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Can a Vibratory Back Massage Induce Neo-Coronary Growth? A Blinded, Randomized Controlled Pilot Study Protocol

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Abstract

Coronary artery disease (CAD) is a leading source of death and morbidity, and the search continues for viable therapeutic options to stimulate new coronary growth. Low frequency vibration (LFV) can induce fluid sheer forces and cyclic stretch/strain to vascular endothelial cells and extracellular matrix which is known to up-regulate expression of pro-angiogenic mediators such as nitric oxide, vascular endothelial growth factor, and other sheer responsive proteins. Further, cyclic stretch of coronary microvascular cells has shown to induce coronary angiogenesis in-vitro, and LFV promoted arteriogenesis has recently been demonstrated in-vivo. Interestingly there has been no work to address whether transthoracic LFV massage could induce neo-coronary growth in CAD patients. We therefore present a single center, prospective, blinded, randomized, controlled pilot study protocol aiming to test whether penetrative LFV (35 Hz) applied to the upper back of refractory angina (RFA) and/or ischemic heart failure (IHF) patients (by daily 30 minute sessions, over a 3 month period) may enhance lasting myocardial perfusion and improve clinical outcomes.

Keywords: Coronary angiogenesis; Arteriogenesis; Refractory angina; Ischemic heart failure; Transthoracic; Vibration; Percussion; Vibro-acoustic therapy

Abbreviations: ACLS: Advanced Cardiac Life Support; bFGF: basic Fibroblast Growth Factor; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; CCS: Canadian Cardiovascular Society (Anginal Class System); ECG: Electrocardiograph; EECP: Enhanced External Counter Pulsation; EF: Ejection Fraction; ERK: Extracellular Signal-Regulated Kinase; ESMR: Extracorporeal ultrasonic Shock wave for Myocardial Revascularization; ETT: Exercise Treadmill Test; IHF: Ischemic Heart Failure; LFV: Low Frequency Vibration; LBBB: Left Bundle Branch Block; LV: Left Ventricular; nMPI: nuclear Myocardial Perfusion Imaging; NIBP: Non Invasive Blood Pressure monitoring; NO: Nitric Oxide; NTG: Nitroglycerin; NYHA: New York Heart Association (Heart Failure Class System); PCI: Percutaneous Coronary Intervention; RFA: Refractory Angina; RWMA: Regional Wall Motion Abnormality; SPECT: Single Photon Emission Computed Tomography; SRS: Summed Risk Score; SSS: Summed Stress Score; VEGF: Vascular Endothelial Growth Factor; WMSI: Wall Motion Score Index

Background

Management of advanced coronary artery disease (CAD) is a difficult challenge. Refractory Angina (RFA) for example is a debilitating disease characterized by severe, easily provoked cardiac pain resistant to all conventional revascularization treatments. These individuals suffer severely impaired health-related quality of life with recurrent and sustained pain and/or breathlessness, poor general health status, psychological distress and activity restrictions. The global prevalence of RFA is increasing [1-4], with available estimates suggesting that RFA affects between 600,000 and 1.8 million people in the United States [2,5-7] with as many as 50,000 new cases each year, and 30,000–50,000 new cases per year in continental Europe [1,2,4]. The European Society of Cardiology concurs that 15% of patients who experience angina can be characterized as having RFA and that as the population ages and CAD mortality decreases, the number of patients with the condition is likely to increase [8]. Surgical and interventional options for RFA patients have usually been exhausted or have resulted in only partial revascularization, so therapy is limited to multiple anti-anginal medications, reduced activity and support group therapy. Ischemic heart failure (IHF) is another debilitating disease, often co-morbid with RFA, and in itself carrying a high prevalence in society [9]. Heart transplantation is an option for very severe IHF cases, however the treatment option is seriously limited by poor viability of subjects and scarcity of donated organs.

