A RANDOMIZED CONTROLLED TRIAL COMPARING THE EFFECT OF CONVENTIONAL AND MODIFIED HANDGRIP EXERCISE TOWARDS THE VEIN SIZE AND BLOOD FLOW OF UPPER LIMBS IN HEALTHY SUBJECTS

BY

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Above all, I would like to express my love and gratitude to my family, for their undivided support and understanding amid my hectic days, and who shared the ups and downs through the four years of my graduate education.

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III. List of Abbreviations

CKD	Chronic kidney disease
ESRD	End-stage renal disease
AVF	Arteriovenous fistula
KDOQI	Kidney Disease Outcome Quality Initiative
MVD	Minimum vein diameter
BFR	Blood flow restricted
NO	Nitric oxide
RCT	Randomized controlled trial
HUSM	Hospital Universiti Sains Malaysia
PI	Primary investigator
DCV	Distal cephalic vein
PCV	Proximal cephalic vein
RA	Radial artery
BA	Brachial artery
RAF	Radial artery flow
BAF	Brachial artery flow
BAFR	Brachial artery flow rate
FMD	Flow-mediated dilation
eNOS	Endothelial-derived nitric oxide synthase
ANOVA	Analysis of variance

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V. Abstrak

Pengenalan

Kadar penyakit buah pinggang tahap akhir yang semakin bertambah telah meningkatkan keperluan pembedahan fistula salur darah (arteriovenous fistula). Penyediaan fistula yang dapat mengekalkan fungsinya untuk jangka masa yang panjang merupakan satu cabaran terutamanya bagi salur vena yang bersaiz kecil. Saiz vena yang terlalu kecil (<2mm) didapati akan mengalami kadar kegagalan fungsi yang tinggi. Latihan genggaman tangan yang dijalankan oleh pesakit-pesakit buah pinggang selepas pembedahan fistula didapati membantu proses kematangan fistula. Disebabkan kesan positif inilah, maka kami mengambil keputusan untuk mengkaji pula kesan latihan genggaman tangan tersebut ke atas salur vena sebelum pembedahan. Kajian ini dijalankan untuk tujuan membandingkan keberkesanan di antara dua jenis latihan genggaman tangan secara konvensional dan modifikasi ke atas subjek sihat.

Kaedah

Seramai 32 subjek sihat (11 lelaki, 21 perempuan) yang terlibat telah dibahagikan kepada 2 kumpulan latihan genggaman tangan. Tangan yang terlibat dalam latihan genggaman ini dipilih secara rawak, manakala tangan yang tidak terlibat berfungsi sebagai kumpulan kawalan. Kedua-dua latihan genggaman tangan dijalankan selama 6 minggu dengan kadar kekerapan yang sama iaitu 30 minit sehari dan kitar genggaman yang sama (5 saat genggaman, 2 saat rehat). Bagi kumpulan modifikasi, genggaman tangan ditambah dengan gerakan penglipatan pergelangan tangan. Bola genggaman yang sama diberikan kepada kesemua subjek yang terlibat. Saiz salur darah dan kadar pengaliran darah diukur dengan menggunakan mesin ultrasound

Doppler sebelum latihan genggaman tangan dan 6 minggu selepas latihan. Kesemua subjek dikehendaki mengelakkan pengambilan kopi, alcohol dan aktiviti lasak selama 48 jam sebelum imbasan ultrasound dilakukan. Juruteknik ultrasound yang menjalankan imbasan ultrasound juga telah dibutakan terhadap jenis latihan yang dilakukan oleh setiap subjek.

Keputusan

Kajian mendapati tiada perbezaan statistic yang ketara di antara latihan genggaman tangan konvensional dan modifikasi apabila dibandingkan saiz salur darah dan kadar pengaliran darah. Apabila setiap kumpulan latihan dibandingkan dengan kumpulan kawalan masing-masing, hanya latihan konvensional yang menunjukkan peningkatan saiz yang ketara pada salur vena "distal cephalic vein" (p=0.003) dan "proximal cephalic vein" (p<0.001) serta peningkatan kadar pengaliran darah pada "brachial artery" (p=0.025). Latihan genggaman tangan modifikasi menunjukkan perubahan kadar peratusan yang lebih tinggi jika dibandingkan dengan latihan konvensional (34.5 vs 27.8%, 26.6 vs 21.1%); namun begitu, keputusan analisis statistiknya adalah tidak ketara (p=0.316, p=0.489).

