Comparison of microbubble presence in the right heart during mechanochemical and radiofrequency ablation for varicose veins

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Circulating microbubbles during varicose vein treatment

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Declarations

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The authors declare that there is no conflict of interest

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KHM, BD, TRAL, HMM and AHD designed the research; KHM and BD performed the search of the literature; KHM, BD, BR, CSL and KS performed the data collection and analysis; KHM, BD and AHD wrote and revised the paper for submission, AHD retained overall responsibility over the research and paper. The authors acknowledge CK for image analysis.

Abstract

Objective: Mechanochemical ablation (MOCA) is a novel technique for ablation of varicose veins utilising a rotating catheter and liquid sclerosant. MOCA and radiofrequency ablation (RFA) have no reported neurological side-effect but the rotating mechanism of MOCA may produce microbubbles. Air emboli have been implicated as a cause of cerebrovascular events during ultrasound guided foam sclerotherapy (UGFS) and microbubbles in the heart during UGFS have been demonstrated. This study investigated the presence of microbubbles in the right heart during varicose vein ablation by MOCA and RFA.

Methods: Patients undergoing great saphenous vein ablation by MOCA or RFA were recruited. During the ablative procedure, the presence of microbubbles was assessed using a transthoracic echocardiogram. Offline blinded image quantification was performed using International Consensus Criteria grading guidelines.

Results: From 32 recruited patients, 28 data sets were analysed. Eleven underwent MOCA and 17 underwent RFA. There were no neurological complications. In total 39% (11/28) of patients had Grade 1 or 2 microbubbles detected. Thirty-six percent (4/11) of MOCA patients and 29% (5/17) of RFA patients had microbubbles with no significant difference between the groups ($p=0.8065$).

Conclusion: A comparable prevalence of microbubbles between MOCA and RFA both of which are lower than that previously reported for UGFS suggests that MOCA may not confer the same risk of neurological events as UGFS for treatment of varicose veins.

Main Text

Introduction

Varicose veins are characterised by excessive dilatation and tortuosity of the superficial venous system and often present as visible bulging, surface veins, felt under the skin (1-3). The disease often affects the quality of life of patients through pain and ulcers with a significant burden to both healthcare systems and the wider socioeconomic climate (4). Over 40,000 operations are performed each year for varicose veins within the National Health Service in England and Wales (5) consuming approximately £40 million in 2005-2006 (6).

As recommended by the National Institute for Health and Care Excellence (NICE) in the United Kingdom, symptomatic varicose veins should be treated with minimally invasive techniques. These include endovenous laser ablation, radiofrequency ablation (RFA) and ultrasound guided foam sclerotherapy (UGFS) (7). The recently introduced mechanochemical endovenous ablation (MOCA) (ClariVein®, Vascular Insights, Madison, USA) catheter is a new treatment that uses a stainless steel tip which rotates at approximately 3500 revolutions per minute and simultaneously releases liquid sclerosant from its rotating tip causing fibrosis within the venous lumen. It has a potential advantage over RFA and laser ablation as tumescent anaesthesia is not required. Additionally, the occlusion rates of MOCA have been shown to be comparable with 90% occlusion at two years post-procedurally (8-10).

Some treatment modalities have had rare yet serious complications reported. Since 1997, there have been 13 cases of reported strokes following sclerotherapy (11). Five of these patients were shown to have bubbles within the circulation with Bush et al demonstrating bubble presence in the vertebral artery using computed tomography (CT) (12). Furthermore, the use of UGFS has been associated with transient events such as visual disturbance (1.4%) (13-15) and stroke-like symptoms such as hemiparesis and dysarthria (0.01 -2%) (12,16-18).

Microbubbles have been shown to be present in the heart in a large number of patients undergoing UGFS (16,19,20). A microbubble is a very small amount of air contained within a stable membrane. It can give marked reflections of acoustic signals such as ultrasound. In particular, Ceulen et al. showed a large number of bubbles on echocardiogram of both right atria and ventricles of all 33 patients undergoing UGFS treatment (16). It is hypothesised that bubbles produced within the treated vein may detach and lead to paradoxical gas embolism possibly through common heart defects such as a patent foramen ovale (PFO), which has a prevalence of 26% in the general population, resulting in reduced cerebral arterial perfusion (19). Endovenous laser ablation, has been associated with one case of stroke in a patient shown to have a PFO (21). The authors of this case report believe that the stroke may have resulted from a paradoxical embolism of saphenic thrombus formed while withdrawing the endovenous catheter.

