Published in final edited form as:

Vasc Med. 2012 February ; 17(1): 3–9. doi:10.1177/1358863X11431837.

Percutaneous intervention in peripheral artery disease improves calf muscle phosphocreatine recovery kinetics: A pilot study

Amy M West¹, Justin D Anderson¹, Frederick H Epstein^{2,3}, Craig H Meyer^{2,3}, Klaus D Hagspiel^{1,2}, Stuart S Berr^{2,3}, Nancy L Harthun⁴, Arthur L Weltman¹, Brian H Annex¹, and Christopher M Kramer^{1,2}

¹Department of Medicine, University of Virginia Health System, University of Virginia, Charlottesville, VA, USA

²Department of Radiology, University of Virginia Health System, University of Virginia, Charlottesville, VA, USA

³Department of Biomedical Engineering, University of Virginia Health System, University of Virginia, Charlottesville, VA, USA

⁴Department of Surgery, Johns Hopkins University, Baltimore, MD, USA

Abstract

We hypothesized that percutaneous intervention in the affected lower extremity artery would improve calf muscle perfusion and cellular metabolism in patients with claudication and peripheral artery disease (PAD) as measured by magnetic resonance imaging (MRI) and spectroscopy (MRS). Ten patients with symptomatic PAD (mean $\pm$ SD: age 57 ± 9 years; ankle-brachial index (ABI) 0.62 ± 0.17 ; seven males) were studied 2 months before and 10 months after lower extremity percutaneous intervention. Calf muscle phosphocreatine recovery time constant (PCr) in the revascularized leg was measured by ³¹P MRS immediately after symptom-limited exercise on a 1.5-T scanner. Calf muscle perfusion was measured using first-pass gadolinium-enhanced MRI at peak exercise. A 6-minute walk and treadmill test were performed. The PCr recovery time constant improved significantly following intervention (91 ± 33 s to 52 ± 34 s, $p < 0.003$). Rest ABI also improved (0.62 ± 0.17 to 0.93 ± 0.25 , $p < 0.003$). There was no difference in MRI-measured tissue perfusion or exercise parameters, although the study was underpowered for these endpoints. In conclusion, in this pilot study, successful large vessel percutaneous intervention in patients with symptomatic claudication, results in improved ABI and calf muscle phosphocreatine recovery kinetics.

Keywords

calf muscle; cardiovascular magnetic resonance; lower extremity percutaneous revascularization; perfusion; peripheral artery disease; phosphocreatine recovery

© The Author(s) 2012

Corresponding author: Christopher M Kramer, Departments of Medicine and Radiology, University of Virginia Health System, Lee Street, Box 800170, Charlottesville, VA 22908, USA, ckramer@virginia.edu.

Conflict of interest

Drs Epstein, Meyer, Hagspiel, Berr and Kramer receive research support from Siemens Healthcare.

Introduction

Peripheral artery disease (PAD) is associated with a decrease in a patient's functional capacity at diagnosis with a further decline over time.¹ Reductions in arterial blood flow clearly do not explain the entire pathophysiology underlying claudication and exercise limitation in PAD. Indeed, invasive arterial monitoring during rest and exercise in patients with PAD found no association between exercise parameters and leg blood flow.² The repetitive cycles of ischemia and reperfusion which occur during exercise appear to mediate a myopathy with changes in skeletal muscle structure and mitochondrial function.³

Previous work from our group⁴ demonstrated that blood flow is not the sole determinant of functional status in PAD as calf muscle energetics also play an important role. Evidence of dysfunctional calf muscle mitochondrial metabolism can be measured as abnormal post-exercise phosphocreatine recovery kinetics with magnetic resonance spectroscopy (MRS) in patients with PAD and correlates with ankle-brachial index (ABI).⁵ Abnormal mitochondrial function is independent of calf muscle tissue perfusion measured with magnetic resonance imaging (MRI), but both correlate with impaired exercise capacity.⁴ This suggests that abnormal calf muscle mitochondrial function impacts exercise performance; however, it is uncoupled from local microvascular tissue perfusion.