Kesimpulan

Latihan genggaman tangan secara konvensional mengikut protokol kajian boleh dilaksanakan oleh pesakit-pesakit buah pinggang sebelum menjalani pembedahan fistula. Memandangkan perubahan kadar peratusan yang lebih tinggi dalam latihan genggaman tangan modifikasi, kajian yang lebih lanjut adalah diperlukan untuk memantau kesan latihan ini sebelum pembedahan dilakukan ke atas kadar kematangan fistula di kalangan pesakit buah pinggang.

VI. Abstract

Introduction

The rising trend of end-stage renal disease (ESRD) has seen a higher rate of arteriovenous fistula (AVF) creation. Creating a durable vascular access for hemodialysis is a challenge especially in the unfavorable vein size. Smaller vein size (< 2mm) is associated with higher AVF failure rate. Post-operative handgrip exercise had been advocated in ESRD patients and results shown better AVF maturation. We took advantage of this favorable outcome to investigate the effect of handgrip exercise in native vein to explore the potential of implementing pre-operative handgrip exercise as part of the management in ESRD patients. The current study compared the efficacy of two types of handgrip exercises (conventional and modified) in healthy subjects.

Method

Thirty-two healthy volunteers (11 male, 21 female) were randomized into two types of handgrip exercises. Exercised hand was randomized and the non-exercising hand served as the control. Both interventions followed the same duration (6weeks), same frequency (30min/day) and same intensity (5 sec contraction, 2 sec relaxation), except for the addition of wrist flexion in the modified group. A standardized stress ball was provided to all subjects. Measurements of vessel diameter and blood flow rate done via Doppler ultrasound were taken before and after 6 weeks of exercise. Prior to imaging, subjects were refrained from coffee, alcohol or strenuous activity for 48 hours. The sonography technician who performed Doppler ultrasound imaging was blinded.

Results

There is no statistically significant difference between conventional and modified handgrip exercise when comparing the vessel diameter and arterial blood flow rate. When compared to their control counterpart, conventional exercise showed significant increment in distal cephalic vein (DCV) ($p=0.003$) and proximal cephalic vein (PCV) ($p<0.001$), as well as improvement in brachial artery flow (BAF) rate ($p=0.025$) but not the modified handgrip exercise. However, the modified handgrip exercise showed a higher percentage of increment in DCV and PCV compared to the conventional group (34.5 vs 27.8%, 26.6 vs 21.1%) although not being statistically significant ($p=0.316$, $p=0.489$).

Conclusion

The conventional handgrip exercise with our proposed protocol could be implemented in ESRD patients before AVF creation. Given the higher percentage of improvement seen in modified handgrip exercise, future investigation is needed to evaluate the outcome of AVF maturation in patients subjected to pre-operative handgrip exercise.

1. Introduction

1.1 Literature Review

1.1.1 Rising trend of chronic kidney disease leads to increased dialysis rate

The rising trend of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is of global concern. After a rising trend seen in the past three decades from 1980 through 2010, the number of incident ESRD cases remains plateaued in both 2011 and 2012. The prevalence of ESRD in the US in 2012 was reported as 636,905 cases with the number of incident of 114,813 cases.(Nishikawa *et al.*, 1997) In Malaysia, there is an increase in the incidence of ESRD over the last 10 years - from 2901 in 2004 to 6222 in 2013 while the prevalence almost triples to 31,637 cases.(*All Renal Replacement Therapy in Malaysia: 21st Report of the Malaysian Dialysis and Transplant Registry 2013*) Once the criteria for renal replacement therapy are met, these patients will be subjected to either dialysis or renal transplantation. In Malaysia, the transplant rate (94 cases in 2013)(*All Renal Replacement Therapy in Malaysia: 21st Report of the Malaysian Dialysis and Transplant Registry 2013*) is much lower as compared to the US (17,305 cases in 2012)(Nishikawa *et al.*, 1997) and dialysis is the mainstay treatment for majority of our ESRD patients. Hence, there is a significant impact on the financial burden of the healthcare system where government subsidies accounts for 58.2% of the total funding for the dialysis treatment in Malaysia.("Dialysis in Malaysia: 21st Report of the Malaysian Dialysis and Transplant Registry 2013,") The global increment of the numbers in CKD and ESRD patients results in the implementation of public policies and surveillance programme to create better management guidelines.