The concern regarding microbubbles and neurological symptoms has been minimal with endovenous radiofrequency ablation (RFA). Sounderajah et al

demonstrated that 5 out of 11 patients, undergoing RFA treatment of incompetent GSVs, had microbubbles in the right atrium and ventricle using transthoracic echocardiogram (22). Despite these findings, there have been no reported neurological complications.

To date, there have been no known neurological complications reported from MOCA (23-26). However, there is theoretical possibility that MOCA may also produce bubbles. The rotational mechanism of the ClariVein catheter in conjunction with liquid sclerosant, which could act as surfactant, shares similarities with the mechanism of microbubble generators used in chemical engineering fields(27). These bubbles have the potential to travel proximally in circulation and result in symptoms seen in UGFS.

Therefore, the aim of this pilot study was to perform imaging of the right atrium and right ventricle of patients to detect microbubble prevalence during RFA and MOCA procedures for varicose veins.

Methods

This was a prospective observational study with approval from the local research ethics committee (Research Ethics Committee reference number 11/LO/1358). Patients undergoing elective treatment of varicose veins at our institution were assessed for eligibility. Patients were included in the study upon agreement to the consent and qualifying to the following inclusion criteria:

- Patients over 18 years of age
- Presenting for treatment of primary refluxing great saphenous vein (GSV)
- Patients being treated by either RFA or MOCA
- Patients who consented to the written and oral information with the details of the study

Patients for treatment of short saphenous vein (SSV) were excluded as they were required to be in a prone position for treatment, thereby precluding transthoracic echocardiogram. Patients with ipsilateral recurrent varicose veins were also excluded as previous treatment may have affected the pathway of bubbles.

This study was performed as a prospective, non-randomised study with decisions regarding treatment modality made by the treating clinical team, Duplex ultrasound and patient preference. RFA was performed using the Covidien® Venefit™ (Covidien, San Jose, California, USA) following infiltration of tumescent anaesthesia around the target vein (50ml 1% lidocaine with 1:200,000 adrenaline in 1000ml of 0.9% normal saline). MOCA procedures were carried out using the ClariVein® catheter (Vascular Insights, Madison, USA) (26) with 2% Sodium Tetradecyl Sulphate (STS) liquid sclerosant used with the device. RFA and MOCA were carried out as previously described in published literature (26,28). The dose of STS was calculated using the length and average diameter of the target vein as recommended by the manufacturer. During both MOCA and RFA procedures, the catheter tip was placed at 2cm distal to the SFJ

Transthoracic Echocardiogram

Transthoracic echocardiogram was performed as previously described for bubble detection (22). A sonographer performed echocardiogram using a Philips iU22 ultrasound platform with an X3-1 curvilinear echo transducer (Philips, Bothell, WA, USA) to obtain a 2 dimensional, apical 4 chamber view of the heart. Negative control was initially established by 30 second footage of each patient's heart prior to the procedure to demonstrate that, in normal conditions, no bubbles were present. For both modalities, patients were supine initially and after a successful venous catheterisation, patients were moved to the Trendelenburg position. Patients remained in this position for the remainder of the procedure. Procedures were performed by three different vascular surgeons all familiar with and approved in both ablative procedures.

During MOCA procedures, the speed of the catheter was determined by patient tolerance to three seconds of the device being operated without sclerosant. An echocardiogram loop of footage was captured during this step. Subsequent loops were captured during formal device activation. As per manufacturer guidance, the catheter was withdrawn within the vein 1cm every 7 seconds whilst simultaneously injecting liquid sclerosant. Loops of footage were repeated for every syringe of sclerosant used during the treatment

During RFA procedures, a 30 second footage loop was captured when the heating phase of RFA treatment commenced. This included 20 seconds of active thermal treatment with the device on and a 10 second interval after treatment to allow time for bubbles to travel to the heart. This was repeated until the end of the RFA treatment which was performed in 3cm or 7cm segments at the operator's discretion. The most proximal segment from the SFJ was double treated as previously described to ensure proximal closure (29). As a result, the number of recordings was dependent upon the number of RFA heating cycles.