The burgeoning field of stimulation of neo-coronary growth (whether by *angiogenesis* – growth of new coronary arterioles and capillaries, or *arteriogenesis* – growth of pre-existing collaterals) offers hope for these patients [10]. The goal of this approach is to induce growth of new or pre-existing vasculature in zones of ischemia in supply of the myocardium to perfuse ischemic territories otherwise unapproachable by angioplasty and bypass surgery. The delivery of angiogenic growth factors has been a major research focus over the last decades, but unfortunately despite encouraging preclinical data has so far shown only at best bare minimal improvements in myocardial perfusion, cardiac function, and clinical outcome [11].

A variety of non-invasive mechanical techniques for inducing neo-coronary growth have been gaining attention as it has been solidly established that introduction of sheer stresses and cyclic stretch or strain to vascular endothelial cells (and/or extracellular matrix) can lead to the endogenous liberation of multiple beneficial pro-angiogenic factors [12-21] and demonstrable growth of new arterioles and capillaries [22-30].

Enhanced external counter pulsation (EECP) for example,

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involving forceful diastolic timed leg compressions (which send retrograde pulses of blood to augment fluid coronary endothelial sheer stresses) has shown to increase treadmill time to ST depression and diminish anginal counts (although without change in NTG usage) in the randomized control MUST-EECP trial [31], although the authors admit the difficulty in blinding patient's from sham therapy hence placebo effect (a strong factor in evaluation of anti-anginal therapies [32]) remains a lingering question. EECP is also generally uncomfortable and can be injury producing to the patient[1], and has shown a suboptimal inverse correlation in effectiveness related to the extent of coronary artery disease - possibly because of the requirement of a proximal patent conduit to transmit the augmented pressure pulse to a diseased vasculature [33,34]. Extracorporeal ultrasonic Shock wave delivery for Myocardial Revascularization (ESMR- Cardiospec, Medispec Ltd) has recently emerged as a safer, less painful non-invasive mechanical technique of delivering ultrasonic imaging guided shock waves to a targeted ischemic myocardium which reportedly induces liberation of angiogenic related growth factors [35]. However a highly skilled professional for targeting the shock waves is needed (hence the technique may not be affordable to all patients) and ESMR's therapeutic impact is somewhat questionable with a noted absence of randomized controlled clinical trials (again placebo effect?) and recent RFA studies showing only borderline to absent improvements of empirically measurable perfusion [36,37].

Hence the search continues for a practical, safe, non-invasive therapy to promote coronary revascularization in advanced CAD cases, preferably one which does not rely upon patent proximal vessels nor advanced imaging techniques, and preferably deliverable by self-administration in the comfort of one's home. In view of very recent industry reports that non-invasively applied Low Frequency Vibration (LFV) massage can promote arteriogenesis in-vivo [38], and given in-vitro data that cyclic stretch of coronary endothelial cells and cardiac myocytes promote coronary angiogenesis [22-24], we have taken a first step in addressing the question whether transthoracic LFV may grow new coronary vessels in the ischemic heart. To that end we provide a blinded, randomized controlled pilot study protocol involving LFV massage to the upper back in RFA and IHF patients via use of the VTS – 1000 Vibro-Acoustic Therapy system (Sound Oasis), a commercially available back massager marketed for home use.

Experience gained by this study should begin to fill the evidence gap as to whether transthoracic LFV may safely lead to improved myocardial perfusion and clinical outcomes in patients with severe CAD.

Methods/Design

Scientific title

Coronary Revascularization by ExtrAcorporeal Transthoracic Epi-myocardial VIBration

Acronym

CREATE-VIB trial

Study type

A single center, prospective, blinded, interventional, randomized control pilot study.

Principle investigator

Not yet established.

[1]Up to 50% of patients using EECP experience adverse effects, including paresthesia, leg edema, skin abrasions/blisters, or pain in legs or back, with up to 10% of patients aborting this form of therapy for those reasons [31].

Conditions to be treated

Refractory Angina (CCS class 3 or 4), and/or Ischemic heart failure (NYHA functional class 2, 3 or 4).

Study location

In hospital or clinic under nursing supervision. Location has yet to be established.

Hypothesis

Penetrative upper back 35 Hz sinusoidal LFV massage applied daily for 30 minute sessions over a 3 month period via the VTS – 1000 Vibro-Acoustic Therapy system will stimulate neo-coronary growth, enhance myocardial perfusion, and improve clinical outcomes in RFA and/or IHF patients.