Dialysis performed 3 times per week for 2.5 to 4.5 hours as the minimum dialysis dose is considered appropriate by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.(Eknoyan and Levin, 2002) Thus, creating a durable and sustainable vascular access is important to maintain long-term patency.

1.1.2 Successful arteriovenous fistula (AVF) depends on appropriate vessel diameter and blood flow

Initiation of dialysis therapy at the appropriate time and with a permanent access should be planned. Pre-dialysis education should begin when patients reach CKD stage 4 to counsel both patients and families regarding treatment options. In addition, there will be sufficient time to allow evaluation of recipient and donor for preemptive renal transplantation. Most importantly, the preparation of a well-planned dialysis treatment using a permanent vascular access can be established in pretreatment education.(Mendes et al., 2002) The preferred type of access is a native AVF, followed by grafts and then central venous catheters.

Vein diameter has been associated as a factor that predicts AVF maturation. The increased in minimum vein diameter (MVD) by each 1.0mm showed a 45% reduction in the risk for failure of maturation and a 36% reduction in the risk of fistula failure.(Dageforde *et al., 2014.*) Radiocephalic fistulae constructed in veins with a less than 2.0mm diameter had only 16% primary patency at 3 months compared with 76% for those with veins greater than 2.0mm.(Mendes *et al.*, 2002) In a meta-analysis comparing the size of vessel diameter, the author found that the mean success rate after fistula creation was significantly different between radial artery diameter >2.0mm (59%) and <2.0mm (40%). The mean fistula success rate was also significantly different between cephalic vein diameter >2.0 mm (71%) and <2.0mm (29%).(Glass, 2009)

1.1.3 Handgrip exercise has potential benefit to improve pre-operative vessel diameter and blood flow

Vein diameter and blood flow rate are the main determinants for a successful AVF.(Glass, 2009; Smith *et al.*, 2012) To determine the maturation of AVF, NKF KDOQI 2006 recommends a minimum vein diameter of 6mm and the blood velocity of 600ml/min. In hemodynamics, the volume flow rate can be estimated by Poiseuille's law where any change in radius will reflect greatly in the volume velocity.(Secomb, 2008) The regulation of blood flow involves a complex interaction between mechanical effect via muscle pump, metabolic substances, shear stress effect and neural control via autonomic nervous system. A study on the acute effect of knee extension exercise demonstrates that mechanical compression by the contracting muscle increase the blood velocity in femoral artery.(Osada *et al.*, 2013a) On the other hand, changes in the metabolism during exercise will induce functional hyperemia, a metabolic vasodilatory response to hypoxia. The role of hypoxia is well-studied by recent studies in blood flow restricted (BFR) exercise.(Credeur *et al.*, 2010; Thijssen *et al.*, 2011) Horiuchi et al reviewed on the effect on BFR exercise on vascular function and found that this alternative form of exercise involved low intensity training with an external cuff compression to occlude venous return and thus increase the metabolic stress. The metabolic response coupled with shear stress post cuff deflation was found to induce greater vasodilatation and blood flow increment in both healthy subjects and end-stage renal patients.(Horiuchi and Okita, 2012; Rus *et al.*, 2005; Salimi *et al.*, 2013) Nitric oxide (NO) is a potent vasodilator which is released when frictional force is transmitted to endothelial due to changes of blood flow. This vasoactive mediator is the most widely studied component in subjects with endothelial dysfunction. While the vasodilator effect is less related to the healthy subjects than those with endothelial dysfunction such as cardiovascular disease, the endothelium-dependent vasodilatation can be improved if there is continuation of exercise after a short-term duration of training. (Green *et al.*, 2004; Tinken *et al.*, 2010)

Handgrip exercise has been proven to improve the maturation of AVF but there is no standard protocol for the method and the duration of such exercise.(Jindal *et al.*, 2006; Kumar *et al.*, 2010; Uy *et al.*, 2013) Traditionally, patients would be advised to do handgrip exercise with a stress ball or handgrip device after AVF creation. The conventional handgrip exercise only involves the contraction of finger flexors (flexor digitorum superficialis and profundus). In this study, a modified handgrip exercise is performed to incorporate other forearm muscles in the anterior compartment through wrist flexion to obtain better results in vein diameter and forearm blood flow. We are postulating that with bigger forearm muscle mass involved in the modified handgrip exercise, there will be more hypoxic drive due to more compressive effect and greater NO-dependent vasodilatory response from shear stress. In addition to post AVF exercise, handgrip exercise also could act as a pre-operative intervention to amend unfavourable vein size to achieve higher rates of AVF maturation.

