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Effect of Low-Intensity Pulsed Ultrasound on Ischaemic Heart Disease Patients (Novel Technique)

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Abstract

Ischaemic Heart Disease (IHD) or Coronary heart disease means that the heart is not getting enough blood and oxygen supply through the coronary arteries. The most common cause of this disease is the process of atherosclerosis in the coronary arteries. Although significant progress has been made in the management of ischaemic heart disease (IHD) The number of severe IHD patients is increasing. The treatment options for IHD have not changed much over the last three decades, which is divided between medications, coronary Angioplasty and Coronary artery bypass surgery. Thus it was crucial to develop new, non-invasive therapeutic strategies in case of Failure of medical or interventional therapy or in case patient is not fit for surgery or angioplasty. In this study, we are pleased to reveal a novel technique that was carried out on a human model. We aimed to develop low-intensity pulsed ultrasound (LIPUS) therapy for the treatment of patients with Ischaemic Heart Disease. We have set up the inclusion and exclusion criteria, the treatment protocol of LIPUS on IHD patients. In this limited group of IHD patients, We found promising clinical results and improvement on myocardial functions.

Keywords

Ischaemic Heart Disease (IHD), Low-Intensity Pulsed Ultrasound (LIPUS)

1. Introduction

Ischaemic heart disease (IHD) or coronary heart disease is the leading cause of Cardiovascular mortality worldwide with more than 4.5 million deaths occurring in the developing world annually [1].

Ischaemic heart disease (IHD) means that the heart is not getting enough blood and oxygen supply through the coronary arteries. The most common

cause of this disease is the process of atherosclerosis in the coronary arteries [1]. In the Atherosclerosis process, a fatty material which is called atheroma can be build up inside the coronary arteries eventually arteries may become narrow that they can't get enough oxygen-rich blood to the heart.

A piece of atheroma breaks off or it can cause a blood clot to form, this clot can block the coronary artery and cut off the supply of blood and oxygen to the heart muscle. This is known as a heart attack.

Symptoms can be different for everyone. Some people don't know they have CHD before they have a heart attack [2]. The common symptoms are chest pain or angina, shortness of breath, feeling faint and palpitations. The risk factors of CHD include high blood pressure, high cholesterol, diabetes, smoking, being overweight, low physical activity, and a family history of heart disease [2]. The disease can be diagnosed by Electrocardiogram, Echocardiogram, Chest X-ray and coronary angiogram.

Although significant progress has been made in the management of ischaemic heart disease (IHD). The number of severe IHD patients is increasing [2]. The treatment options for IHD have not changed much over the last three decades which are divided between medications, coronary Angioplasty and Coronary artery bypass surgery [2].

Thus it was crucial to develop new, non-invasive therapeutic strategies in case of failure of medical or interventional therapy or in case the patient is not fit for surgery or angioplasty. This study was carried on the human model. We aimed to develop low-intensity pulsed ultrasound (LIPUS) therapy for the treatment of patients with ischaemic heart disease. We have set up the inclusion and exclusion criteria, the treatment protocol of LIPUS on IHD patients. In this limited group of IHD patients, we found promising clinical results and improvement in myocardial functions.

2. Patients and Methods

2.1. Participants

With Institutional Review Board approval at AL Assad University Hospital in Damascus 17 patients were enrolled in our study in the period between January 2017 till June 2020. Unfortunately 8 patients were dropped out of study basically for financial reasons or difficulty to travel to our center from different cities. Two patients were reluctant to sign the consent form for this new treatment.

Inclusion criteria include: patients agreed to consent to study, patients had previous angioplasty or cardiac surgery and they are not fit for further surgery or angioplasty and Patients should be symptomatic with no improvement with medical therapy.

Exclusion criteria include: patients with permanent pace maker (PPM), patients diagnosed with cancer, patients with recent heart surgery and patients with STEMI or NSTEMI.

Basic clinical characteristics of patients is shown in **Table 1**.

Table 1. Patient's clinical characteristics.

