J Vasc Access 2013; 14 (2): 157-163
DOI: 10.5301/jva.5000116

ORIGINAL ARTICLE

Impact of isometric handgrip exercises on cephalic vein diameter in non-AVF candidates, a pilot study

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ABSTRACT

Purpose: **Incident arteriovenous fistula (AVF) rates remain low. AVF placement is often not attempted because of small cephalic vein (CV) diameter. We postulated that isometric handgrip exercises would increase forearm CV diameter and allow successful AVF creation in non-AVF candidates.**

Methods: **Adult subjects without prior vascular access (eGFR<25mL/min/1.73m^2; CV<2.5mm) were prospectively enrolled. They performed daily handgrip exercises in the preferred access arm (EA), with the nonexercised arm (NEA) as control. Adherence was assessed by exercise logs and grip strength. CV diameter was measured at baseline, four and eight weeks by ultrasound. The primary endpoint was the mean increase in CV diameter. Secondary endpoints were mean CV diameter increase from baseline, increased proportion of potential AVF sites and successful AVF placement.**

Results: **A total of 17 subjects were enrolled and 15 completed the study. EA grip strength increased significantly. Mean CV diameter increased in both the EA and NEA by 0.48-0.59 and 0.71-0.81mm (P=NS), respectively. Compared to baseline, all CV diameters increased significantly (P<.05) after four weeks. In the EA, mean distal and proximal CV increased from 1.66 to 2.13 mm and from 2.22 to 2.81 mm, respectively. Similar changes were noted in the NEA. There were also significant increases in the number of sites and subjects eligible for AVF creation. Five subjects had successful AVF placement.**

Conclusions: **Isometric handgrip exercises resulted in significant CV diameter increases after four weeks, in both the EA and the NEA and potentially allows for AVF creation in those not previously deemed candidates.**

Key Words: Arteriovenous fistula, Chronic kidney disease, End stage renal disease, Hemodialysis, Isometric exercise, Vascular access, Vein mapping

Accepted: September 30, 2012

INTRODUCTION

End-stage renal disease (ESRD) accounts for an estimated $24 billion or 5.8% of total Medicare expenditure annually, and approximately $1 billion of this is spent on vascular access-related morbidity. The cost of arteriovenous grafts (AVG) and central venous catheters (CVC) are 18% and 25% higher, respectively, than arteriovenous fistulas (AVF) (1), and AVF have been associated with improved patient outcomes (2-4). The NVAII set up the Fistula First initiative in 2003, which had a goal of using AVF in at least 50% of newly commenced dialysis patients and in at least 66% of current hemodialysis patients with the ultimate aim of eventually matching international rates of AVF use of 70% to 80%. The prevalent AVF aim was met before the proposed deadline, but the rate of incident AVF is still well below the 50% goal with only 16% of patients in the US being initiated with AVF in 2011 (5).

There are multiple barriers to successful AVF placement (6). Certain groups of patients are not considered the best candidates for AVF creation. For example, the prevalence of AVF is lower in women, African Americans, obese and older patients as well as those with peripheral vascular disease (7). Some of these patient groups such as women and the obese, appear to have smaller veins, and insufficient vein diameter is the most common vascular deterrent for AVF creation (8). Assessment of the vessel size with pre-operative duplex ultrasound has been found to correlate with peri-operative findings and maximizes the number of AVFs placed and used successfully (9-10). Vein diameters < 2.5 mm on vein mapping have been associated with primary AVF failure (11), and most surgeons will opt for AVG placement in this setting.

We hypothesized that small vein diameter may be a

modifiable risk factor for primary AVF failure. Prior studies suggest that an increase in vein size is possible with an exercise intervention (12-14). The precise mechanism is not known, but is proposed to involve increased arterial flow, flow-induced adaptation and endothelium dependent vasodilatation (12). We hoped to add to this literature focusing on the population that may be overlooked for initial AVF based solely on vessel size. The aim of this pilot study was to assess whether or not an exercise intervention may increase venous size and allow AVF placement in patients who were not AVF candidates because of small vein size.

