

Can a simple vibratory back massage induce neo-coronary growth? a literature review and initial experience in view to pilot testing

Abstract

Background: Coronary Artery Disease (CAD) is a leading source of morbidity, and search continues for viable therapeutic options to stimulate neo-coronary growth. Low sonic Frequency Vibration (LFV) can induce fluid shear forces and cyclic stretch / strain to 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 shear 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 which address whether transthoracic LFV could induce neo-coronary growth in CAD patients.

Methods: To investigate feasibility we present an initial experience (n=1) in use of transthoracic LFV whereby an eighty year old male with New York Heart Classification (NYHC) Class 3 heart failure and inferior ischemia (by Persantine 99mTc Myoview scan) was provided a vibrator (27-35Hz, 6mm) for application to his upper back for 15-30 minute daily home based massage sessions planned for a three month period. Time spent and feelings regarding treatment were recorded.

Results: Home delivered device use was feasible, averaging ~3 times per week. There were no lasting adverse safety concerns – although transient musculoskeletal discomforts were reported. While effectiveness of the therapy was not a focus of this study, repeat Myoview testing following 3.5 months of therapy in this single test subject showed an absence of resting and provokable ischemia with reportedly “homogenous uptake - no defects”, and patient’s heart failure improved from Class 3 to 2.

Conclusion: We report an initial experience in use of transthoracic LFV in an IHF patient in view to promoting neo-coronary growth. In view of correlative data that shear producing and oscillative therapies reportedly induce neo-arterial growth, further pilot testing of transthoracic LFV in a statistically relevant number of CAD patients appears warranted.

Keywords: vibration, vibroacoustic therapy, upper back massage, coronary angiogenesis, arteriogenesis, refractory angina, Transthoracic, ischemic heart failure

Volume 1 Issue 2 - 2016

Andrew Hoffmann,¹ Harjit Gill,² Arkady Uryash³¹Department of Research and Development, Ahof Biophysical Systems Inc, Canada²In-Vitro Laboratories, Canada³Parallel Biotechnologies LLC, USA

Correspondence: Andrew Hoffmann, Department of Research and Development, Ahof Biophysical Systems Inc, 3858 Regent St, Burnaby, BC Canada, V5V 4G8, Tel: 604 779 357, Fax: 604 437 796, Email andrew.hoffmann1@gmail.com

Received: October 25, 2016 | **Published:** December 01, 2016

Abbreviations: bFGF, basic fibroblast growth factor; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EECF, enhanced external counter pulsation; EF, ejection fraction; ERK, extracellular signal-regulated kinase; ESMR, extracorporeal ultrasonic shock wave for myocardial revascularization; IHF, ischemic heart failure; LFV, low sonic frequency vibration; NO, nitric oxide; NYHA, new york heart association (heart failure class system); PCI, percutaneous coronary intervention; RFA, refractory angina; SPECT, single photon emission computed tomography; VEGF, vascular endothelial growth factor

Introduction

Management of advanced Coronary Artery Disease (CAD) is a difficult challenge. Refractory Angina (RFA) for example is a debilitating disease characterized by severe, easily provokable

cardiac pain resistant to all conventional treatments for CAD. 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.¹ 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 comorbid with RFA, and in itself carrying a high prevalence in society.⁸

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.⁹ The goal of this approach is to induce growth of new or pre-existing vasculature to perfuse ischemic myocardial 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 have so far shown only at best bare minimal improvements in myocardial perfusion, cardiac function, and clinical outcome.¹⁰

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 endothelial cells (and/ or the extracellular matrix between the cells) can lead to the endogenous liberation of multiple beneficial pro-angiogenic factors¹¹⁻²⁰ and growth of new arterioles and capillaries.²¹⁻²⁹ Enhanced External Counter Pulsation (EECP) for example, involving forceful diastolic timed leg compressions (which send retrograde pulses of blood to augment fluid sheer stresses to coronary endothelial cells) 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 trial³⁰ although the authors admit the difficulty in blinding patient's from sham therapy hence placebo effect (a strong factor in evaluation of anti-anginal therapies³¹) remains a lingering question. EECP however is also uncomfortable and can be injury producing to the patient¹, 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.^{32,33}

