Testing of a Valsalva Assist Device (VAD) to assess effects on vagal tone and strain pressures achieved compared to a standard manometer in healthy volunteers performing standard and modified Valsalva manoeuvres.

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Lay Summary

The Valsalva manoeuvre (VM) is a recommended initial treatment for supraventricular tachycardia (SVT), a common abnormal fast heart rhythm. The VM is a safe physical technique involving the forced exhalation against resistance, which causes a physiological response that slows the heart and can correct the SVT during an attack (cardioversion).

Research to date has demonstrated that a controlled strain (40mmHg pressure for 15 seconds) combined with a postural modification gives the best chance of success and avoids the need for drug treatment. However, the physiological benefit of this posture modification has not been confirmed. There is also no standard, easy to use device available on the market to generate the required strain. A modified blood pressure gauge (sphygmomanometer) can be used but is bulky and inconvenient. Blowing into an empty syringe has also been used but has been shown to be unreliable in generating the required pressures.

A small, easy to use device that reliably reproduces the conditions most likely to affect cardioversion would be advantageous as it could be used in emergency departments and ambulances and given to patients to take away for home use, as attacks can reoccur.

A prototype for such a device, the Valsalva Assist Device (VAD), has been conceived by the lead applicant and developed in collaboration with Meditech. The device is now ready for testing in healthy volunteers. There is a need to ensure the device can deliver the required strain and to evaluate the physiological response (lowered heart rate) to its use with and without postural modification.

Research Questions

- Does postural modification to the VM induce greater vagal tone compared to a supine VM?
- Does the device (VAD) used to deliver a VM in healthy volunteers reproduce the physiological vagal effects of a VM (slowed heart rate)?
- Can the device (VAD) deliver the appropriate level of strain compared to a manometer in both a standard position and with postural modification (lying flat with leg elevation at end of strain) in healthy volunteers performing a VM?

Rationale and background

The VM is an established and internationally recommended first line treatment for SVT.[1] It causes a transient reflex physiological slowing of the heart (vagal tone) in healthy subject and can terminate attacks of SVT in patients. It is an extremely safe physical manoeuvre which mimics normal physiological responses e.g. straining at stool, child birth or when blowing up a balloon.

However, in routine clinical practice, this physical manoeuvre has a low (5-20%) rate of success for treating SVT[2] requiring the subsequent use of unpleasant intravenous treatments. Recent studies have shown that much better cardioversion rates approaching 50% can be achieved using a postural modification to the manoeuvre together with a controlled strain using an adapted manometer.[3] Using a manometer in routine care is not practical and cannot be given to patients to use out of hospital (attacks can recur and patients can perform their own VM).

Blowing on an empty 10ml syringe has been suggested as a surrogate for the pressure required for the best VM.[4] However, other recent studies have demonstrated syringes are unreliable in providing correct and consistent pressures during the VM strain.[5] A prototype device has been developed based upon well-established anaesthetic breathing circuit devices which provide resistance to exhalation (positive end expiratory pressure release pop-off valves). These have been modified to provide the recommended VM strain pressure (40mmHg) resistance, are small and portable and are now ready for testing in healthy volunteers.

The device is a small plastic tube with a standard disposable mouth piece to which can be fitted a standard breathing circuit (HME) filter to allow reuse of the device and connection of a manometer to monitor the strain without risk of cross contamination of the device (see figure 1). The device's pop off valve prevents users from blowing a pressure in excess of 40mmHg and also allows a slow leak once this pressure is achieved giving audible feedback to the user and researcher that the correct pressure is being achieved. This leak also prevents use of just mouth pressure and ensures intrathoracic pressure is appropriately raised a key component of the VM.