Neurological symptom questionnaire

Patients were examined by the operating vascular surgeons prior to consent. Post-operatively, patients were assessed for any symptoms using a questionnaire (Appendix 4) encompassing commonly reported neurological symptoms from varicose vein treatment (12,15,20,23,30,31). The questionnaire assessed for visual and speech disturbances, headache, motor symptoms, dizziness, nausea, vertigo and patients were also asked to report any other systemic symptoms that they experienced including pulmonary symptoms. Previously published literature displayed the presence of microemboli from UGFS in the right atrium and ventricles ranging from 45 seconds to 50 minutes after foam injection (16,17,19). Therefore, patients were assessed using the questionnaire immediately and 30 minutes after endovenous ablation.

Primary outcome

The Digital Imaging and Communications in Medicine (DICOM) echocardiogram loops were quantified offline by two independent blinded, trained observers; a radiology registrar (BD) and an ultrasound engineer (CK) both with over two years' experience of microbubble quantification enabling both intra- and inter-reader

reproducibility. They were visually scored according to the International Consensus Criteria grading guidelines (32,33) used to assess the bubbles seen in a cardiac shunt test. Table 1 describes the echocardiogram for each grading and Figure 1 shows visual examples of the scans.

Statistical analysis

The patient details were anonymised and procedural groups compared with the Mann-Whitney test using Prism version 6.01 (Graphpad Software, La Jolla, CA, USA). The inter- and intra-rater agreement of visual grading scales were analysed by Cohen's Kappa Co-efficient score using MedCalc® version 13.2.0.0 (MedCalc Software bvba).

Results

Sixty three consecutive patients were assessed for study eligibility between March and May 2014. After application of eligibility criteria and informed consent, 32 patients were recruited into the study. The study could not be completed in 2 patients due to failed venous cannulation from vasospasm of the GSV. Therefore, 30 patients were available for echocardiogram grading. Two scans were excluded during analysis due to poor scan quality from excessive out of plane imaging secondary to patient movement. The remaining 28 patient data collected were fully interpreted and included for statistical analysis. Further details are shown in the STARD flow diagram in Figure 2.

17 patients underwent RFA and 11 patients underwent MOCA treatments. Statistical analysis in all baseline demographic fields collected showed no significant differences between RFA and MOCA groups (Table 2).

Echocardiogram results

Four out of 11 patients (36%) in the MOCA group and 7 out of 17 patients (41%) in the RFA group had bubbles present in the right heart. The bubble gradings were all grade 1 (example shown in Figure 3) except one patient undergoing RFA which was reported as grade 2. The difference in the bubble grading between each group was not significant ($p=0.8065$). These findings are summarised in Figure 4.

The grading by the International Consensus guideline exhibited good reproducibility amongst observers indicated by Cohen's kappa value of 0.793 and 0.719 for intra- and inter-rater agreement, respectively.

No neurological complications were found in any of the 28 patients immediately and 30 minutes after the procedure.

Discussion

This study provides the first documented evidence of the presence of bubbles in the right heart following MOCA of varicose veins. Our results also add to previous work by Sounderajah et al (22) demonstrating the presence of bubbles in the right heart during RFA of varicose veins.

A statistically similar incidence and grading of bubbles produced between RFA and MOCA, infers that, if neurological complications are produced by bubbles, varicose vein treatment by MOCA appears to have a similar safety profile to RFA with regard to neurological complications. Previously, bubble grading has been largely Grade 3 during UGFS (16,20), however, in this study both MOCA and RFA produced fewer bubbles with the majority being Grade 1. Whilst the proposed theory that central neurological complications are caused by bubbles acting as air emboli in the cerebral circulation, findings suggest that a high intensity of bubble production is required for this to occur as demonstrated by the incidence of neurological symptoms after UGFS as compared to the reported safety profile of RFA(12,16,17,20).

Nevertheless, Caggiati's report of stroke after the laser ablation treatment of varicose vein in 2010 (21), brings the safety of RFA into question as they are both endothermal ablation treatments that achieve closure of veins by heat. Higher temperatures decrease the solubility of gases in liquid (34), therefore, this could increase the number of bubbles produced, thereby increasing the grading intensity of bubbles produced during treatment. However, Caggiati suggested the cause of stroke was likely to be saphenic thrombi emboli rather than gas emboli.