The ABI is the traditional non-invasive measure of PAD and is related to walking distance; however, the ABI does not have a consistent relationship with maximum claudication distance.⁶ Furthermore, in a study of patients followed after lower extremity bypass surgery, there was an improvement in ABI to near normal levels, but functional measures such as walking distance improved only modestly.⁷ These studies support the concept that there is more to patients' functional limitations in PAD than simply a reduction in lower extremity blood flow.

Over a quarter of a million lower extremity revascularization procedures are performed annually in the United States⁸ but the mechanisms of benefit and downstream consequences are incompletely understood. In the present study, we aimed to study the effects of revascularization on calf muscle perfusion, phosphocreatine recovery kinetics and exercise capacity.

Methods

Study design

Patients between the ages of 30 and 85 years with symptoms of intermittent claudication and an ABI between 0.4 and 0.9, based on vascular lab testing done during the screening period, and scheduled for lower extremity percutaneous arterial intervention were eligible for inclusion. Exclusion criteria included rest pain, critical limb ischemia, contraindication to MRI/MRS, pregnancy and co-morbidities that severely limited patients' ability to perform a walking treadmill test. Patients provided written informed consent prior to study enrollment. The study protocol was approved by the Human Investigation Committee at the University of Virginia.

Study protocol

As previously described,⁴ the study was divided over 2 days to allow sufficient time between exercise portions of the protocol to avoid fatigue and ischemic pre-conditioning. A total of 87 patients were screened over a 1-year period and of these 10 were subsequently scheduled for a clinically ordered lower extremity percutaneous revascularization. Patients were admitted overnight to the General Clinical Research Center. Owing to imaging time constraints, only the most symptomatic and therefore treated leg was studied by MRI/MRS.

Patients were studied at baseline and a goal of 1 year after revascularization to allow sufficient time for any improvements to occur.

Magnetic resonance protocols

MRI protocols were completed on an Avanto 1.5-T scanner and MRS protocols on a Sonata 1.5-T scanner (both Siemens Healthcare, Erlangen, Germany) as MRS hardware and software was only available on the latter. Calf muscle perfusion was measured immediately after plantar flexion exercise at a rate of 10–12 rpm using a magnetic resonance-compatible foot pedal ergometer affixed to the MR table with first-pass gadolinium-enhanced imaging with contrast injected at peak exercise and images immediately obtained throughout recovery.⁹ Patients performed the plantar flexion exercise until limiting claudication or fatigue, and work expenditure was recorded. Time intensity curves were generated with Argus software (Siemens Healthcare, Princeton, NJ, USA) for a region of interest in the calf muscle area with the greatest increase in signal intensity and the corresponding artery (typically the popliteal). The slope of the time intensity curve in the calf muscle defined tissue perfusion. The arterial input was calculated from the slope of the time intensity curve in the popliteal artery. The tissue perfusion index was measured by dividing the tissue perfusion by the arterial input in order to measure local calf microvascular blood flow⁹ (Figure 1). The tissue perfusion index is a measure of local calf muscle microvascular blood flow as it is indexed to the nearby arterial input.

Phosphocreatine concentration in the calf muscle was measured as previously described⁵ by phosphorus-31 MRS immediately following peak exercise. Patients performed a symptom-limited plantar flexion exercise using a pedal ergometer while supine in the MR scanner until severe claudication or fatigue. The duration of exercise was recorded. The phosphocreatine recovery time constant (PCr) was then calculated as previously described⁵ (Figure 2). Magnetic resonance angiography (MRA) was performed with a moving table/bolus chase technique in three stations from the abdominal aorta to the foot, following intravenous infusion of gadopentetate dimeglumine (0.2 mmol/kg). Stenosis grading for the contrast-enhanced MRA was performed by two experienced observers by visual consensus using the MRA index¹⁰ and MRA run-off resistance,¹¹ as previously described.⁴ For reference, normal values for the MRA index and run-off resistance are: MRA index = 0 and run-off resistance index = 4. Values from normal subjects for the perfusion index⁹ = 0.69 ± 0.17 and for PCr⁵ = 35 ± 16 s.