MATERIALS AND METHODS

Study design and population

We performed a prospective pilot study to assess the effects of isometric handgrip exercises on cephalic venous diameters < 2.5 mm. Subjects were recruited from the Walter Reed Army Medical Center (WRAMC) Nephrology, Organ Transplant and Vascular Surgery clinics. Both men and women military health beneficiaries age 18 and older were offered enrolment if they had a diagnosis of CKD Stage IV or V (eGFR < 20 or < 25 mL/min/1.73m^2 with diabetes) and had a distal forearm cephalic vein < 2.5 mm in diameter in one or both arms, noted on vein mapping as part of their routine predialysis care. Exclusion criteria included prior vascular access surgery, positive Allen test or physical exam findings consistent with poor arterial flow or severe calcifications. Other exclusion criteria included ESRD, physical or mental disability limiting access placement or ability to perform exercises and medical contraindications for vascular access surgery. Written informed consent was obtained from all subjects, and the study was approved by the WRAMC Institutional Review Board #358151-6.

Exercise regimen

Subjects were asked to perform isometric forearm strengthening exercises in their preferred access arm, with the non-exercised arm serving as control. During the initial visit, subjects were consented and provided with a squeeze ball. Subjects were asked to perform 10 sets of 20 isometric handgrip exercises daily in the study arm for a total of eight weeks. Each set consisted of 20 contractions per minute with each contraction held for approximately three seconds for a total of five minutes per set. Subjects were allowed to perform each set throughout the day with at least five minutes rest in between sets. This regimen was chosen for its simplicity in an effort to maximize adherence. Isometric handgrip exercises were demonstrated and subjects were asked to record the number of exercises performed daily on an exercise log.

Study procedures

Subjects were followed in clinic at 0, 4 and 8 weeks. Subjects were contacted by telephone to verify that exercises were being performed at two and six weeks. At each visit, the highest of three measurements was recorded for grip strength, which was measured with a dynamometer (Baseline®). Subjects were also asked to demonstrate the handgrip exercises at each visit and return the self-reported exercise log. They also returned a blood pressure log and reported any adverse effects.

Venous diameter measurements were obtained by the same vascular technologist at predetermined anatomic locations in both arms based on 1.0 cm below the antecubital fossa (proximal) and 1.0 cm above the ulnar process (distal). Gray-scale/BMODE imaging of the cephalic vein were obtained using a L8-L18i transducer (GE Logic 9, Milwaukee, WI, USA). The cephalic vein within each forearm was imaged and measured with the use of a tourniquet at the upper arm. Cross-sectional area measurements were obtained within each forearm, which consisted of anterior/posterior and transverse measurements of bilateral cephalic veins. The vascular technologist was blinded to the intervention arm and to the study week number in order to avoid bias. We measured subject adherence objectively with serial measurements of grip strength and through the self-reported exercise logs.

Outcomes

Our null hypothesis is that isometric hand exercises have no effect on vein diameter in patients with kidney disease. The primary endpoint was the mean change in venous diameter between the control (non-exercised) arm and the study (exercised) arm at 0 and 4 weeks, and 0 and 8 weeks. Secondary endpoints were the proportion of subjects that achieved at least one cephalic venous diameter > 2.5 mm, the proportion of potential forearm access sites with at least one cephalic venous diameter > 2.5 mm, and the proportion of subjects that had a successful AVF placement.

Statistical analysis

The primary endpoint was mean change in venous diameter between the exercised and non-exercised arm at 0 and 4 weeks, and 0 and 8 weeks. For the primary endpoint, we used the Student's *t* test to compare mean changes in vein sizes from baseline of the exercised and nonexercised arms at weeks 4 and 8. Secondary endpoints were mean change in vein size from baseline (paired *t* test), and a comparison of proportions of subjects and access sites with vein size ≥ 2.5 mm at 4 and 8 weeks (χ^2 or mid-p exact test). The proportion of subjects with

successful AVF placement, and a comparison of high risk subgroups (male sex, body mass index < 30, GFR ≥20, tobacco use, age < 70 and diabetes mellitus), were evaluated although we did not anticipate adequate power for subgroup analysis in this pilot study.