1.2 Rationale of study

Vascular access for end-stage renal patients remains a challenge. To overcome this problem, renal patients are counseled early in regards to renal replacement therapy. Handgrip exercise is implemented to improve the vein size to a more favorable diameter in order to have a successful AVF. Literatures found that handgrip exercise can increase the vein size and blood flow in both healthy subjects and ESRD patients. However, there is no protocol mentioned for the duration and types of handgrip exercise. This study is undertaken to compare the effectiveness between a modified method of handgrip exercise and the conventional method. An exercise protocol is designed and to be evaluated in the study for the effectiveness in improving vein size and blood flow. Although the vein of a healthy subject is much different from a renal patient who has endothelial dysfunction, we are conducting the study in healthy subjects in anticipation of high dropout rates in ESRD patients due to their frequent medical follow up and also the potential non-compliance. Another problem that is anticipated if ESRD patients are recruited is the bias in choosing the exercised hand compared to the control. AVF is usually done on the non-dominant hand as the first choice unless the vessels are not favorable in size. In addition to that, most of the renal patients have undergone AVF on one upper limb, which render it impossible to have a control group for non-exercised hand. On the other hand, the contralateral upper limb will be the only site for cannulation during routine blood taking and this will compromise the vessel that will be evaluated. For those patients who had undergone previous AVF surgery, the corresponding artery and vein are unable to be evaluated, rendering it impossible to be compared among other subjects. Thus, this study will be conducted in healthy subjects to compare the efficacy between the conventional handgrip exercise and our proposed modified protocol before it is implemented to the ESRD patients.

Different exercise protocols exist in the current settings and it is unknown which one works better. By the end of this study, we hope to propose a handgrip exercise protocol for ESRD patients who are planned for AVF surgery.

2.0 Study Protocol

A Randomized Controlled Trial Comparing the Effect of Conventional and Modified Handgrip Exercise towards the Vein Size and Blood Flow of Upper Limbs in Healthy Subjects

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1.4. Justification of study

Vascular access for end-stage renal patients remains a challenge. To overcome this problem, renal patients are counseled early in regards to renal replacement therapy. Handgrip exercise is implemented to improve the vein size to a more favorable diameter in order to have a successful AVF. Literatures found that handgrip exercise can increase the vein size and blood flow in both healthy subjects and ESRD patients. However, there is no protocol mentioned for the duration and types of handgrip exercise. This study is undertaken to compare the effectiveness between a modified method of handgrip exercise and the conventional method. An exercise protocol is designed and to be evaluated in the study for the effectiveness in improving vein size and blood flow. Although the vein of a healthy subject is much different from a renal patient who has endothelial dysfunction, it is more feasible to conduct the study in healthy subjects due to the frequent follow up imaging and the issue of exercise compliance. ESRD patients have multiple co-morbid and often busy with clinic appointments, thus to enroll them as subjects will increase their burden of travel and default of follow up will be a problem. Another potential problem if ESRD patients are recruited is the bias in choosing the exercised hand compared to the control. AVF is usually done on the non-dominant hand as the first choice unless the vessels are not favorable in size. In addition to that, most of the renal patients have undergone AVF on one upper limb, which render it impossible to have a control group for non-exercised hand. On the other hand, the contralateral upper limb will be the only site for cannulation during routine blood taking and this will compromise the vessel that will be evaluated. It is hope that the result of the study could be translated into practice and implemented in the management of pre and post AVF surgery.

2. Objectives

2.1. General objective

To investigate the effects of conventional and modified handgrip exercise on vessel diameter and blood flow of upper limb in healthy subjects.

2.2. Specific objective

2.2.1 To compare the effects of conventional and modified handgrip exercise on vessel diameter and blood flow of upper limb.

2.2.2 To compare the effects of conventional handgrip exercise on vessel diameter and blood flow of upper limb with the non-exercised limb (control)

2.2.3 To compare the effects of modified handgrip exercise on vessel diameter and blood flow of upper limb with the non-exercised limb (control)

2.3. Hypothesis

Modified handgrip exercise can increase the vessel diameter and improve the blood flow of upper limb in healthy subjects.