Medical device to be evaluated

VTS – 1000 Vibro-Acoustic Therapy System[2] (Sound Oasis).

Intervention type

Thirty test subjects will be divided into two parallel matching groups[3], where after the groups will be randomized to receive half hour sessions of penetrative (high setting) 35 Hz vibration via the VTS – 1000 system to their upper back vs. non-penetrative (low setting) sham therapy. Interventions planned daily - over a 3 month period[4].

Patient enrollment strategy

Invitation by participating Cardiologists.

Seek balance of RFA, IHF and RFA and IHF patients in view to matching similar subjects into two parallel groups prior to randomization. For safety reasons (regarding monitoring during therapy) limit enrollment to a maximum of 10 patients with Ejection Fractions (EF) of < 35%.

Enrollment dates

To be announced.

Patient inclusion criteria

- Adults (>35 years of age), any race, male or female.
- Patient weight, ≤ 120 kg.
- Stable, CCS class 3 or 4 angina pectoris, and/or NYHA functional class 2, 3 or 4 ischemic heart failure.
- A positive exercise treadmill test (ETT), and at least one of a Nuclear SPECT MPI perfusion study showing evidence for reversible myocardial ischemia, and/or a Stress Echo showing at least one provoked regional wall motion abnormality (RWMA).
- An interpretable QRS complex enabling ST analysis during stress testing (i.e. no left bundle branch block – LBBB, or paced beats during stress).[5]

[2]The FDA has listed the VTS – 1000 as a class one medical device saleable to the public (with allowable claims of relief of pain, increase of blood circulation and relaxation).

[3]Matched according to condition (RFA, IHF, or both RFA and IHF) as well as CCS anginal and NYHA heart failure functional class.

[4]A 75% compliance rate (i.e. to attend a minimum of 3/4 appointments) will meet the expectations of the study.

[5]As outcome measures rely on time to ST depression as well as assessment of myocardial perfusion by SPECT and inducible RWMAs by stress- echo (whereby interpretations by these modalities become problematic in presence of LBBB or paced beats).

- Ability to present for daily hospital appointments (with a minimal expected compliance of at least 75%), over a three month period.
- Patient was declined to Coronary artery bypass graft (CABG) surgery and/or percutaneous coronary intervention (PCI) by the attending cardiologist or surgeon, and has no plans to undertake other forms of coronary angiogenic therapy (e.g. EECP, ESMR etc.) during the study period.
- Patient has received optimized medical therapy.

Patient exclusion criteria

- LBBB
- Paced rhythm
- Severe aortic stenosis (valve area ≤ 1.0 cm^2)
- Patient's weight>120 kg
- Cannot walk on treadmill

Primary outcome measures

- Stress SPECT MPI[6] (maximal exercise) to assess myocardial perfusion by global perfusion at rest (SSS – summed stress score) and stress (SRS – summed rest score), pre vs. post therapy. Time to 1 mm and 2 mm ST depression, time to and degree of anginal symptoms, and functional capacity (total time on treadmill) should be additionally documented on a case by case basis.
- Stress echo[7] to assess evaluation of inducible RWMAs by hypo-akinetic segment count and Wall motion score index (WMSI) - pre vs. post therapy.
- Walking test (20 to 100 meter; patient encouraged to walk as long and as brisk as possible) to assess NHYA heart failure classification and CCS anginal class- pre vs. immediate post, 3 months and 6 months post therapy.

Secondary outcome measures

- Anginal count by month long diary record (average frequency of anginal episodes per day), pre vs. immediate post, three and six months post therapy.
- Nitroglycerine (NTG) use count by month long diary record (average frequency of NTG usage per day), pre vs. immediate post, three and six months post therapy.[8]

Potential adverse events

The VTS-1000 Vibroacoustic Therapy System is an FDA class 1 non-invasive medical device marketed for use to the general public for vibratory back massage in view to enhancing relaxation, decreasing pain, and improving circulation. The device labelling lists the following cautions: To seek doctors advisement prior to use for the following conditions: if pregnant or have a pacemaker. Device labelling has the following contra-indication: Do not use the device directly on swollen or inflamed areas, or skin eruptions.