RESULTS

Seventeen subjects were enrolled in the study. One subject was excluded because baseline venous mapping revealed that all forearm veins were > 2.5 mm in diameter. One subject dropped out after enrolment and did not complete the exercise regimen. The vascular technologist was unable to visualize veins in the control arm at baseline for two subjects, although the veins were noted on follow-up ultrasounds at four and eight weeks. Baseline characteristics of the 15 subjects who completed the study are listed in Table I. There were eight women and seven men. The mean age was 68.7 years old with a mean eGFR of 21 mL/min/1.73m^2. There were eight subjects with a history of tobacco abuse, three with a history of DM and five subjects who were obese. The nonexercised arm was typically the dominant arm, which would account for the increased grip strength and larger baseline venous diameter (Tab. I).

TABLE I - BASELINE DEMOGRAPHIC AND CLINICAL INFORMATION ON 15 SUBJECTS WHO COMPLETED THE STUDY

Baseline variable	N(%) or Mean ± SE
Age (years)	68.7 ± 4.2
Male sex	7 (46.7%)
African American race	7 (46.7%)
Asian race	1 (6.7%)
Caucasian race	7 (46.7%)
MDRD eGFR (mL/min/1.73m^2)	21.5 ± 1.3
Body Mass Index > 30	5 (33.3%)
Diabetes Mellitus	3 (20.0%)
Tobacco Use	8 (53.3%)
Meds (Aspirin)	12 (80.0%)
Meds (Clopidogrel)	1 (6.7%)
Meds (Fish Oil)	3 (20.0%)
Grip-NEA (kg)	27.83 ± 2.68
Grip-EA (kg)	25.67 ± 2.24
Diameter (mm) of distal (forearm) cephalic vein (NEA)	1.55 ± 0.19
Diameter (mm) of distal (forearm) cephalic distal vein (EA)	1.66 ± 0.17
Diameter (mm) of proximal (forearm) cephalic vein (NEA)	2.17 ± 0.24
Diameter (mm) of proximal (forearm) cephalic vein (EA)	2.22 ± 0.21

EA = exercised arm; NEA = non-exercised arm; SE = standard error of the mean.

Regarding subject adherence, there was a statistically significant increase in grip strength in the exercised arm from 0 to 8 weeks (24.50 ± 2.05 to 27.04 ± 2.20 kg; *P*=.025), and there was no change in the control arm (26.68 ± 2.60 to 26.82 ± 2.40 kg; *P*=.929). No significant change in grip strength was noted at four weeks in either group. Only 13 subjects submitted exercise logs, and only 11 subjects submitted logs for the entire eight week period. Of the 11 subjects with complete logs, there appeared to be a decrement in adherence with exercises during the last four weeks of the study

For the primary outcome, there was no statistically significant difference in the change in venous diameter (Tab. II). There were positive venous diameter increases (range 0.32 to 0.59 mm) in the exercised arm, but there were also increases in the venous diameters of the control arm (range 0.43 to 0.81mm). To assess subgroup outcomes, we assessed the impact of certain demographic variables (male sex, body mass index < 30, GFR ≥ 20, tobacco use, age < 70, and diabetes mellitus) on the primary outcome, but found no significant interactions.

When compared to baseline, there was a significant increase in cephalic vein diameter. This was only noted at four weeks for the exercised arm, but at both four

TABLE II - COMPARISON OF MEAN CHANGE IN CEPHALIC FOREARM VEIN DIAMETER BETWEEN EXERCISED AND CONTROL ARMS

	Exercised Arm	Control Arm	p
Variable	Mean Change ± SE	Mean Change ± SE	
Distal Cephalic Vein 0 weeks to 4 weeks (mm)	0.48 ± 0.16	0.81 ± 0.20	0.209
Distal Cephalic Vein 0 weeks to 8 weeks (mm)	0.32 ± 0.20	0.65 ± 0.15	0.217
Proximal Cephalic Vein 0 weeks to 4 weeks (mm)	0.59 ± 0.25	0.71 ± 0.20	0.726
Proximal Cephalic Vein 0 weeks to 8 weeks (mm)	0.52 ± 0.32	0.43 ± 0.20	0.826

SE = standard error of the mean.

and eight weeks for the control arm (Tab. III). To assess subgroup outcomes, we assessed the impact of certain demographic variables (male sex, body mass index < 30, GFR ≥ 20, tobacco use, age < 70 and diabetes mellitus) on this secondary outcome. Among men, there was a statistically significant increase in distal venous diameter at eight weeks (*P*=.006) and a trend towards increase in proximal venous diameter at eight weeks (*P*=.059). No interactions were noted for the other subgroups.