Extracorporeal ultrasonic Shock wave delivery for Myocardial Revascularization (ESMR- Cardiospec, Medispec Ltd) has recently emerged as a safer, less painful non-invasive technique which delivers ultrasonic imaging guided shock waves to a targeted ischemic myocardium which purportedly induce liberation of angiogenic related growth factors.³⁴ However a highly skilled professional for targeting the shock waves is needed (hence the technique may not be available or 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 RFA studies showing only borderline to absent improvements of empirically measurable improved perfusion.^{35,36}

Hence a safe, inexpensive, practical, non-invasive therapy for treatment of chronic myocardial ischemia is required, 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 sonic Frequency Vibration (LFV) can promote arteriogenesis *in vivo*,³⁷ and given in-vitro data that periodic cyclic stretch of coronary endothelial cells and cardiac myocytes promote coronary angiogenesis,²¹⁻²³ we have taken a first step in addressing the question whether transthoracic LFV may grow

¹Up 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.²⁵

new coronary vessels in the ischemic heart. To that end we provide a feasibility case study involving LFV massage to the upper back in an elderly male with documented IHF as a self-administered home based therapy. Experience gained by this study should assist in device selection and protocol development for future pilot work in this field.

Materials and methods

This study was performed by Ah of Biophysical Systems Inc. (Burnaby, BC, Canada), following institutional approval consistent with the ethical standards on human experimentation per the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from a single Volunteer (n=1); an 80 year old retired male living in an assisted living facility with documented inferior wall myocardial ischemia - apex to base - both at rest, and with further extension of the perfusion defect with stress (according to Persantine 99mTc Myoview nuclear scan). Additional informed consent was also obtained regarding use of the Volunteer's photograph and medical images as was required in publishing this article.

We hypothesize that upper torso LFV therapy administered for 15-30 minutes daily treatment sessions over a three to four month period may lead to a correction of myocardial ischemic zones and improvement of heart failure status, perhaps by a mechanism of neo-coronary arterial growth. The aim of this study was to gain an initial experience (i.e. to assess feasibility and insights towards safety) regarding use of this technique. We hope information gleaned by this study may offer insights towards device development and later pilot study planning with a statistically relevant number of participants.

Volunteer's demographics and medical findings preceding LFV therapy

Age: 80 years

Gender: Male

Weight: 200 lbs

Height: 67 inches

Non smoker

Resting EF: 41% (By Persantine Myocardial Perfusion Scan), with "Global hypokinesis, most conspicuously at the inferior wall".

Heart Rhythm: Chronic AF, with VVI pacemaker.

Functional Limitation: NYHC 3, marked SOB requiring rest after slowly walking 3 minutes on a flat (no incline). Unsteady on feet, (poor balance) even for short distances.

Exercise routine: Independent daily dressing, walking to bathroom and for meals, walks dog short distance outside once a day with multiple rest breaks.

Medication List

Furosemide 40mg-1 tablet AM, and at lunch

Quinine Sulphate 200 MG,-1 capsule at bedtime

Warfarin 2mg.-1 tablet in the evening

Simvastatin 20mq-1 tablet in the evening

Flomax CR 0.4mg-1 tablet per day

Bisoprolol 10 mg-1 tablet daily
Ramipril 5mg-1 capsule in the morning
Venlafaxine XR 75mg-1 capsule at bedtime
Ranitidine 150mg-1 tablet morning and evening
Detrol 2mg-½ tab, twice a day
Venlafaxine 37.5mg-1 capsule at bedtime

We chose a commercially available percussive vibrator which had an output of 6 mm displacements applicable at a range of selectable impact frequency settings (level 1-20Hz, level 2-24Hz, level 3-27Hz; level 4-31Hz and level 5-35Hz).

The Volunteer was instructed to place the vibrator behind his upper back and recline against it while sitting in a chair with the contact nodes of the device disposed to the left and right of the spine predominantly between the shoulder blades. The Volunteer was further instructed to use the highest frequency/intensity level tolerable (to a level of comfort) daily, for 15-30 minute sessions for a period of at least 3 months and up to when a repeat Myoview scan could be arranged. It was recommended to apply LFV while watching television, and that a session should be immediately terminated (with the investigator contacted) should the Volunteer feel light headed, weak, shortness of breath, chest pain or undue back pain during or immediately after a therapy session. The Volunteer had reportedly never utilized a vibration massager for routine use on his back previously. Figure 1 showing the Volunteer relaxing watching TV with device applied.



Figure 1 The Volunteer watching TV while reclining against the vibrator. To view this scene in action a video is available on the internet at https://www.youtube.com/watch?v=qj43Kf_z3oY.