There is difference between in the effectiveness of conventional and modified handgrip exercise on vessel diameter and blood flow of upper limb.

3. Methodology

3.1. Study Design

This is a randomized controlled trial (RCT) study that will be conducted in Hospital Universiti Sains Malaysia (HUSM). Healthy subjects will be recruited and randomized using simple random sampling method. The subjects will first be randomized into two interventional groups; the modified handgrip exercise and the conventional handgrip exercise. Subsequently, another randomization will be used to determine the hand to be exercised within each group. Both randomizations will be done using random number generator in website (www.random.org). The non-exercised hand will act as the control group.

A standardized stress ball will be used for both male and female participants. It will be the limitation of this study as there is difference in maximal handgrip strength between male and female. As there will be randomization in the exercised hand, no gender matching will be done and a subgroup analysis will be done to examine any outcome difference.

Throughout the study, the ultrasonographer will be blinded. The primary investigator (PI) will recruit the subjects and screen for eligibility to participate. Subjects who fulfill the inclusion criteria will be given a briefing in separate sessions regarding the types of hand exercise to be done. Before the commencement of the handgrip exercise, a baseline imaging study will be arranged for each subject

3.2. Subjects

Advertisement (Appendix 1) will be put up at notice boards throughout HUSM. Healthy volunteers who are interested will be recruited by PI and explanation will be given regarding the study protocol and the purpose of the study. Subjects will be screened for eligibility and informed consent will be taken once they agreed to join the study. They will be randomized into two interventional groups. Pre and post study measurements will be done via Doppler ultrasound (ACUSON Cypress, Siemens Medical Solutions USA,Inc.)

Inclusion, Exclusion and Withdrawal Criteria:

Inclusion criteria:

Healthy males and females. Age group: 20-40 years old and willingness to participate in the study.

Exclusion criteria:

Subject with diabetes mellitus, hypertension or obesity.

Subject with any orthopedic trauma or surgery in upper limbs.

Subject with any cardiovascular/ orthopedic/ neurological/ vascular disease.

Subject who is pregnant.

Subject who is actively smoking for the past 3 months.

Subject who consumes regular medication which may affect vascular function (vasodilator/ vasoconstrictor/hormone).

Withdrawal Criteria:

Participants are allowed to withdraw from the study at any time without any penalty.

3.3. Experimental Design

3.3.1. Sample Size

The sampling method is convenience sampling. All volunteers that register their interest will be included in the study.

Based on the literature review, there is no report on the significant change expected on the vein size after handgrip exercise in healthy subjects. Comparing to other similar studies (Credeur *et al.*, 2010; Mc Loughlin *et al.*, 2012; Roseguini *et al.*, 2011) of handgrip exercise in healthy subjects, the sample size of 12 is sufficient to show significant results.(Credeur *et al.*, 2010) Hence, with inclusion of 20% drop-out rate, the total number of subjects should be 28. However, due to the small sample size, we included a total sample of 32, with 16 subjects in each group.

3.3.2. Exercise Protocols

Prior to study, all subjects will have to complete a medical history and health habits questionnaire. Each of the subjects will have to sign and agree to an informed consent form and the study procedures. All protocols were approved by the ethics committee of the HUSM. There is no risk to subjects if they participate in this study. The subjects may refuse to take part in the study or may stop participation in the study at anytime. A polyurethane stress ball will be provided for the study purpose. Subjects who complete the study will be given a small token of appreciation.

All selected subjects will be randomly divided into 2 groups, conventional handgrip exercise (EXP1) (n=16) and modified handgrip exercise EXP2 (n=16). The EXP1 group will perform a conventional handgrip exercise by using a standardized stress ball in a sitting position with forearm resting on the thighs (Figure 2). Meanwhile, the EXP2 group will perform a handgrip exercise similar to EXP1 but with inclusion of wrist flexion of 45° to incorporate forearm muscles (Figure 3). The exercise protocol consists of squeezing the rubber ball for 30 min/day in a continuous manner and to be carried out daily for 6 weeks duration. The subject is required to perform handgrip on the ball with a sustained contraction of 5 seconds and relaxation for 2 seconds. All subjects will not be allowed to break the exercise regime into multiple sessions per day to avoid non-compliance. The decision of which hand to be exercised will be randomized to avoid hand dominance bias. The non-exercised hand will serve as the control for each corresponding type of handgrip exercises.