Table IV shows how the number of potential AVF access sites and the number of subjects with potential AVF access sites changed over the course of the study. At baseline, there were 12 sites with vein diameter ≥ 2.5 mm, and this number increased to 33 (*P*<.001) and 23 (*P*=.047), after four and eight weeks of exercise, respectively. Among subjects, there were five and six exercised and nonexercised arms that may have been eligible for an AVF based on at least one potential access site with vein diameter of ≥ 2.5 mm. After four weeks of this study, the number increased to 11 (*P*=.028) and 12 (*P*=.082) study and control arms, respectively. After eight weeks of exercise, the number of subjects was still above baseline, but not statistically significant.

A total of six subjects have had a dialysis access placed, five with an AVF and one with an upper extremity AVG. Of note, the subject who received AVG had adequate vein size for AVF placement, but the attending physician preferred not to wait for an AVF to mature based on the subject's clinical deterioration. Of the five AVF and one AVG that were placed, two AVFs are currently being used successfully for dialysis. The remainder of the subjects are still predialysis, and none of the subjects have required additional interventions to maintain patency.

TABLE III - CHANGES IN FOREARM CEPHALIC VENOUS DIAMETER (MM, BY DUPLEX ULTRASOUND) AT FOUR AND EIGHT WEEKS COMPARED TO BASELINE

Vein Diameter (mm)	N	Pre Mean ± SE	Post Mean ± SE	P
Exercised Arm (EA)				
Distal; 0 to 4 weeks	15	1.66 ± 0.17	2.13 ± 0.15	.011
Distal; 0 to 8 weeks	15	1.66 ± 0.17	1.98 ± 0.19	.130
Proximal; 0 to 4 weeks	15	2.22 ± 0.21	2.81 ± 0.26	.031
Proximal; 0 to 8 weeks	15	2.22 ± 0.21	2.74 ± 0.31	.125
Non-exercised Arm (NEA)				
Distal; 0 to 4 weeks	13	1.55 ± 0.19	2.36 ± 0.22	.002
Distal; 0 to 8 weeks	13	1.55 ± 0.19	2.20 ± 0.22	.001
Proximal; 0 to 4 weeks	13	2.17 ± 0.24	2.88 ± 0.23	.004
Proximal; 0 to 8 weeks	13	2.17 ± 0.24	2.60 ± 0.25	.048

EA = exercised arm; NEA = non-exercised arm; SE = standard error of the mean.

TABLE IV - NUMBERS OF ACCESS SITES AND SUBJECTS WITH VEIN DIAMETER ≥2.5 MM AFTER FOUR AND EIGHT WEEKS OF EXERCISE

	Baseline	Week 4	P	Week 8	P
Study					
# sites ≥ 2.5mm	5/30	16/30	.003	11/30	.079
# subjects ≥ 2.5mm	5/15	11/15	.028	7/15	.487
Control					
# sites ≥ 2.5mm	7/26	17/30	.025	12/30	.304
# subjects ≥ 2.5mm	6/13	12/15	.082	7/15	.980
Total					
# sites ≥ 2.5mm	12/56	33/60	<.001	23/60	.047
# subjects ≥ 2.5mm	8/15	13/15	.061	8/15	>.999

Legend: Comparisons are between 0 and 4 weeks and 0 and 8 weeks. Total number of subjects = 15; however, two subjects did not have a detectable distal cephalic vein at baseline in the NEA. Each arm for each subject had two potential venous sites: proximal and distal forearm cephalic vein. Thus the number of potential sites in either the EA or NEA is twice the number of subjects, and the total number of potential sites is four times the number of subjects.