By connecting this device to a manometer, its performance can be tested during the VM strain. As there is a normal physiological response to the VM which varies according to the degree of vagal tone, the effects of a VM using the device can also be compared to a strain using a manometer alone and with and without postural modification by assessing the fall in pulse rate during the manoeuvre.[6]

Demonstrating the device is as effective as a manometer and works with a posture modified VM in normal volunteers would support its use in routine care and enable further evaluation in patients. The device, packaged with instructions for use, would be a useful piece of equipment for use in emergency departments and by paramedics and for patients who suffer from SVT.

Aims and objectives

Aims:

- The aim of this study is to confirm the physiological effects of a modified VM and evaluate the performance of a novel Valsalva assist device in healthy volunteers

Objectives:

- To evaluate whether there is a difference in vagal tone (drop in heart rate) in healthy volunteers performing a modified VM verses a standard supine VM using the VAD.
- To evaluate whether there is a difference in vagal tone (drop in heart rate) in healthy volunteers performing a modified VM verses a standard supine VM using a manometer.
- To measure and compare peak strain pressure and duration produced using the device compared to a standard manometer in supine and modified postures

Figure 1. Valsalva Assist Device (VAD). Fitted with disposable mouth piece and filter

Research Design

We will conduct a single centre repeated measures observational study of use of the device to generate a Valsalva strain initially in a sample of healthy adult volunteers from the University of Exeter or RD&E Hospital staff, this is not related to their role within RD&E of University of Exeter, but due to convenience as the study is happening at the University of Exeter clinical research facility on the RD&E site, this will hopefully increase the likelihood of people taking part. All participants will be screened for eligibility (Figure 2) and undergo informed written consent prior to participation. If participants fail screening due to abnormal clinical readings or vital signs, the chief investigator will review them, any urgent abnormalities (very unlikely) would be reviewed by the chief investigator or delegated emergency department doctor as soon as they are discovered. Depending on the severity, is treatment is required urgently then they will be treated in the emergency department. Otherwise they will be referred back to their Gp. Potential participants will be given written information about the study at least 24 hours prior to recruitment and interested individuals invited to attend screening, recruitment and testing.
Potential participants will be invited to express an interest in taking part by responding to trial poster. These posters will be displayed in the student common room in the RILD, the medical department of St Luke's and in the ED department noticeboard. Our main target population will be medical students and medical sciences students and ED department staff; students will be directed to the trial poster at some medical student lectures. The potential participant contacts the researcher leading the practical aspects of the trial by phone or email. Respondents will be asked how they would like to receive further information (post, email, and phone) and offered an appointment at the Clinical Research Facility (CRF) for screening and written consent if eligible, at their convenience but at least 24 hours after receiving the information sheet. Given the simple, safe and quick nature of the interventions, participants will be given the choice to take part after written consent or to return on another date, whichever they would prefer, to ensure minimal visits whilst giving participants further time to consider taking part should they wish.

The VM is an extremely safe, physiological manoeuvre which is used in everyday life (eg straining at stool) and has been used in trial conditions and clinical practice many thousands of times with no serious adverse events. We will exclude participants who could conceivably be at any risk of harm from performing a VM or from use of the device.

Screening will include 12 lead ECG and physical examination including observations of pulse, oxygen saturations, respiratory rate and blood pressure. Any participants with any detected abnormalities whether they are excluded from participation or not will be informed and referred to their primary care physician as appropriate. All testing will be conducted in the clinical research facility (CRF) of the Royal Devon & Exeter Hospital, according to a strict trial protocol.

Figure 2. Inclusion and Exclusion Criteria

Inclusion Criteria:
Adult Volunteers between 18 and 60 years old from University of Exeter or RD&E Hospital staff
Sinus rhythm on initial ECG
Self-reported good health

Exclusion Criteria:
Any regular medication other than the oral contraceptive
Previous cardiovascular or respiratory disease
Any contra-indication to performing a VM strain. (Eg. Known aortic stenosis, recent myocardial infarction, glaucoma, retinopathy)
Pregnancy