On introductory use (during a home visit), effective penetration from our Volunteer's upper back to thoracic cavity was confirmed by what we have termed the "ahhhhh test"², whereby the subject with device applied uttered the phrase "ahhhhh", whereby vibratory undulation in the subject's voice confirmed effective transthoracic penetration. The volunteer was instructed to always check for a positive "ahhhhh test" at the beginning and periodically during each daily therapy session to optimize device positioning. An investigator paid bi-weekly home visits to the Volunteer, to ensure maintenance of the device and that the subject had no significant adverse events.

Results

Over a 109 day testing period the device was reportedly used with a compliance of about 50 % (i.e. 54 out of 109 potential treatment days), as our Volunteer stated on interview that he generally sometimes "didn't feel like using the device", partly because of "depression" plus a variety of other reasons, such as generally "feeling unwell", or various body aches. Further, the Volunteer testified that sometimes the device, especially early on in the course therapy, made his back and thoracic region "feel sore", however this seemed to generally improve for at least a time with habituation. The Volunteer elaborated that "back soreness" meant that he felt his back had been through a workout (similar to an aggressive session with a chiropractor), and it wasn't necessarily a "bad sore" or "painful", and that the soreness usually was gone by the following day. However, later in the protocol

²To view the Volunteer undergoing the "ahhhhh" test, a video can be accessed on the Internet at the following address: <https://www.youtube.com/watch?v=5u3s1yr1x9o>

with the device used at higher intensity levels further comments of "back sore" were again noted whereby the Volunteer missed a pair of following daily sessions. The Volunteer indicated that he was not at all certain however that the device caused his back to feel sore as he often experienced similar symptoms "naturally" (regardless of use of the device), which he felt was brought on typically by "nervous anxiety" or "tension". It was also noted by diary record that the Volunteer did not always use the device the day before his reported back symptoms, and on one occasion he even indicated that the device "seems to be helping my back".

Of particular concern midway through the course of therapy our Volunteer recorded "My heart has begun to be sore, the machine may be too strong". On bi-weekly visit the Volunteer was counseled that he should have called the Investigator on this occasion and sought hospital attention by dialing 911. The Volunteer indicated however that he was actually uncertain at the time whether the discomfort was originating from his heart or upper back, and that the discomfort was only briefly noted immediately following use of the device, and seemed to have a postural component ("got better in certain positions and with stretching"). Our Volunteer indicated however that he was generally worried about using the device until he received reassurance from his physicians, (including his General Practitioner and Cardiologist), and that he had therefore temporarily stopped using the device. This was of course agreed upon by the Investigators, and the Volunteer reported he had received re-assurance from his physicians that it was safe to use the device (which is a regulatory class 1, therapeutic massager) at his discretion preferably at low to medium levels to start where-after vibration therapy commenced.

Other device use reportings included “head ache”, “neck sore”, “sore stomach”, “private parts sore”, “bones sore”, however upon interview it appeared that he was experimenting with the device and placing it at times to his lower back and hip region, whereby after therapy he noticed soreness to “stomach” and “private parts”. After experiencing these sensations the Volunteer reportedly kept use of the device to the mid and upper back, and stated that there were no subsequent like adverse occurrences to at least the lower torso region.

Typical use was at home, reclining against the vibrator, while watching TV. Our Volunteer used three differing vibro-percussion frequencies / intensity levels depending how he felt for the day, all being at 6 mm amplitude: a) (27Hz, low intensity), b) (31Hz – moderate intensity) and c) (35Hz – highest intensity). The subject did not reportedly alter his medications or his general life style (including exercise regimen) over the course of the study. A log of patient’s use of the device has been transcribed from original data, provided in Table 1.

Following 109 days of prescribed upper back LFV therapy, repeat Persantine 99mTc Myoview scan SPECT images were acquired and interpreted by a third party qualified Nuclear Medicine physician (Surrey Memorial Hospital, B.C. Canada) as normal with “no evidence of ischemia or infarction” and with the attenuation corrected perfusion images demonstrating “homogenous uptake and no defects” (Figure 2, showing pre and post stress VLA Spect images). Moreover, we took the patient for a normal paced walk (100 meters, no incline), without evidence of undue dyspnea or fatigue. Our Volunteer’s resting ejection fraction remained substantially unchanged from baseline, at 40%.



Left: Spect VLA stress view prior to LFV therapy.

Right: Same Spect VLA stress view post LFV therapy.

Figure 2 Note enhanced perfusion particularly in the inferior-posterior wall extending to the apex.