Figure 1: Conventional handgrip exercise

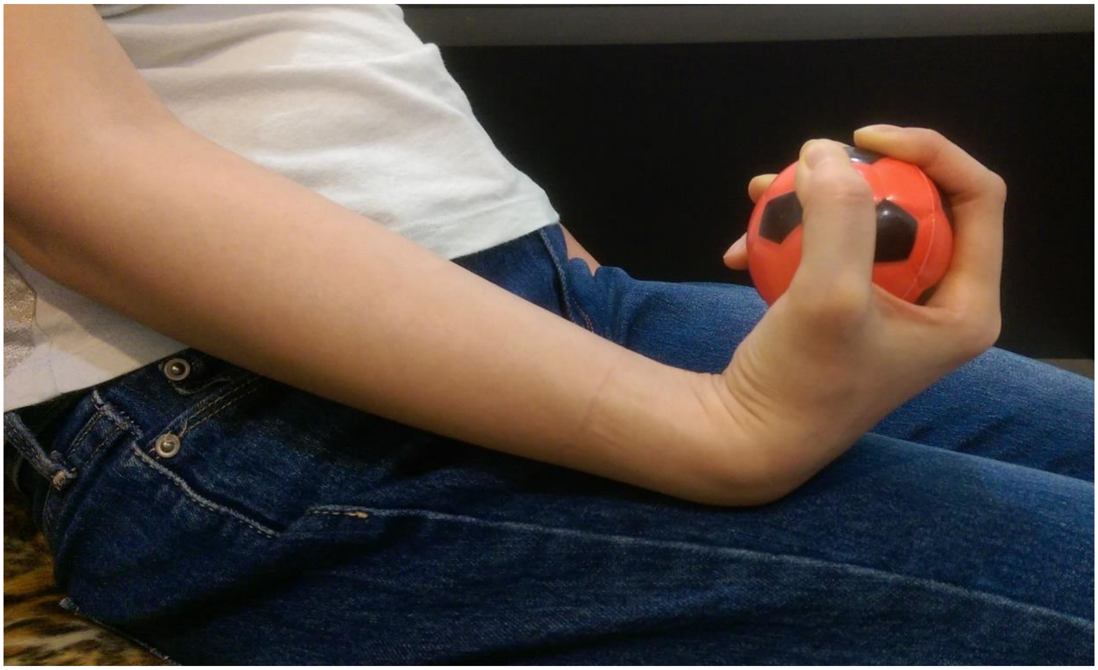

Figure 2: Modified handgrip exercise

3.3.3. Study Procedures

All subjects will be asked to refrain from caffeine, alcohol or strenuous activity for 48 hours prior to imaging. Baseline ultrasound images will be obtained in a supine position with forearm supinated. In order to eliminate unconscious bias, there will be one appointed ultrasonographer and he will be blinded in this study. All measurements will be documented in a proforma kept by the ultrasonographer. The vascular diameter and blood volume flow rate will be assessed pre and post exercise with a Doppler ultrasound machine.

All imaging procedures will be done using the Doppler ultrasound (ACUSON Cypress, Siemens Medical Solutions USA, Inc.) in our vascular assessment clinic. The ultrasound imaging will be first done to the right upper limb and followed by left upper limb. The diameter of the distal cephalic vein (DCV) and radial artery (RA) will be measured at approximately 1cm proximal to radial styloid process. For the brachial artery (BA) and proximal cephalic vein (PCV), the imaging procedure will be obtained at 4cm proximal to antecubital fossa. To assess both the radial artery flow (RAF) and brachial artery flow (BAF) rate, the transducer is placed at an angle of 30° from the longitudinal axis of the vessel. When the transducer is placed perpendicular to the direction of flow, there will be no Doppler shift as the cosine of 90° is zero. Thus, in order to obtain a more accurate measurement of blood flow, the angle of insonation is usually placed within 30°-60°.

As the study involves measurement of vessel caliber, efforts will be made to reduce confounding factors. Subjects are not allowed to perform strenuous exercise especially hand exercise using weights. Caffeine and alcohol consumption is discouraged. Subject is given 5 minutes rest before any imaging is done. As the vessels are sensitive to temperature change, the room temperature is maintained at 27°C.