Any ECG abnormality
Any contra-indication to postural modification (any reason the participant can't lie flat and have both legs lifted to 45 degrees, eg prosthetic hip
Inability or refusal to give written consent to take part
Observations of pulse, oxygen saturations, respiratory rate or blood pressure outside the normal range. Specifically blood pressure less than 100 systolic
Caffeinated drinks within 6 hours prior to testing
The use of stimulant drugs or alcohol within 24 hours prior to testing

Test Valsalva Manoeuvres:

Participants will undergo a total of 4 VMs of the following 4 variations in random order, stratified by method of strain generation to ensure balance between the order of manometer and device use:

1. *Supine VM using manometer.* Supine Valsalva strain using a manometer visible to the participant with a target of 40mmHg for 15 seconds
2. *Supine VM using device.* Supine Valsalva strain using the device connected to manometer invisible to the participant but visible to a researcher for 15 seconds
3. *Modified VM using manometer.* Semi-recumbent (at 45 degrees) Valsalva stain using a manometer visible to the participant with a target of 40mmHg for 15 seconds followed by supine positioning and passive 45 degree leg lift immediately at the end of the strain for a further 15 seconds (the modified VM)
4. *Modified VM using device.* Semi-recumbent (at 45 degrees) Valsalva strain using the device connected to manometer invisible to the participant but visible to a researcher for 15 seconds followed by supine positioning and passive 45 degree leg lift immediately at the end of the strain for a further 15 seconds (the modified VM)

All testing will be performed on a standard hospital trolley with a manually adjustable back rest. A 45 degree angle template guide will be used to ensure consistent back rest and leg elevation angles where needed. Participant will rest for 5 minutes prior to testing to ensure they start with a resting heart rate. Participants will be given clear, standardised instructions for each manoeuvre. The strains are intuitive with feedback from the manometer or device noise and no practices will be allowed. A stop watch will be used to time strains and will be visible to participants. Participants will be instructed to stop blowing after the 15 second strain but no other encouragement or instruction will be allowed. No participant will be allowed to blow more than 50mmHg on either the manometer or device.

Blowing over 40mmHg is not likely as the manometer (with target marked) will be visible to participants when using the manometer delivered strain and the devices are set to release at pressures over 40mmHg. However as a safety measure, the researcher will ensure no participant exceeds this level during any of the VMs. In the rare event of device malfunction (ie it provides no resistance or resistance is greater than 50mmHg), the VM will be immediately abandoned and the malfunction recorded as an adverse incident. The particular manoeuvre will be restarted using a new device, only if the participant is happy to continue.

A new mouth piece and HME filter for the device and a new 92cm length of green oxygen bubble tubing, for the manometer, will be used for each participant.

There will be a three minute washout period between strains including two minutes rest after any change in posture. Continuous 3 lead ECG monitoring on a standard print enabled monitor will be used to assess heart rate during the manoeuvre. ECG rhythm strip traces would be printed for 45 seconds (15 seconds before, during and 15 seconds after each VM). They will be marked at the onset of each Valsalva strain, labelled with a code and subsequently analysed, blind to technique according to the method described by G Smith6:

Pre-manoeuvre heart rates will be determined by calculating the mean R-R interval of the 10 beats preceding each manoeuvre before converting it to heart rate in beats/minute. The lowest post manoeuvre heat rate will be determined by measuring and recording the longest R-R interval during and up to 15 seconds post manoeuvre. This will also be converted to a heart rate in beats per minute. The difference between the pre and post manoeuvre heat rate will indicate the degree of vagal tone or slowing of heart rate induced by each manoeuvre.

Peak sustained pressures achieved as observed on the manometer and duration of longest strain attempt during all VMs will be recorded on a standard report card. This will allow comparison of the different strain techniques.

Participants will be closely monitored for any adverse events. Though none are expected, if any participant feels unwell or develops any significant or persistent ECG abnormalities, the individual will be immediately withdrawn from further testing and appropriate further clinical assessment will be arranged. All adverse events will be recorded, graded and reported immediately to the CI and sponsor and reviewed by the study team.