Exercise testing

Subjects exercised until symptom-limited claudication, exhaustion or completion of study protocol for a 6-minute walk. The 6-minute walk protocol involved patients walking up and down a 100-foot (30.5 m) corridor for 6 minutes. The total walking distance and initial claudication distance were recorded. The standardized graded Skinner–Gardner exercise treadmill test was stopped when patients developed severe claudication, exhaustion or completion time of 20 minutes.¹² The total treadmill exercise time, time to initial claudication, symptom-limited maximal oxygen consumption (VO_2), and pre/post-exercise ABI were measured during the treadmill test as previously described.⁴ Metabolic measurements for VO_2 calculation were collected using standard open circuit spirometry (Viasys 229; Yorba Linda, CA, USA).

Statistical analysis

Primary outcomes were changes in perfusion index and phosphocreatine recovery time constant before and after intervention. The MRA parameters (index and run-off resistance) and exercise performance were secondary outcomes. All patients' baseline characteristics were presented as mean $\pm$ SD for continuous variables and n (%) for categorical variables.

Student's paired *t*-test was used to compare changes before and after revascularization. Linear regression analysis was used to compare changes in the PCr recovery time constant with changes in ABI. A *p*-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics 18, release version 18.0.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients

The baseline patient characteristics for the study are presented in Table 1. Patients were evaluated a mean of 62 ± 74 days before and 317 ± 98 days after study leg percutaneous intervention. The percutaneous lower extremity interventions included nine stent placements (iliac artery ($n = 5$), superficial femoral artery ($n = 3$), distal aorta ($n = 1$)) and one superficial femoral artery angioplasty.

MRI/MRS results

There was no difference in perfusion index before and after revascularization, from 0.52 ± 0.18 to 0.57 ± 0.17 , $p = \text{NS}$. The mean per patient change score for perfusion index was 0.05 ± 0.29 . The work expended during the plantar flexion exercise for calf muscle perfusion was similar before and after revascularization, 176 ± 76 J to 155 ± 62 J, $p = \text{NS}$. For the exercise prior to ^{31}P spectroscopy, there was a trend towards an improvement in time spent using the pedal ergometer: 157 ± 51 s to 332 ± 321 s, $p < 0.09$. Despite this trend towards longer exercise time, there was a reduction in the PCr recovery time constant with revascularization, from 91 ± 33 s to 52 ± 34 s, $p < 0.003$. However, it did not return to levels seen in normal subjects (normal PCr recovery time constant = 35 ± 16 s).⁵ The change score for the PCr recovery time constant was 39 ± 30 S.

MRA at follow-up demonstrated patency of all stented and angioplastied segments, although the degree of stenosis within the stent could not be visualized in all patients due to stent-induced susceptibility artifact. In order to assess progression of disease in other vascular beds, the segments treated with stents were excluded from calculation of the MRA index and MRA run-off resistance index. Neither MRA parameter showed a significant change over time (MRA index: 0.44 ± 0.60 to 0.51 ± 0.76 , $p = \text{NS}$; MRA runoff resistance index: 9.5 ± 6.1 to 9.3 ± 5.7 , $p = \text{NS}$). The change scores for MRA index and MRA run-off resistance were 0.09 ± 0.35 and 0.2 ± 2.9 .

Functional testing

Results are reported in Table 2. The resting ABI improved after revascularization (from 0.62 ± 0.17 to 0.93 ± 0.25 , $p < 0.003$). Likewise, the post-exercise ABI increased with revascularization (from 0.33 ± 0.15 to 0.67 ± 0.37 , $p < 0.02$). However, there was no change in total treadmill exercise time, 6-minute walk distance or peak exercise VO_2 . Similarly, there was no difference in the time of claudication onset using the treadmill test (321 ± 200 s to 340 ± 243 s, $p = \text{NS}$). However, there was a trend towards an improvement in the distance until onset of claudication during the 6-minute walk (466 ± 250 feet to 731 ± 426 feet, 142 ± 76 m to 223 ± 130 m, $p = 0.10$). When the ABI in the contralateral leg (excluding the one patient with distal aortic stent) was evaluated over time, there was no change (0.87 ± 0.22 to 0.79 ± 0.27 , $p = \text{NS}$).