Discussion

A feasibility case study is reported where a simple, semi-regular home use of a low frequency vibrator used in the ~27-35Hz range was intermittently employed over a three and a half month period in treatment of an eighty year old male with known CAD (evidenced by inferior wall ischemia extending from apex to base, by Persantine 99mTc Myoview nuclear scan) and NYHC class 3 heart failure. To the Author’s knowledge this is the first reported experience relating to an LFV application (in this case applied locally to the upper back) in an IHF patient.

It should be stressed that this study’s purpose was only to explore an initial experience relating to LFV as a home based therapy in a CAD

patient with a moderately reduced ejection fraction, and should be viewed only as a first step in pursuit of device selection / development and pilot testing in treatment of RFA and / or IHF.

It is well accepted that increased levels of fluid shear stress and cyclic stretch / strain (or deformation) of vascular endothelial cells and / or extracellular matrix triggers activation of neo-arterial growth,²¹⁻²⁹ and this is importantly true with cardiac myocytes and coronary microvascular endothelial cells.²¹⁻²³ As LFV is characterized by rapidly changing compressive and expansive forces in tissue it is reasonable to postulate that the fluid and endothelial cells within the vasculature would be exposed 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,³⁸ 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.³⁹ LFV is also known to trigger Nitric Oxide (NO) release⁴⁰⁻⁴² which particularly along with ischemia is a well known pro-angiogenic mediator in up-regulation of VEGF transcription.⁴³ LFV has also shown to be a potent vasodilator particular in arteries with pre-existing spasm or heightened vascular tone,^{44,45} whereby this may hold additional relevance in that changing vascular wall tension has been suggested to lead to release of proteases initiating endothelial cell proliferation.²⁵ 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.⁴⁶⁻⁴⁸ Also, the intensive growth of endothelial cells exposed to pulsed electromagnetic fields in vitro (which leads to a mechanical oscillatory response to the cells)⁴⁹ further foreshadows a potential mitogenic effect by oscillatory stress.

Importantly LFV at 30Hz (within the range of frequencies used in our study) has been shown to significantly increase activation of ERK1/2 (a shear responsive protein involved in cell proliferation) and up-regulate expression of Endothelin-1, a potent mitogen and proliferator for endothelial cells.^{50,51} Further, liberation of circulating levels of VEGF have also been shown by Suhr et al.⁵² in their studies of cyclists upon a vibrating platform (30Hz, 4mm).⁵² 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.³⁷

It should be addressed that from a safety perspective a preferred LFV system in IHF applications should be programmable to periodically cease emissions during the early to mid force generation phase of left ventricular systole, as systolic timed LFV has been suggested to cause a negative inotropic effect (i.e. a decreased strength of heart contractions) in the ischemic heart.⁵³ Paradoxically however, diastolic timed LFV has advantageously shown to augment ischemic left ventricular performance in animals and human volunteers, purportedly by improved left ventricular diastolic relaxation with augmented stroke volume by the Frank Starling mechanism.⁵⁴⁻⁵⁷

We therefore suggest in future studies that patient’s with diminished ejection fractions of less than 35% receiving indiscriminately

(including systolic) applied LFV should have (at least on first visit) their vital signs monitored to make sure they can safely tolerate the therapy, whereby if evidence of hemodynamic decompensation or heart failure were to develop then diastolic timed LFV may be considered as an alternative. The application of diastolic timed LFV requires specialized tracking by the electrocardiogram (where vibrations are periodically halted prior to the peak of the R wave and re-initiated just prior to the midpoint, or beginning of terminal downslope of the T wave), and this has been worked on by the Department of Engineering Science at Simon Fraser University⁵⁸ and most recently by Parallel Biotechnologies LLC (Miami Beach, Florida, USA) in development of their “Yes –Reflow” Vibro-Acoustic Therapy System (Figure 3)-a programmable, non-invasive device applicable to the upper torso to assist coronary blood flow in treatment of heart attack³.



Figure 3 The “Yes –Reflow” Vibro-acoustic therapy system (parallel biotechnologies LLC).

Penetrability of LFV from upper back to the heart was confirmed in our study by a method we refer to as the “ahhhhh” test, whereby it is 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.^{53,54} in human volunteers by use of substantially lower stroke amplitude (i.e. 2mm)^{53,54} than what we used in our study. We should also emphasize that given our relatively large impact stroke length (6mm), that our Volunteer did complain of musculoskeletal soreness likely related to the strength of the device. For this reason a slightly less intense vibratory instrument (although which still passes the “ahhhhh” test) is suggested for future studies⁴.