Data Management

The data will be de-identified and stored on encrypted and password protected computers and laptops. Personal data such as name and e-mail address will be held separately. All data will be stored on University of Exeter computers with a designated University of Exeter member of staff responsible for destruction. Paper copies need to be scanned and destroyed and electronic records kept for a period of 5 years following the completion of the study, in line with University guidelines. The member of staff responsible for data storage and disposal will be the Chief Investigator (Andy Appelboam) or their designated deputy from the research team at the University of Exeter.

Software

Data will be stored on Excel and analysed using STATA.

Statistical Analysis (Revised

The heart rates measured under each of the four testing scenarios will be summarised appropriately, e.g. mean and SD, or median and IQR if necessary; it is expected that heart rate will be approximately normally distributed.

The contrasts of interest are to compare heart rate for:

1. Supine VM vs modified VM (recognising that this comparison may or may not be different according to which instrument is used – manometer or device)
2. Manometer vs device (recognising that this comparison may or may not be different according to the posture adopted – supine or modified)

The analysis will be based on mixed effects linear regression (with appropriate prior assessment of assumptions, e.g. Normality), with individual as a random effect, position (supine/modified) as a fixed effect and instrument (manometer/device) as a fixed effect. An interaction term (position x instrument) will be examined to consider whether there is any evidence of a differential effect (of device according to position, or equivalently position according to device), but will be dropped from the model if $p>0.1$. If the interaction term is retained then comparison 1 between postures will be presented separately by device, and comparison 2 between devices will be presented separately by posture type; otherwise the two comparisons will be presented overall.

Sample size calculations are based on a simple paired t-test. There is no obvious way to determine a “smallest clinically important difference”, but we have used 4 beats per minute as a reasonably small difference, below which is unlikely to be important clinically. The SD reported in G Smith et al is about 12 (similar for individual measures and for differences between measures). With these parameters, a sample size of at least 73 participants provides 80% power at the 5% level of significance.

Project management

The programme team consists of a multidisciplinary team with complementary skills and expertise as follows:
Dr Andy Appelboam is the Chief Investigator and will lead the project and provide clinical expertise and advice.
Prof Paul Ewing is a statistician and director of the research design service. He will advise on design and statistical aspects of the project.
Izzy Fitzgerald will run the day to day practical aspects of the study as part of her Intercalated Master by Research Project
Iain Lang will act as academic supervisor and provide academic support to the project.
The project team will meet regularly for the duration of the study.

Dissemination

The results will be presented at UK Emergency Medicine conferences (RCEM Scientific Meeting), the National Clinical Studies Group Meeting and South West Emergency Academic Team (SWEAT) Meeting. If the results are sufficiently strong, then a paper will be written for publication in an appropriate emergency medicine journal.

Patient involvement

The initial study will be conducted in healthy student volunteers, however if the device performs as expected, there will be a need for it to be tested in a wider population and there may be an opportunity to involve patients in the design and conduct of this stage of research through the Exeter 10,000 project. We have had feedback on our information sheet from lay representatives of the Exeter 10,000, and have re-worded the information sheet in light of these comments Should this be the case, volunteers from this scheme will be involved in designing a modified protocol and information aimed at patients. In addition, the Arrhythmia Alliance, a patient support charity, who were partners in the original research underpinning this project and can provide further help with dissemination of results or findings relevant for patients. We will also be showing actual SVT patients the device and informally be asking for patient opinions during the lifetime of the project to prepare for the next stages if the evaluation is successful in volunteers.

Timelines

Months	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
2017/18	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	April	May	June	July
Ethics Approval														
R&D Approval														
Trial Procedures Design														
Recruitment &Testing														
Data Analysis														
Write Up & Examination														
Project Meetings														

References

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[4] Smith G, Boyle M. The 10ml syringe is useful in generating the recommended standard of 40mmHg intrathoracic pressure for the Valsalva manoeuvre. Emerg Med Aust 2009;21:449-454

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