Potential adverse events however may theoretically occur in RFA and/or IHF patients, as continuously applied transthoracic vibratory heart stimulation has been suggested to promote a negative inotropic effect (i.e. a decreased strength of LV contraction) in ischemic heart disease according to a clinical trial run by Koiwa et al. [39]. This might be caused by vibration's interference of LV cross-bridge kinetics during the force generation period of systole, and could lead to decreased systemic blood pressures and elevated LV end diastolic pressures (in turn which may provoke light headedness, angina pectoris, and shortness of breath). However, it should be noted that substantially higher powered vibrations (i.e. 2 mm @ 100 Hz) were utilized by Koiwa's vibrator than what can be generated by VTS – 1000 device (up to about 1 to 1.5 mm at 35 Hz), and Koiwa's vibrations were focused to the rib-spaces of the anterior precordium (closer to the heart) rather than the upper back. Never-the-less ACLS trained nurses will carefully monitor and document test subject's for evidence of hemodynamic compromise, shortness of breath, arrhythmia, and provocation of angina during LFV treatment sessions – with termination of a session and a disqualification of the subject from future sessions mandated in case of any dangerous adverse effects during therapy (defined more thoroughly below).

Study protocol

Pre-study workup: Within a month prior to initiation of therapy study patients should receive a baseline nuclear SPECT MPI perfusion study (via the Bruce or Modified Bruce Protocols - maximal effort) to evaluate extent of reversible myocardial ischemia. Time to 1 mm and 2 mm ST depression, arrhythmia, and onset and degree of patient symptomology (as well maximal exercise time) should be carefully documented. Patient's should also receive a Stress Echo (optionally performed concurrent with SPECT MPI perfusion study) to evaluate and score inducible RWMAs. Patients should be instructed to keep a log of anginal attacks and use of NTG over the month immediately preceding therapy. A 20 to 100 meter walk test on a flat (brisk pace, whatever the patient is capable of) should be performed and video recorded to document baseline NYHA heart failure and/or CCS anginal class within a week prior to initiation of therapy.

Study administration: Following informed consent 30 CAD patients will be matched as best as possible according to CCS angina and NHYA functional heart failure class and placed in two parallel groups. The two groups will thereby be randomized to receive VTS – 1000 therapy to the upper back (high, penetrative setting) vs. sham treatment (low, tactile but non-penetrative setting). Treatment sessions are planned for 30 minutes daily, over a three month period. All patients to undergo therapy in hospital or clinic under nursing supervision. Vital signs (including non-invasive ECG, NIBP and O2 saturations) will be monitored, with patient comments and/or symptoms documented during the treatment session. Provocation of signs or symptoms of heart failure (i.e. a sustained BP drop to below 90 mm Hg, or sustained O2 Sat drop to below 93%), unmanageable angina pectoris (un-abating chest, arm or jaw discomfort despite administration of oxygen and/or nitroglycerine), and/or provocation of hemodynamically unstable ventricular arrhythmia during use of the device will lead to termination of the session and disqualification of the patient from further sessions. A 12-lead ECG system and crash cart with defibrillator should also be immediately available, and a responsible physician should be on call (at the testing location) to deal with patient complications.

[6]Nuclear isotope may be injected at target heart rate, or per the discretion of the operator (i.e. if the patient is actively expressing a moderate to severe level of angina or is demonstrating marked ST depression of >3 mm, regardless of achieved heart rate).

[7]Patient dismount from treadmill should occur at maximal level of endurance as declared by the test subject, or if: moderate to severe angina, ominous ventricular arrhythmia, or a sustained, pathologic decrease in blood pressure is noted (as per standard stress test safety guidelines). If feasible, nuclear isotope in the MPI test may be injected during the stress echo procedure.

[8]To ensure patient compliance a small fee may be paid to the patient entitling an operator to call the patient on a weekly basis to remind them about filing out the diary.