We chose the upper back rather than chest wall for LFV applications since the Volunteer’s ischemia was inferior / posterior (rather than anterior), and it was felt that application to the back (essentially equivalent to a “back massage”) would be more comfortable, safer, and easier to self-apply. However for treatment of anterior ischemia

³See the September and December 2016 issues of Cath Lab Digest (open access, available online) for further details regarding use of diastolic timed vibration to enhance coronary flow and the “Yes-Reflow” Vibro-Acoustic Therapy system.

⁴We recommend study of the “Yes Reflow” Vibro-Acoustic Therapy system (Figure 3) which enables programmable waveforms, selective diastolic timed emissions, and offers a substantially more gentle massaging action (but still easily passes the “Ahhhhhh” test).

an application site over the chest wall, in order to bring the source of LFV 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 also be discussed that while for the most part only single, selected impact frequencies were utilized during our Volunteer’s treatment sessions, 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 co-ordinated to music (with correlated listening, as common to vibro-acoustic therapy systems)⁵⁹ may tend to accentuate the multi vectored velocity patterns and convective currents (or turbulence) invoked within a diseased vasculature region.⁶⁰ The hypothesis that turbulent flow may enhance pro-angiogenic effects is indirectly supported by Davies et al.⁶¹ who increased mitotic activity in endothelial cell cultures with turbulent, but not laminar shear stress. Moreover because of device limitations the maximum frequency used in our study was 35Hz, however slightly higher frequencies may be considered. Koiwa et al.^{54,55} has in particular demonstrated enhanced left ventricular relaxation and coronary flow in CAD patients via a 50Hz diastolic timed, sinusoidal waveform.

A preferred candidate for mechanical sheer producing coronary angiogenic therapy would tend to comprise the patient sub group with a coronary anatomy non amenable to standard invasive therapy approaches – (e.g. poor distal vessels or highly diffuse – non discrete – lesions), or wherein co-morbid risks make angioplasty or coronary artery bypass surgery 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 this type of therapy as an alternative to CABG, to see if their exercise tolerance and myocardial perfusion scans improve hence alleviating the need for an unwanted surgery.⁶² While not advocated by the medical community at this time there has been considerable anecdotal and some empirical data to support this approach.⁶³

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. Moreover LFV (or percussive tapping) to the chest wall has found common use in respiratory therapy to assist pulmonary drainage in cystic fibrosis. As LFV is applied indiscriminately through tissue and thereafter by internal transmission along the epi-myocardium and arteries⁶⁴⁻⁶⁶ 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 case study is presented demonstrating feasibility of a self administered home based upper back LFV therapy over a three and a half month period in an elderly NYHA Class 3 IHF patient (n=1) with known inferior wall ischemia based on Persantine Myoview scan. Patient’s compliance in use of the device was about 50% and

no adverse safety concerns (other than transient musculoskeletal discomforts) were documented. In view of correlative mechanistic data that shear stress producing and oscillative therapies purportedly induce neo-arterial growth, continued pilot testing of this technique in a statistically relevant number of IHF and RFA patients appears warranted. We recommend study of Parallel Biotechnologies' Yes-Reflow™ Vibroacoustic Therapy system, as it can be applied to either the chest wall or upper back, enables programmable waveforms including selective diastolic timed emissions, and provides a substantially less intense (but still penetrative) massaging action.

Acknowledgements

We thank Stanley Kita for his contribution of performing a literature search regarding the field of employing mechanical stimuli to vascular tissue as a means for promoting angiogenesis, many of the publications of which we have recently reviewed and cited in the writing of this paper. We also thank Arianna Hoffmann for her assistance in photography.

Disclosure

This study 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. The Author (AU) is CEO and director of Parallel Biotechnologies LLC, developer of the Yes ReFlow Vibro-Acoustic Therapy System. Otherwise no conflicts of interest are declared.

Disclaimer

The Authors cannot warrant the safety of transthoracic LFV in humans with CAD, however vibration massagers similar to what was used in our case study are generally commercially available and regulatory certified tools for therapeutic back massage, and massage to the chest wall (such as for mobilizing pulmonary secretions in CF patients). Further the author cannot warrant the effectiveness that LFV to the thoracic cavity would indeed induce coronary angio or arterio genesis as there as of yet has been no statistically relevant clinical trials to prove such effectiveness.