Variable	Results
Male/Female	8/1
Mean Age ± SD	62 ± 13
Smoking	
Current Smoker	7
Ex smoker	2
DM	
NIDDM	2
IDDM	0
Hypercholesterolemia	5
Obesity	5
Previous PCI	5
Previous Surgery	6
NYHA Class	
IV	1
III	4
II	4
CCS Class	
III	2
II	7

IDDM: Insulin Dependent Diabetes Myelitis; PCI: Percutaneous Intervention; NYHA: New York Heart Association; CCS: Canadian Cardiac Society.

2.2. Interventions

All patients received LIPUS treatment sessions using Sonopuls 490 Machine. With calculated applied power on the surface of the heart (0.05 mw/cm^2 for one minute with repetition frequency 100 Hz) at 3 different short axis level.

All Patients underwent echocardiogram study at the admission and then once a week during the course of the treatment. The course of the treatment was over 30 days. Patients received one session or two every day. The cost of the treatment is 20 USD per session.

2.3. Outcome Measures

Outcome was assessed by:

1) improvement in the clinical symptoms NYHA and CCS class.

2) improvements in EF% and WTF% parameters with serial of echocardiogram studies during the treatment period.

2.4. Statistical Methods

Data were prospectively entered onto case report forms and subsequently transferred into a Microsoft Access 2000. database. Data are expressed as mean ± 1 SD, Paired samples t-tests were used to compare changes in EF% and WTF%.

Due to the small sample size, results were validated with Wilcoxon signed rank sum test. P-value less than 0.05 was considered to be statistically significant.

3. Results

Nine patients finished the course of treatment for over almost 30 days. Patient received on average 35 ± 7 sessions of LIPUS treatment. All patients showed improvement in clinical symptoms. All of them were in Class I NYHA and Class I CCS by the end of the treatment course. Both LVEF% and WTF% were improved (Table 2, Figures 1-3).

(LVEF%) was significantly improved. (From 29% ± 0.04% to 38.8% ± 0.06% in 5 patients with poor LV function and From 48.3% ± 0.05% to 60.43% ± 0.13% in 4 patients with reasonable LV Functions. $P < 0.05$) and (WTF%) was significantly improved. (From 11.3% ± 0.05% to 41.1% ± 0.05% in 5 patients with poor LV function and From 47.8% ± 0.12% to 58.6% ± 0.11% in 4 patients with reasonable LV Functions. $P < 0.05$) without any adverse effect.

Table 2. Improvement in LVEF% and WTF%.

Reasonable LV Functions (4)	Pre Treatment	Post Treatment
LVEF%	48.3% ± 0.054%	60.43% ± 0.13%
WTF%	47.8% ± 0.12%	58.6% ± 0.11%
Poor LV Functions (5)		
LVEF%	29% ± 0.04%	38.8% ± 0.06%
WTF%	11.3% ± 0.05%	41.1% ± 0.05%

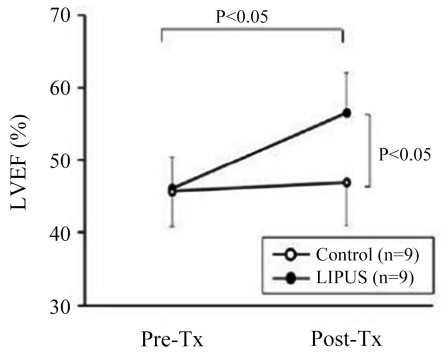

Figure 1. Improvement of LVEF% post LIPUS treatment.

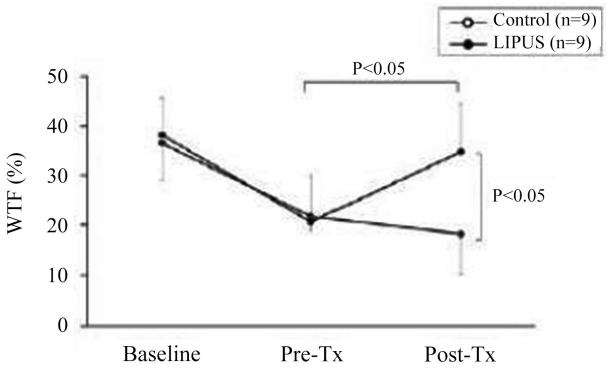

Figure 2. Improvement of WTF% post LIPUS treatment.