Our findings contribute to the current debate over causes of neurological symptoms reported from UGFS, where bubbles from foam sclerosant are believed to cause transient cerebral ischaemia by passing through a PFO in the heart and occluding the cerebral circulation (12,16,17,20). This study did not assess PFO in the subjects, however, PFO prevalence in the general population is reported to be 26% although the prevalence of right to left shunt may indeed be greater in patients with GSV incompetence (35,36). Despite this, our data showed a microbubble presence of 39% with no neurological symptoms in any of the subjects compared to the reported rates of neurological symptoms after foam sclerotherapy of 2% (13,30,37,38). This highlights that despite the presence of bubbles from vein treatment, neurological symptoms are much lower than the prevalence of PFO.

This pilot study was limited by a small sample size of non-randomised prospectively treated patients. At our institution, treatment modality decisions are performed by the treating clinician in conjunction with patient preference, therefore,

randomisation was not deemed appropriate for this pilot study. In accordance with NICE guidance, UGFS is not a first line treatment modality for GSV incompetence at our institution (7), therefore, the investigation of microbubble presence during UGFS was not undertaken in this study. However, using similar transthoracic echocardiogram image acquisition and blinded quantification (29), relative comparison of published literature demonstrating the presence of microbubbles during UGFS was possible (12,16,17,20). Only peri-procedural analysis of bubble detection and assessment of neurological symptoms was performed, however, based on previous literature this is when the majority of both of these events occur (16,17,19). Additionally, with a small sample size, neurological symptoms were very unlikely to occur in this patient cohort, however, as discussed the primary outcome of this study was to assess and compare the presence of microbubbles in the right heart during venous ablation.

Conclusion

This study reports, for the first time, the detection of bubbles in the right heart during MOCA. We have also confirmed bubble presence in the right heart during RFA and shown no difference in prevalence or grade of bubbles between MOCA and RFA.

This similarity in bubble production between the two modalities, in conjunction with no previous reports of neurological complications from RFA, suggests that MOCA has similar safety profile with RFA. If neurological symptoms are caused by procedural bubbles, this study demonstrates that MOCA does not confer the same risk of neurological symptoms observed with UGFS.

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Tables and Figures

Table 1

Grading System used in interpretation of the microbubbles from the echocardiogram

Table 2

Demographics of the patient population in each treatment modalities. VCSS (Venous Clinical Severity Score)

Figure 1

A visual depiction of the grading scale that was devised. The numbers indicate the grade assigned to amount of microbubbles presence (22). Grade 0 shown top left represents absence of any bubbles. Grade 1 on the top right is indicative of presence of few microbubbles in inconsistent intervals. Grade 2 shown on bottom left demonstrates stream of microbubbles. Grade 3 represents opacification by a large area of microbubbles.

Figure 2

STARD flow diagram of the patient recruited in this study, 63 patients were assessed for eligibility. 32 were consented after exclusion criteria were applied. 2 procedures of consented patients failed and subsequently excluded from the study. 2 poor scan quality participants were excluded. 28 participant data set were analysed.

Figure 3

An example of a transthoracic echocardiogram scan from one of the participants showing grade 1 microbubbles

Figure 4

Number of subjects in each treatment modality. Each pie chart is showing the proportion of patients who had microbubbles detected in the echocardiogram and those who did not.

Grading	Interpretation
0	No microbubble demonstrated
1	Presence of few microbubbles in inconsistent intervals
2	Stream of microbubbles
3	Opacification by a large area of microbubbles

	RFA	MOCA	Unpaired t-test
Number of subjects	17	11	
Mean age	55	46	p = 0.1347
Mean weight	76.7kg	72.7kg	p = 0.6262
Mean VCSS	4.9	5.5	p = 0.4531
Leg treated	Left: 10 Right: 7	Left: 3 Right: 8	p = 0.1367
Gender	Male: 5 Female: 12	Male: 5 Female: 6	p = 0.444

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ABLATION

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MOCA

$p=0.8065$

RFA

■ Microbubble detected

■ No Microbubbles detected