TABLE V - SUMMARY OF PRIOR STUDIES EVALUATING THE EFFECT OF FOREARM ISOMETRIC EXERCISE ON VENOUS DIAMETER

Study	Population	Exercise regimen	Grip strength	Vein (intervention)	Vein (control)	Artery
Rus, 2003[1]	14 Slovenian hemodialysis patients with AVF; mean age 49; 7 females; 5 with diabetes; 3 with tobacco use	20 repetitions/minute; 30 total minutes; duration 8 weeks	The maximal handgrip strength increased from 24.1 ± 2.95 kg before training to 26.2 ± 3.06 kg after 4 weeks (p = 0.005) and to 28.5 ± 3.17 kg after 8 weeks (p < 0.001).	Baseline 2.97±0.18 mm 4 weeks 3.10 ± 0.19 mm 8 weeks 3.18 ± 0.18 mm (p<0.001)		Increase in radial artery diameter; no changes in flow or velocity
Leaf, 2003[2]	5 male veterans with CKD; mean age 53; mean GFR 33.7; 3 with diabetes;	Controlled heating 4 times per week for 6 weeks; 6 weeks of exercise at 30-40% MVC for 80-360 seconds with increased frequency over time	Paradoxically, the increase in venous size was unaccompanied by an increase in handgrip strength	Cephalic Baseline 2.8 ± 0.27 mm After 6 weeks 5.6 ± 0.22 mm (p<0.05)	Cephalic Baseline 1.7 ± 0.05 mm After 6 weeks 2.5 ± 0.01 mm	Not assessed
Kumar, 2010[3]	23 patients with stage 3-4 CKD; median age 66; 13 females; 14 with diabetes	20 repetitions/minute; 30 minutes per day; duration 4 weeks	Increased by median of 4kg on exercised arm; not control arm	Baseline Median (iqr) 2.5 (1.8-3.2) mm Median (iqr) increase of 0.6 (0.4-1.2) mm	No change reported	Significant increase in radial and brachial diameters and velocities
Uy, 2012 (present study)	15 patients; mean age 68; mean GFR 21; 3 with diabetes; 8 females; 5 obese; 8 with tobacco use	10 sets of 20 repetitions/minute; duration 8 weeks	Increase in the exercised arm from 0 to 8 weeks [24.50 ± 2.05 kg to 27.04 ± 2.20 kg; p=0.025], no change in control arm [26.68 ± 2.60 kg to 26.82 ± 2.40 kg; p=0.929].	Baseline distal 1.66 ± 0.17 mm 4 weeks 2.13 ± 0.15 mm 8 weeks 1.98 ± 0.19 mm Baseline proximal 2.22 ± 0.21 mm 4 weeks 2.81 ± 0.26 mm 8 weeks 2.74 ± 0.31 mm	Baseline distal 1.55 ± 0.19 mm 4 weeks 2.36 ± 0.22 mm 8 weeks 2.20 ± 0.22 mm Baseline proximal 2.17 ± 0.24 mm 4 weeks 2.88 ± 0.23 mm 8 weeks 2.60 ± 0.25 mm	Not assessed

AVF (arteriovenous fistula), CKD (chronic kidney disease),GFR (glomerular filtration rate), MVC (maximal voluntary contraction) iqr (interquartile range)

[1]Rus RR, Ponikvar R, Kenda RB, Buturovic-Ponikvar J. Effect of local physical training on the forearm arteries and veins in patients with end-stage renal disease. Blood Purif. 2003; 21(6):389-94.

[2]Leaf DA, MacRae HS, Grant E, Kraut J. Isometric exercise increases the size of forearm veins in patients with chronic renal failure. Am J Med Sci. 2003 Mar; 325(3): 115-9.

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DISCUSSION

We were unable to disprove our null hypothesis since the difference in vein diameter change was not significantly greater in the exercised arm. However, on further review of these data, the lack of statistical difference results from the fact that both groups (exercised and control arms) had an overall positive increase in vein size ranging from 0.32 ± 0.20 mm to 0.59 ± 0.25 in the exercised arm and 0.43 ± 0.20 to 0.81 ± 0.20 mm in the non-exercised arm (Tab. II). The non-exercised arm was typically the dominant arm, which may account for the larger increase noted in this arm. Based on these values, we would not expect a significant difference even if there were a larger sample size. This result was unexpected, and the etiology of this is unclear. This could be secondary to the systemic effects of exercise which may disproportionately affect the dominant arm. It has been demonstrated that five weeks of unilateral isometric handgrip exercise can have a systemic effect such as reduced mean arterial pressure (15). It is also possible that subjects exercised both arms, although this is not supported by the grip strength data. A similar study also noted an increase in the non-exercised cephalic vein diameter (1.70 ± 0.05 to 2.50 ± 0.01 mm) after six weeks of exercise, but this difference was not reported to be statistically significant (13).