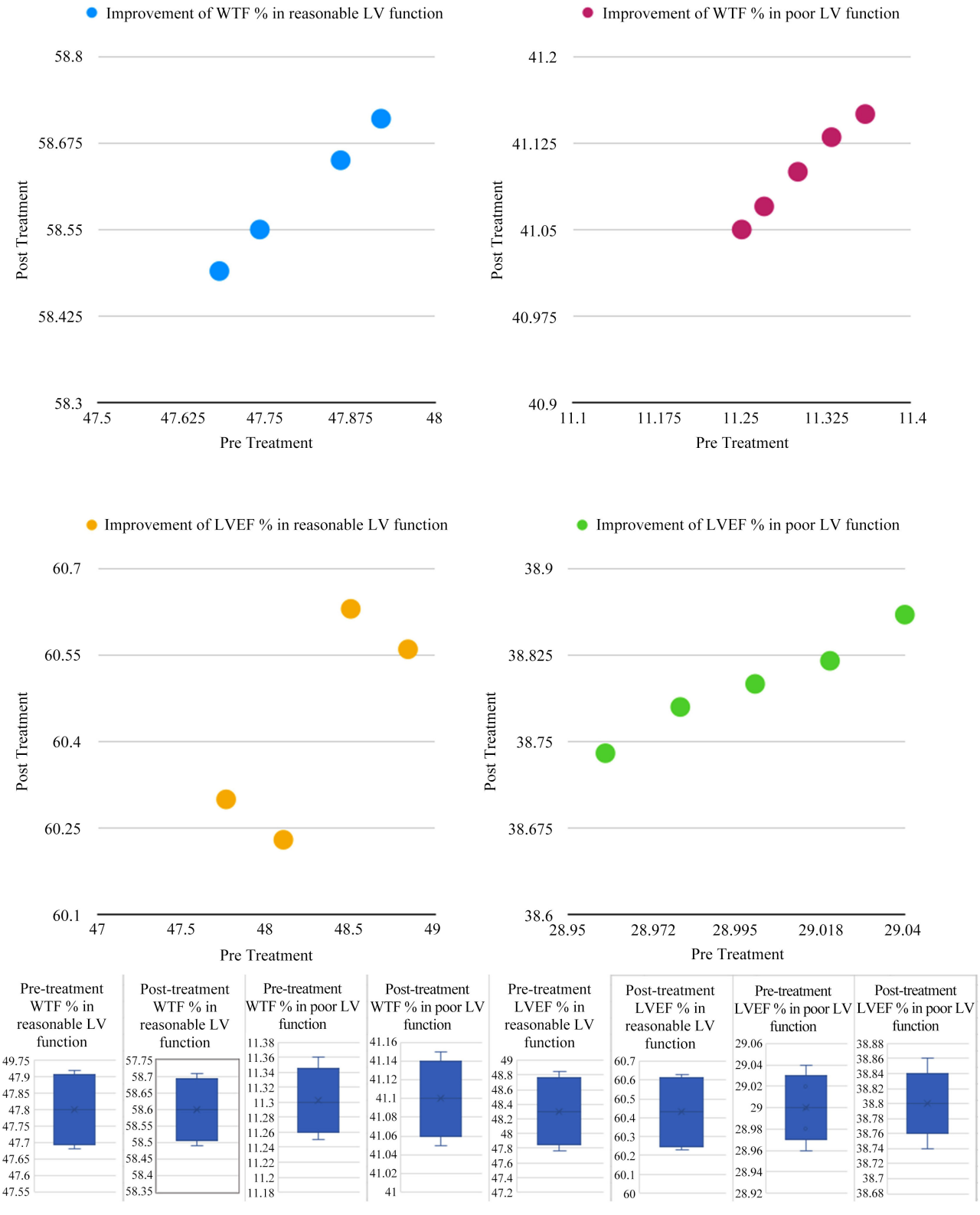

Figure 3. Scatter and box plots representing improvement in LVEF WTF percentage post-treatment.

4. Discussion

Therapeutic ultrasound has been used in soft tissue lesions [3] and has been

shown many benefits in its thermal effects like increase in tissue extensibility, increase blood flow, modulation of pain, reduction in joint stiffness, and reduction of muscle spasm [3].