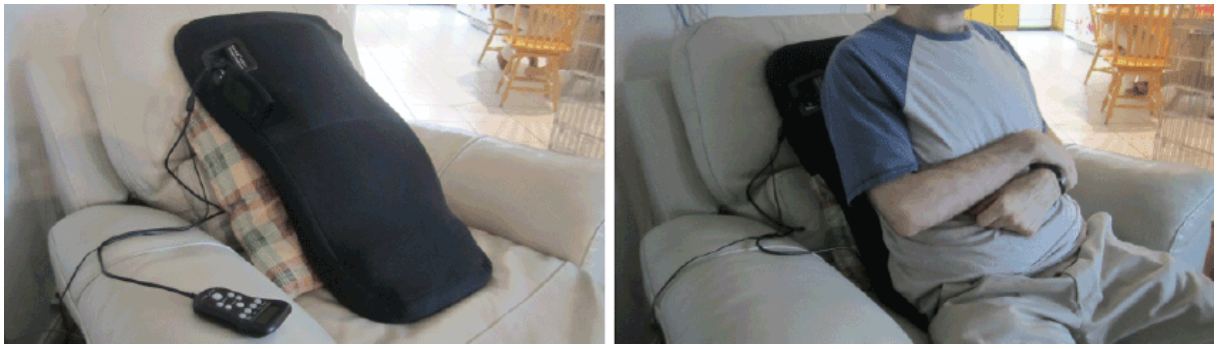

Figure 1: Positioning of the VTS 1000 system.

Device positioning: The VTS - 1000 device (comprising a portable backrest with an embedded programmable woofer speaker) should be placed in an upside down and inverted position upon a reclining chair or stretcher - with the speaker thereby protruding to enable flush engagement between a test subject's shoulder blades while reclining on the device. To promote optimized transthoracic vibratory penetration, the chair should be initially placed in semi-fowler's position to promote sufficient engagement force of the speaker system within the device against the patient's upper back. See Figure 1 (left and right) above, depicting the positioning of the VTS 1000 system.

Assessment of transthoracic vibratory transmission: Appropriate transthoracic vibratory penetration should be periodically ensured (only in the treatment group - checked initially, and rechecked thereafter in 5 minute intervals) by nursing staff by what the author's have termed the "ahhhhh" test, whereby the patient vocalizes "ahhhhhhhh" whereby audible vibratory undulations in the subject's voice confirm adequate transthoracic vibratory penetration to the heart within the thoracic cavity.

See web-link https://www.youtube.com/watch?v=5u3s1yr1x9o to view an example of the "ahhhhh" test.

Absence of a positive "ahhhhh" test at any point during therapy prompts re positioning of the device (which may have migrated away from the upper back position under the patient), and/or an establishment of greater engagement force which may be accomplished by further reclining the chair[9] (thereby placing increased weight of the patient against the device) until the vocal undulations from the "ahhhhh" test are re-established. In the unlikely scenario that there is an inability to pass the "ahhhhh" test on first day of the study despite adjustments, this will disqualify the subject from treatment, and a new candidate may be offered his/her place in the study.

Care should be taken to keep penetrative vs. sham therapy test subjects from meeting, with a separated waiting area and exit and at least a 30 minute delay between finishing one study and starting the other. Care should also be taken not to alert the sham therapy group to the meaning and intent of the "ahhhhh" test.

Post study evaluation measures: Following three months of therapy with at least a 75% participation rate test subjects should repeat the pre-test diagnostic procedures in same manner for comparative analysis regarding clinical outcomes and assessment for empirically measurable evidence for myocardial reperfusion. Patients should return at 4 months and at 7 months to repeat the 20 to 100 meter walking test, for ongoing reassessment of functional NYHA heart failure and CCS anginal class. Patient monthly diary records should be completed for immediate post therapy, month 3 and month 6 – so that they can hand in their diary at time of their walking test.