Conflict of interest

The author declares no conflict of interest.

References

1. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina report from the ESC joint study group on the treatment of refractory angina. *Eur Heart J.* 2002;23(5):355–370.
2. Bhatt AB, Stone PH. Current strategies for the prevention of angina in patients with stable coronary artery disease. *Curr Opin Cardiol.* 2006;21(5):492–502.
3. Chow CM, Donovan L, Manuel D, et al. Regional variation in self-reported heart disease prevalence in Canada. *Can J Cardiol.* 2005;21(14):1265–1271.
4. Thadani U. Recurrent and refractory angina following revascularization procedures in patients with stable angina pectoris. *Coron Artery Dis.* 2004;15(suppl 1):S1–S4.
5. Yang E, Barsness G, Gersh B, et al. Current and future treatment strategies for refractory angina. *Mayo Clin Proc.* 2004;79(10):1284–92.
6. American Heart Association. *Heart disease and stroke statistics.* Dallas, TX: American heart association, USA; 2005.
7. Kiernan T, Sandhu G, Boilson B, et al. Cellular interventional therapy for non-revascularizable coronary artery disease: how many patients are eligible? *Am J Cardiol.* 2007;100: S2(abstract).
8. Adams KF, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the acute decompensated heart failure national registry (ADHERE). *Am Heart J.* 2005;149(2):209–216.
9. Satran D, Traverse J, Barsness GW, et al. Emerging therapies for refractory angina. *Minn Med.* 2009;91(1):36–39.
10. Sella C. Angiogenic therapy; is it still viable? *Heart Metab.* 2013;58:20–24.
11. Hsieh HJ, Li NQ, Frangos JA. Shear stress increases endothelial platelet-derived growth factor mRNA levels. *Am J Physiol.* 1991;260(2 pt2):H642–H646.
12. Lacooley P. Mechanical influence of cyclic stretch on vascular endothelial cells. *Cardiovasc Res.* 2004;63(4):577–579.
13. Malek AM, gibbons GH, Dzau VJ, et al. Fluid shear stress differentially modulates expression of genes encoding basic fibroblast growth factor and platelet-derived growth factor B chain in vascular endothelium. *J Clin Invest.* 1993;92(4):2013–2021.
14. Mitsumata M, Fishel RS, Nerem RM, et al. Fluid shear stress stimulates platelet-derived growth factor expression in endothelial cells. *Am J Physiol.* 1993;265(1):H3–H8.
15. Fisher A, Chien S, Barakat A, et al. Endothelial cellular response to altered shear stress. *Am J Physiol.* 2001;281:L529–533.
16. Sumpio B. Hemodynamic forces and the biology of the endothelium: signal transduction pathways in endothelial cells subjected to physical forces *in vitro.* *J Vasc Surg.* 1991;13(5):744–746.
17. Davies P. How do vascular endothelial cells respond to flow? *Physiol Sci.* 1989;4(1):22–25.
18. Wilson E, Mai Q, Krishnankutty S, et al. Mechanical strain induces growth of vascular smooth muscle cells via autocrine action of PDGF. *J Cell Biol.* 1993;123(3):741–747.
19. Seko Y, Takahashi N, Tobe K, et al. Pulsatile stretch activates mitogen-activated protein kinase (MAPK) family members and focal adhesion kinase (p125^{FAK}) in cultured rat cardiac myocytes. *Biochem Biophys Res Commun.* 1999;259(1):8–14.
20. Seko Y, Takahashi N, Shibuya M, et al. Pulsatile stretch stimulates vascular endothelial growth factor (VEGF) Secretion by Cultured Rat Cardiac Myocytes. *Biochem Biophys Res Commun.* 1999;254(2):462–465.
21. Zheng W, Christensen LP, Tomanek RJ. Differential effects of cyclic and static stretch on coronary microvascular endothelial cell receptors and vasculogenic/angiogenic responses. *Am J Physiol Heart Circ Physiol.* 2008;295(2):H794–800.
22. Zheng W, Christensen L, Tomanek R. Stretch induces upregulation of key tyrosine kinase receptors in microvascular endothelial cells. *Am J Physiol Heart Circ Physiol.* 2004;287(6):H2739–2745.
23. Zheng W, Seftor E, Meininger C, et al. Mechanisms of coronary angiogenesis in response to stretch: role of VEGF and TGF-beta. *Am J Physiol Heart Circ Physiol.* 2001;280(2):H909–917.
24. Ichioka S, Shibata M, Kosaki K, et al. Effects of shear stress on wound-healing angiogenesis in the rabbit ear chamber. *J Surg Res.* 1997;72(1):29–35.
25. Hudlicka O. What makes blood vessels grow? *J Physiol.* 1991;444:1–24.

