.

Ultrasound diagnosis	Cohorts					
	Low acoustic energy			High acoustic energy		
Numbers of patients	199		P-value	251		*P-value
Characteristics	BP	AP		BP	AP	
Heart rate (bpm)	76±7	77±7	0.133	77±7	78±7	0.133
% Oxygen saturation	96±2	95.7±2	0.115	95.7±1.5	96±2	0.079

BP – before percutaneous coronary interventions; AP – after percutaneous coronary interventions. Data are presented as mean±standard deviation (SD). The paired *t*-test was performed for statistical analyses. *P*<0.05 was considered significant.
* Comparisons between before and after percutaneous coronary interventions.

Safety study

High acoustic energy could not affect heart rate (*P*=0.133) and oxygen saturation (*P*=0.079). The detailed parameters of heart rate and oxygen saturation are reported in Table 4.

Discussion

The study reported therapeutic effects of contrast-enhanced ultrasound with high acoustic energy e.g., improved coronary flow after percutaneous coronary interventions especially at 1-month from baseline interventions in patients with ST-segment elevation myocardial infarction. Low acoustic energy ultrasound with shorter pulse duration is generally used to diagnose myocardial perfusion and wall motion criteria [15]. The results of the study were consistent with the results of a single-blind randomized trial [3], randomized clinical studies [8,16], experimental model studies [7,17], and CLOTBUST trial [9]. Diagnostic ultrasound with longer pulse duration before and after percutaneous coronary interventions prevents microvascular coronary obstructions and its complications [3] because high acoustic energy ultrasound cause microbubbles to cavitate during the period of insonation [7] which creates

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shear stress and dissolves thrombus [17]. Moreover, animal model studies provided evidence for microvascular sonothrombolysis by ultrasound-mediated microbubble [7,18,19]. High acoustic energy ultrasound with longer pulse duration can be used to improve the microvascular and epicardial coronary flow. Sonothrombolysis is an emerging technique to improve treatment of myocardial infarction. The authors performed a retrospective study in a remarkable number of patients with ST elevation myocardial infarction. In these patients' ultrasound enhancing agents were administered and two different imaging techniques were applied. To our knowledge there has been only 1 randomized clinical trial with less patients related to contrast-ultrasound treatment of patients with ST elevation myocardial infarction [3,16]. The results in the current study could become important to further promote sonothrombolysis in patients with myocardial infarction.

High acoustic energy decreased wall motion score index and an improved ejection fraction of the left ventricle. These results of the study were consistent with the results of a single-blind randomized trial [3] and a randomized clinical study [16]. Coronary blood flow abnormalities are associated with morbidities and mortality [20]. High acoustic energy ultrasound might help in the improvement of coronary blood flow for long-term effects.

Contrast-enhanced ultrasound with low-acoustic energy also reported parts of beneficial therapeutic effects like an increase in% ST-segment resolution and ejection fraction. The results of the study were consistent with the animal model study [21]. Low-acoustic energy ultrasound can improve downstream and upstream perfusion but it can be reversed due to the absence of synthetase inhibitor(s) [3]. Ultrasound can improve parameters of patients with ST-segment elevation myocardial infarction in the risk area.

High acoustic energy ultrasound had no effects on heart rate and oxygen saturation. The results of the study were consistent with the results of a single-blind randomized trial [3]. High acoustic energy ultrasound with long-duration impulses may have no potential harm to patients with ST-segment elevation myocardial infarction.

Despite recent warnings regarding contrast agent, the study used the first-generation contrast agent (Optison™). It is useful diagnostic tool for coronary artery diseases and is safe too [22]. The choice of the contrast agent has no effect on sonothrombolysis but definitely has a specific impact on diagnosis of coronary thrombus.

Although the study addressed potential and life-threatening issues by non-invasive methods, there are several limitations of the study, for example, retrospective analysis and absence of the control group, the large multi-central controlled clinical trial is required to validate the hypothesis. Culprit vessels were considered as TIMI flow grades 1 or 2 but flow grades 1 and 2 are different predictors of clinical outcomes [23]. Besides ultrasound, invasive coronary angiographies were performed for the assessment of culprit vessels. The gender differences have an impact on cardiovascular disease [24] but the study did not evaluate such parameters. A lot of confounders and recalling bias reported in the study. Therefore, an adjusted model should be used to calculate the real effect size. The inter- and intra-observer variability did not perform.

Conclusions

The diagnosis of patients with ST-segment elevation myocardial infarction with high acoustic energy ultrasound might improve coronary blood, an ejection fraction of left ventricle, and wall motion score after percutaneous coronary interventions. The study results could be used to address life-threatening salvaging myocardial tissue problems. A dynamic study is required to study the effects of high acoustic energy ultrasound on congestive heart failure and mortality.

Acknowledgments

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Availability of data and materials

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Conflict of interest

None.

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