And in non-thermal effects it showed stimulation of fibroblast activity, increase in protein Synthesis, increase of blood flow to tissues with tissue regeneration and enhancing bone healing [3]. Ultra sound has been used commonly in the treatment of most soft tissue complaints, particularly lesions of tendon ligament and bursa (tenditis, bursitis) [3].

FDA has approved modes for ultrasounds therapy [3] like uterine fibroid ablation, glaucoma relief, laparoscopic tissue ablation, skin tissue tightening, kidney stone commination, planter fasciitis, and lens removal. Also it has been approved in tissue cutting and vessel sealing. Another use of ultrasound was in transdermal drug delivery, intravascular thrombus dissolution, and in expediting bone fracture healings [3]. Patients should be fully informed of possible risks as well as expected benefits of the ultrasound treatments [3].

Many studies [4] [5] [6] [7] [8] showed the potential effects of a low-intensity pulsed ultrasound on the treatment of ischaemic heart or limb diseases. In this study [4] they examined the effect of LIPUS in a porcine model of chronic myocardial ischaemia with reduced left ventricle ejection fraction (LVEF) (n = 28). The heart is treated with LIPUS (32-cycle with 193 mw/cm^2 for 20 minutes with repetition frequency 7 kHz) at 3 different short axis levels. Four weeks after the treatment left ventricle ejection fraction (LVEF) was significantly improved (46% ± 4% to 57% ± 5%. $P < 0.05$) without any adverse effect.

Capillary density in the ischaemic region was significantly increased. Regional myocardial blood flow was also significantly improved with up-regulation of vascular endothelial growth factor (VEGF) with the improvement of wall thickening fraction (WTF) formula. WTF = 100X (end-systolic wall thickness- end diastolic wall thickness).

The novel finding of this study is that LIPUS therapy induces angiogenesis in the ischaemic myocardium and normalizes myocardial function in a porcine model of chronic myocardial ischaemia. This study was the first report that demonstrated the potential usefulness of LIPUS therapy as a non-invasive treatment of IHD.

In another study [5] showed that low-intensity pulsed ultrasound improved the functional properties of cardiac mesoangioblasts. This study showed that LIPUS stimulation of cardiac mesoangioblasts isolated from mouse and human hearts results in significant cellular modifications that provide beneficial effects to the cells including increased malleability and improved motility. LIPUS stimulation increases the number of binucleated cells and induced cardiac differentiation. LIPUS stimulation increased the expression of myosin light chain-2 together with up-regulation of B1 integrin and RHOA, highlighting a potentially important role for cytoskeleton reorganization.

Another study [6] showed that non-invasive transthoracic, low-frequency ultrasound Augmented thrombolysis in a canine model of acute myocardial in-

farction. Transcutaneous application of low-frequency ultrasound (27 kHz) over the chest greatly augmented the efficacy of t-PA-mediated thrombolysis at 90 minutes. The mean TIMI grade flow in the t-PA alone group was 0.92 ± 1.4 compared with 2.42 ± 1.9 in the t-PA plus ultrasound group (p = 0006).

Another study [7] showed that application of low-intensity pulsed ultrasound to a culture of human circulating angiogenic cells(CACS) augmented the generation and migration capacities of (CACS), increased concentrations of angiopoietin 2 and nitrogen oxides in the culture medium and increased the expression of endothelial nitric oxide synthase in (CACS) in western blotting.

Low-intensity pulsed ultrasound using the SX-1001 device [8] showed improvements of the clinical symptoms in patient with Buerger disease and limb ischaemia.

With its limited factors (small size, no rehabilitation programme associated) our study showed that LIPUS improved the clinical symptoms of the patients. All of them were in Class I NYHA and Class I CCS by the end of the treatment course.

Both LVEF% and WTF% were improved as explained. **Table 2**, **Figures 1-3** In conclusion low-intensity pulsed ultrasound (LIPUS) is a non-invasive form of mechanical energy that can be delivered into biological tissues as acoustic pressure waves. This could be a new strategy in treatment of ischaemic heart disease with future directions in expanding its indications. Further studies are recommended.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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