When compared with baseline, there were significant increases noted in vein size after four weeks of exercise in both proximal and distal forearm cephalic veins for both the exercised and nonexercised arms (Tab. III). While not all of the means in our study crossed

the 2.5 mm threshold, the increases were noteworthy. These results substantiate the findings of prior studies performed in slightly different patient populations. These studies demonstrated the following significant increases in cephalic vein diameters after similar exercise regimens (0.21 mm mean increase after eight weeks [12]; 2.8 mm mean increase after six weeks [13]; 0.6 mm median increase (0.4 - 1.2 interquartile range) after four weeks [14]). Two of these studies also noted increases in arterial diameters and flow velocities, although the results were not consistent (Tab. V) (12,14). These results and ours suggest a need for a randomized controlled trial to further investigate and substantiate these findings.

It is also important to note that we did note a slight reduction in vein sizes at the eight week measurement. Despite the reductions, there were still statistically significant increases in vein sizes noted in the proximal and distal forearm veins of the non-exercised arm. The reasons for this decrement are not clear. Review of the submitted exercise logs suggests that there was decreased adherence with frequency of exercise over time. However, the grip strength data supports an overall strength increase at the end of the eight week period that was not evident at four weeks. This finding may suggest that there is some reversibility to these vascular changes suggesting that exercises would need to be continued until AVF placement, and this may suggest that the ideal timing to commence exercise is four weeks prior to planned AVF.

Of note, there was a significant increase in the number of subjects and vein sites potentially eligible for AVF creation over time (Tab. IV), and several of the subjects eventually had an AVF placed. At the time of manuscript preparation, there are five subjects who have had an AVF placed and two of these are currently using the AVF successfully for hemodialysis.

Limitations

There were several limitations to this pilot study. Our subjects were older with a mean age of 69, and few of our subjects had DM, which may not be representative of the general CKD/ESRD population in the United States. Regarding exercise adherence, there was variability with respect to subject completion of the self-reported logs. However, our objective measure of adherence (grip strength) increased over the eight week study period, suggesting that subjects were adherent to the exercise regimen.

Our study did not assess changes in arterial diameter, arterial flow, resistive indices, or central vein patency, which are also important components of assessing a potential AVF candidate. Sonography is highly operator dependent, but we used the same blinded vascular technologist and used objective anatomic landmarks. However, inter-assessment variability between vein measurements is possible as are vein diameter changes related to temperature or volume status. It is also important to note that we used venous diameter increase as a surrogate marker, which has not been validated for the definitive primary outcome of successful AVF placement.

To conclude, despite being the most cost effective hemodialysis access in the United States, the AVF remains underutilized. Based on vascular duplex imaging and comorbidities, some patients are deemed AVG candidates and await access placement until closer to commencing dialysis. Female sex, older age, obesity and diabetes are known associations for poor AVF suitability and outcomes. For these patients, we would propose a trial of isometric forearm exercises in an attempt to increase vein size, which could alter their candidacy for AVF. In our study four weeks of isometric handgrip exercises results in a significant increase in vein sizes in subjects with advanced CKD and several of the subjects underwent successful AVF placement. This intervention is simple, inexpensive, and may facilitate AVF placement in patients previously deemed poor candidates for AVF.

Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of Army, the Department of the Navy, the Department of Defense, or the United States government.

Financial support: This study was supported by the Walter Reed Army Medical Center Department of Clinical Investigation.

Conflict of interest: The authors have no conflicts of interest to disclose.

Informed consent: Institutional Review Board (IRB)/Ethics Committee approval was obtained.

Meeting presentation: These data were presented as a poster at the American Society of Nephrology Meeting in November 2011. As a result of the poster presentation, the abstract from the meeting was published in a Supplement in the Journal of the American Society of Nephrology with the citation below:

Uy AL, Yuan CM, Jindal RM, Hurst FP. Isometric Handgrip Exercises Improve Success Rates in Arteriovenous Fistula (AVF) Placement in Unsuitable Candidates. ASN Renal Week 2011, J Am Soc Nephrol 2011; 22: 562A.

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