26. Hudlicka O, Brown M, Egginton S. Angiogenesis in skeletal and cardiac muscle. *Physiol Rev.* 1992;72(2):369–417.
27. Milkiewicz M, Doyle J, Fudalewski T, et al. HIF -1alpha and HIF -2alpha play a central role in stretch-induced but not shear-stress -induced angiogenesis in rat skeletal muscle. *J Physiol.* 2007;583(2):753–766.
28. Pipp F, Boehm S, Cai W, et al. Elevated fluid shear stress enhances postocclusive collateral artery growth and gene expression in the pig hind limb. *Arterioscler Thromb Vasc Biol.* 2004;24(9):1664–1668.
29. Sweeney N, Cummins P, Cotter E, et al. Cyclic strain-mediated regulation of vascular endothelial cell migration and tube formation. *Biochem Biophys Res Commun.* 2005;329(2):573–582.
30. Arora R, Chou T, Jain D, et al. The Multicenter study of enhanced external counterpulsation (MUST-ECP): Effect of ECP on exercise-induced myocardial ischemia and anginal episodes. *Am J Coll Cardiol.* 1999;33(7):1833–1840.
31. Boissel JP, Philippon AM, Gauthier E, et al. Time course of long-term placebo therapy effects in angina pectoris. *Eur Heart J.* 1986;7(12):1030–1036.
32. Lawson W, Hui J, Zheng Z, et al. Can angiographic findings predict which coronary patients will benefit from enhanced external counterpulsation? *Am J Cardiol.* 1996;77(12):1107–1109.
33. Lawson W, Hui JC, Tong G, et al. Prior revascularization increases the effects of enhanced external counterpulsation. *Clin Cardiol.* 1998;21(11):841–844.
34. Wang CJ, Wang FS, Yang KD, et al. Shock wave therapy induces neovascularization at the tendon-bone junction: A study in rabbits. *J Orthop Res.* 2003;21(6):984–989.
35. Cassar A, Prasad M, Rodriguez Porcel M, et al. Safety and efficacy of extracorporeal shock wave myocardial revascularization therapy for refractory angina pectoris. *Mayo Clin Proc.* 2014;89(3):346–354.
36. Prasad M, Cassar A, Wan Ahmad W, et al. Extracorporeal shockwave myocardial revascularization improves anginal symptoms, exercise tolerance and ischemic burden in patients with refractory angina pectoris: a multicenter study. *J Am Coll Cardiol.* 2014;63(12).
37. Ellin P. Vibro-Pulse corporate overview, *Science and Technology-Physiological Effects*; 2011.
38. Yue, Z, Mester J. On the cardiovascular effects of whole-body vibration part 1. longitudinal effects: hydrodynamic analysis. *Studies in Applied Mathematics.* 2007;119(2):95–109.
39. Zou J, Pyykko I, Sutinen P, et al. “Vibration induced hearing loss in guinea pig cochlea: expression of TNF-alpha and VEGF.” *Hear Res.* 2005;202(1-2):1–2.
40. Colleen Maloney Hinds, Jerrold SP, Grenith Zimmerman, et al. The role of nitric oxide in skin blood flow increases due to vibration in healthy adults and adults with type 2 diabetes. *Diabetes Technol Ther.* 2009;11(1):39–43.
41. PEI Zhaohui, CHEN Jingzao, ZHU Miao Zhang, et al. The effects of infrasound on the secretion of the nitric oxide in rat plasma and the expression of VEGF in vascular endothelia. *Chinese Heart Journal.* 2004;1:20–22.
42. Weitzberg E, Lundberg JO. Humming greatly increases nasal nitric oxide. *Am J Respir Crit Care Med.* 2002;166(2):144–145.
43. Ramanathan M, Giladi A, Leibovich SJ. Regulation of vascular endothelial growth factor gene expression in murine macrophages by nitric oxide and hypoxia. *Exp Biol Med (Maywood).* 2003;228(6):697–705.
44. Lindblad LE, Lorenz RR, Shepherd JT, et al. Effect of vibration on canine cutaneous artery. *Am J Physiol.* 1986;250(3):H519–523.
45. Ljung B, Silvertsson R. Vibration-induced inhibition of vascular smooth muscle contraction. *Blood Vessels.* 1975;12(1):38–52.