Comparative analysis: We suggest the following strategy to enable comparative analysis of the pre vs. post study imaging outcomes:

- With regards to the nuclear SPECT MPI perfusion and stress echo data we recommend evaluation of the pre and post therapy images (including ECG waveforms) by consensus of two blinded accredited physicians[10] experienced in interpretation of the modality. Changes in SSS, SRS, inducible RWMA count, WMSI, time to angina symptom, and time to ST depression between the two test groups (sham vs. treatment) will be tallied and evaluated for their statistical difference.
- With regards to the 20 to 100 meter walking test, the pre and post walk should be video – recorded (and compiled for serial comparison) and then assessed for CCS anginal and NYHA heart failure class by consensus of two blinded Cardiologists. The patients should return for a walk at end of 3 months and 6 months post therapy. Changes in class between the two test groups (sham vs. treatment) will be tallied and evaluated for their statistical difference.
- With regards to angina and NTG use counts, the results of the two test groups (sham vs. treatment) will be tallied and evaluated for statistical difference.

Ethical considerations

The study shall ensure

- Informed consent by all participants.
- Confidentiality and anominity will be maintained as per participant's request.
- Adequate safety measures will be placed to ensure no harm is done to the participants (i.e. Two ACLS trained nurses available for 15 test subjects during therapy; on-call physician located at the treatment center during therapy; crash cart, defibrillator, 12 lead ECG, and life sign monitoring – including NIBP, ECG, O2 Sat - equipment all available at treatment location).
- Monetary reward strategy to participants having received sham therapy.

[9]Lying flat to the point of breathing tolerance.

[10]Note: In case of interpretation discrepancy the two reviewers will be invited to discuss their disagreement and look over the case in question to see if they can come to a consensus. If no agreement, then a third blinded qualified physician will be brought as an arbitrator.

- Institutional Review Board ethical and safety acceptance by the accredited medical center to run the study.[11]

Results dissemination plan

The results of this study are planned to be presented for peer review in view to publication in a respected angiogenesis, or cardiological journal.

Budget

Nursing Staff (two) – 200 1 hr sessions (at $75/hr) × 2: $30,000.

Physician on call- already in hospital (one shared honorarium)[12]: $5,000

SPECT MPI (30) (at $750 ea.): $22,500

Stress Echo (30) (at $1000 ea.): $30,000

Physicians to interpret tests

60 nuclear MPI tests (at $200): $12,000.

60 Stress Echo tests (at $200): $12,000.

Lease clinic space including reclining chairs (3 months at $1000): $3000.

Crash Cart with Defibrillator: $3000.

Lease 12-lead ECG machine: $1000

Lease O2 sat/NIBP/ECG monitoring systems (15 X $500): $7,500.

VTS 1000 Vibro-Acoustic Therapy Systems (15 X $500): $7500

Principle Investigator: $25,000

Compensation to sham therapy patients: $15,000[13]

Miscellaneous:$1500

Total estimated cost of study: $175,000 K.

Discussion

To the Author's knowledge this is the first reported protocol relating to the application of transthoracic LFV massage (in this case applied to the upper back) in RFA and IHF patients in view to stimulating neo-coronary growth.

Despite the increased cost we strongly recommend a randomized controlled trial (with a control group receiving sham therapy), in order to mitigate placebo effect in the evaluation of post therapy clinical outcome measures.

It is well accepted that increased levels of fluid sheer stress and cyclic stretch/strain (or deformation) of vascular endothelial cells and/or extracellular matrix triggers activation of neo-arterial growth [22-30], and importantly this is true including with cardiac myocytes and coronary microvascular endothelial cells [22-24]. As LFV is characterized by rapidly changing compressive and expansive mechanical forces in tissue it is reasonable to postulate that LFV would expose the fluid and endothelial cells within the vasculature to such pro-angiogenic stimuli. Indeed, hydrodynamic analysis indicates that shear stress at the wall of vessels (including the coronaries) is significantly increased during bodily exposure to LFV in the low sonic ranges [40], hence the triggering of neo-arterial growth by vibration can therefore be hypothesized.

That LFV in particular may yield neo-arterial growth has been supported by Zou and his associates who found that locally applied transcranial vibration at 250 Hz demonstrated an increased expression of VEGF (a key player in extravasations of plasma proteins, endothelial cell proliferation and migration), as well as VEGF-R2, TNF-alpha, TNF R1 and R2 in the Guinea Pig cochlea [41]. LFV is also known to trigger Nitric Oxide (NO) release [42-44], which particularly along with ischemia is a well-known pro-angiogenic in up-regulation of VEGF transcription [45]. LFV is also a known potent vasodilator particular in arteries with pre-existing spasm or heighted vascular tone [46,47], whereby this may hold additional relevance in that increased or changing vascular wall tension has been suggested to lead to release of proteases initiating endothelial cell proliferation [26]. Moreover mechanical perturbations such as stretching of endothelial cells or extracellular matrix (basement membrane) has been shown to release stored bFGF - an angiogenic cytokine responsible for endothelial and smooth muscle cell proliferation [48-50]. Also, the intensive growth of endothelial cells exposed to pulsed electromagnetic fields in vitro (which leads to a mechanical oscillatory response to the cells) [51] further foreshadows a potential mitogenic effect by oscillatory stress.

Importantly LFV in the 30 Hz range has been shown to significantly increase activation of ERK1/2 (a sheer responsive protein involved in cell proliferation) and up-regulate expression of Endothelin-1, a potent mitogen and proliferator for endothelial cells [52,53]. Further, liberation of circulating levels of VEGF have also been shown by Suhr et al. in their studies of cyclists upon a vibrating platform (30 Hz, 4 mm) [54]. Moreover recent advances in LFV wound healing by promotion of arteriogenesis have just recently been unveiled by use of Vibrant Medical's Vibropulse® cycloidal vibration mat – at frequencies of less than 75Hz [38].

Penetrability of LFV from upper back to the heart is confirmed by our study by a method we have referred to as the "ahhhhh" test, whereby it was inferred that robust undulations in vocal tone during upper back percussion demonstrates adequate vibratory transmission. While this technique only yields an *inference* that the heart and coronary vasculature are being vibrated (as the trachea and vocal cords are located in close proximity, and just anterior to the heart), effective transthoracic LFV transmission (as measured by transesophageal accelerometer and LV catheter) has been verified by Koiwa et al. in human volunteers by use of a vibration device with comparable frequency and stroke amplitude emit table by the VTS – 1000 Vibro-Acoustic Therapy System [55,56].

We chose the upper back rather than the chest wall for LFV applications since application to the back (essentially equivalent to a "back massage") would be more comfortable, safer, and easier to self-apply. However for anterior ischemia an LFV application site over the chest wall, in order to bring the source of the vibration closer to the left coronary system, may be a subject for future study. The Investigators have noted (by self-application) that chest wall and upper back vibration leads to similar "ahhhhh" test results, hence substantiating the general transthoracic penetrative equivalency of the two techniques.

It should be addressed that from a safety perspective an LFV system for more severe IHF patient's would preferably be programmable to

[11]An investigational device exemption may be required.

[12]Physicians on call would only be compensated if called to deal with a patient complication (nominal rate, $200 per call).

[13]After completion of the study sham therapy patients may be identified and compensated given they fully complied with their test subject responsibilities. This will give all test subjects an incentive to complete LFV therapy (minimum of 75% compliance, and faithfully fill out their diaries – and allow follow up/reminder phone calls - with regards to anginal count and NTG use.

periodically cease vibrations during the initial force generation phase of left ventricular systole, as systolic LFV has been suggested to cause a negative inotropic effect in the ischemic heart [39].

Paradoxically however, *diastolic* timed transthoracic LFV has advantageously shown to *augment* ischemic left ventricular performance (and increase coronary flow), purportedly by improved left ventricular diastolic relaxation with augmented stroke volume by the Frank Starling mechanism [55,57,58]. We therefore have stressed that IHF patient's with ejection fractions of less than 35% undergoing upper back LFV therapy should be flagged for vigilant, vital signs monitoring to make sure they can safely tolerate the therapy, and that they should be excluded if any significant safety concerns. Disqualified IHF patients may be considered for diastolic timed LFV in a future study. The application of diastolic LFV would likely require specialized tracking by the electrocardiogram (where vibrations would temporarily cease for a short duration starting just prior to the peak of the R wave), and this has been worked on by the Department of Engineering at Simon Fraser University [59].