46. Schweigerer L, Neufeld G, Friedman J, et al. Capillary endothelial cells express basic fibroblast growth factor, a mitogen that promotes their own growth. *Nature.* 1987;325(6101):257–259.
47. Folkman J, Klagsbrun M, Sasse J, et al. A heparin-binding angiogenic protein -basic fibroblast growth factor- is stored within basement membrane. *Am J Pathol.* 1988;130:393–400.
48. Gajdusek C, Carbon S. Injury-induced release of basic fibroblast growth factor from bovine aortic endothelium. *J Cell Physiol.* 1989;139(3):570–579.
49. Yen-Patton G, Patton W, Beer D, et al. Endothelial cell response to pulsed electromagnetic fields: stimulation of growth rate and angiogenesis *in vitro.* *J Cell Physiol.* 1988;134(1):37–46.
50. White CR, Haidekker MA, Stevens HY, et al. Extracellular signal-regulated kinase activation and endothelin-1 production in human endothelial cells exposed to vibration. *J Physiol.* 2004;555(pt 2):565–572.
51. Salani D, Taraboletti G, Rosano L, et al. Endothelin-1 induces an angiogenic phenotype in cultured endothelial cells and stimulates neovascularization *in vivo.* *Am J Pathol.* 2000;157(5):1703–1711.
52. Suhr F, Brixius K, Bolck B, et al. Effects of short-term vibration and hypoxia during high-intensity cycling exercise on circulating levels of angiogenic regulators in humans. *J Appl Physiol.* 2007;103(2):474–483.
53. Koiwa Y. Clinical Demonstration of Vibration -induced depression of left ventricular function. *Tohoku J Exp Med.* 1989;159(3):247–248.
54. Koiwa Y, Honda H, Takagi T, et al. Modification of human left ventricular relaxation by small-amplitude, phase-controlled mechanical vibration on the chest wall. *Circulation.* 1997;95(1):156–162.
55. Koiwa Y, Kikuchi JI, Takagi T, et al. Human left ventricular wall vibration responded to precordial minute vibration. *Tohoku J Exp Med.* 1989;159(1):79–80.
56. Koiwa Y, Naya T, Honda H, et al. Diastolic vibration from the precordium increases coronary blood flow in humans. *J Cardiovasc Diagn Procedures Abstract (FRI- POS07).* 1994;12:110.
57. Takagi T, Koiwa Y, Kikuchi J, et al. Diastolic vibration improves systolic function in cases of incomplete relaxation. *Circulation.* 1992;86:1955–1964.
58. Marzencki M, Kajbafzadeh B, Khosrow-khavar F, et al. Diastolic timed vibrator: noninvasive pre-hospitalization treatment of acute coronary ischemia. *IEEE Trans Biomed Circuits Syst.* 2013;8(3):313–324.
59. Hoffmann A. *Percussion Assisted Angiogenesis. US Patent.* 2008;8:734,368.
60. Wata K, Morishita M, Sakai T, et al. Evaluation of turbulence-induced vibration of a circular cylinder in supercritical Reynolds number flow. *JSME International Journal Series B.* 2001;44(4):721–728.
61. Davies P, Remuzzitt A, Gordon E, et al. Turbulent fluid shear stress induces vascular endothelial cell turnover *in vitro.* *Proc Natl Acad Sci USA.* 1986;83(7):2114–2117.
62. Jueteronke GJ. Passing on bypass using external counter pulsation: An FDA cleared alternative to treat heart disease without surgery. *Drugs or Angioplasty.* 2nd ed. USA: Pikes Peak Press; 2001.
63. Lawson WE, Hui JCK, Burger L, et al. Five-year follow-up of morbidity and mortality in 33 angina patient treated with enhanced external counter pulsation. *J Invest Med.* 1997;45:212A.
64. Smith D, Ishimitsu T, Craige E. Mechanical vibration transmission characteristics of the left ventricle: implication with regard to auscultation and phonocardiography. *J Am Coll Cardiol.* 1984;4(3):517–521.
65. Hashiguchi R, Koiwa Y, Ohyama T, et al. Dependence of instantaneous transfer function on regional ischemic myocardial volume. *Circ Res.* 1998;63:1003–1011.
66. Farber JJ, Purvis JH. Conduction of cardiovascular sound along arteries. *Circ Res.* 1963;12:308–316.