It should also be discussed that while only a single impact frequency of 35 Hz is planned in our study, the employment of varying patterns of LFV may at least theoretically carry additional benefits. It has been speculated for example that varying or randomizing the emission frequency or wave-shape of LFV, or employing vibration timed or coordinated to the beat of music (as common to vibro-acoustic therapy systems) [60], may tend to accentuate the multi vectored velocity patterns and convective currents (or turbulence) invoked within a diseased vasculature region [61]. The hypothesis that turbulent flow may enhance pro-angiogenic effects is indirectly supported by Davies et al. [62] who increased mitotic activity in endothelial cell cultures with turbulent, but not laminar shear stress.

The preferred candidate for mechanical sheer producing coronary angiogenic therapy would tend to comprise the sub group of patients with a coronary anatomy non amendable to standard invasive therapy approaches – (e.g. poor distal vessels or highly diffuse – non discrete – lesions), or wherein co-morbid risks make angioplasty, coronary artery bypass surgery or heart transplant an unattractive or a high risk option. However, it should be pointed out that in the "real world" at least some patients have been electing to try non-invasive angiogenic therapy as a first alternative to CABG, to see if their exercise tolerance and myocardial perfusion scans improve hence alleviating the need for an unwanted surgery [63]. While not advocated by the medical community at this time there has been considerable anecdotal and some empirical data to support this approach [64].

In summary we have provided a prospective, blinded, randomized controlled protocol relating to the practical application of localized transthoracic LFV which, if proven to be safe, could be utilized at home by RFA and/or IHF patients. LFV massage to the upper back especially following a degree of habituation has a long history of providing a generally pleasurable and relaxing feeling and has for years been available and utilized by chiropractors, physiotherapists, and masseuses to relieve muscle strains and tension. As LFV is applied indiscriminately through tissue and thereafter by internal transmission along the epi-myocardium and arteries [65-67] the sheer producing forces would intersect healthy and disease tissue non-selectively, and thereby reach even the most distal small vessels regardless of the degree of stenosis or blockages preceding them. LFV is also cheap to apply, and should not rely upon expensive imaging equipment and a high medical expertise requirement to implement the therapy.

Conclusion

A prospective, blinded, interventional, randomized controlled pilot study protocol is presented to test safety and effectiveness of transthoracic LFV via the VTS – 1000 Vibro-Acoustic Therapy system over a three month period in view to stimulating neo-coronary growth to improve clinical outcomes in RFA and IHF patients. In view of correlative mechanistic data that sheer stress producing and oscillative therapies reportedly induce neo-arterial growth, pilot testing of transthoracic LFV in a statistically relevant number of CAD patients appears warranted. Use of a control is strongly suggested to properly evaluate post therapy clinical outcome measures relating to angina counts and NTG use.

Author's Contributions (in writing the protocol)

AH: Cardiology testing modalities including patient inclusion and exclusion criteria.

HG: Introduction, Discussion, as well as Safety and Ethical Considerations relating the proposed technology.

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Competing Interest and Funding Statement

The writing of this protocol was sponsored by a grant awarded by ABS Inc., an entity holding financial shares in a patent relating to use of transthoracic vibration massage for stimulating coronary angiogenesis. The Author (AH) is a director and has shares in ABS Inc. Otherwise no conflicts of interest are declared. The Author (HG) has received grants from ABS Inc. for this and other projects. Otherwise no conflicts of interest are declared.

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Disclaimer

The Authors cannot warrant the safety of transthoracic LFV in humans with CAD, however vibration massagers similar to what we advocate for our study are generally commercially available for therapeutic back massage as well as for percussion to the chest wall (such as for mobilizing pulmonary secretions in CF patients). Further the authors cannot warrant the effectiveness that LFV to the thoracic cavity would indeed induce coronary angio or arteriogenesis as there as of yet has been no statistically relevant clinical trials to prove such effectiveness.

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