There was no correlation seen between change in the PCr recovery time constant and ABI after intervention, $p = 0.9$. Likewise, there was no correlation seen between change in the PCr recovery time constant and post-exercise ABI after intervention, $p = 0.6$.

Discussion

This study examined a group of 10 patients with PAD before and after percutaneous lower extremity revascularization. We used a combination of MRI and MRS techniques and exercise studies to comprehensively evaluate functional changes before and after revascularization. Percutaneous lower extremity revascularization in PAD patients with progressive intermittent claudication symptoms was effective at improving calf muscle phosphocreatine recovery kinetics, suggesting an improvement in mitochondrial function. Both rest and exercise ABI improved with revascularization. Neither peak exercise tissue perfusion nor exercise parameters improved, although the study was underpowered for these endpoints.

The improvement in post-exercise calf muscle phosphocreatine recovery kinetics may result from several factors. Prior work from our group⁴ demonstrated that calf muscle tissue perfusion and phosphocreatine recovery kinetics are uncoupled from each other although both correlate with traditional exercise parameters. This suggests that other factors must impact calf muscle phosphocreatine recovery kinetics independent of local tissue perfusion. Perfusion index by MRI measures tissue blood flow in the calf corrected for arterial inflow, thereby measuring microvascular perfusion. With large vessel revascularization, bulk blood flow to the calf improves, which may enhance endothelial function and/or nitric oxide production that could impact the post-exercise phosphocreatine recovery time constant. Despite this, perfusion at the microvascular level may remain depressed.

The trend towards improvement in distance to onset of claudication with the 6-minute walk suggests a relationship with PCr recovery kinetics; however, it is not known if this is a causal relationship. The study was underpowered to detect an improvement in calf muscle perfusion. We may be able to detect a change in perfusion with larger patient numbers or alternative methods to evaluate calf muscle blood flow such as direct quantification with arterial spin labeling MRI.

Similar to prior studies, the improvement in ABI to near normal range with revascularization did not translate into an equal improvement in exercise capacity.⁷ In our study, the lack of improvement in functional capacity may be in part because only one leg was treated and PAD is typically a bilateral disease. However, there was no change in the contralateral leg ABI over the study. There was a trend towards an improvement in the distance until onset of claudication during the 6-minute walk. It may be that changes in PCr recovery kinetics are necessary for improvements in low-intensity exercise. With larger patient numbers we would anticipate greater power to detect changes in exercise parameters with percutaneous revascularization.

There is evidence of a skeletal muscle myopathy in PAD based on both histologic and biochemical abnormalities. Using light microscopy, skeletal muscle samples from PAD patients demonstrate myopathic changes which correlate with the extent of disease,¹³ and electron microscopy further delineated abnormal mitochondrial structure.¹⁴ In addition, there is biochemical evidence of abnormal mitochondrial oxidation of carbohydrates¹⁵ and impaired acylcarnitine metabolism¹⁶ in patients with PAD.

Our lab and others have demonstrated the utility of ³¹P magnetic resonance spectroscopy in the non-invasive evaluation of skeletal muscle metabolism in PAD.^{5,17} However, there are limited data regarding changes in cellular energetics for patients treated with medical therapy or revascularization in PAD. We have shown that low-density lipoprotein (LDL) lowering does not improve PCr recovery kinetics in a similar patient population.¹⁸ Zatina et al.¹⁹ found that an improvement in calf muscle phosphocreatine kinetics did not occur until several months after successful lower extremity bypass surgery. Similar to the present study,

Schunk et al.²⁰ found an improvement in PCr recovery kinetics in 31 patients with PAD who underwent percutaneous transluminal angioplasty (PTA) or vascular surgery. Further studies are needed to elucidate the mechanism of improvement in PCr recovery kinetics with revascularization.

The clinical factors which predict improvement in walking distance after percutaneous revascularization were studied by Afaq et al.²¹ as a reported history of walking after the procedure and prior coronary artery bypass surgery. However, almost half of the study patients were lost to follow-up and as a result the clinical predictors of exercise ability after revascularization need additional prospective evaluation.

The study by Zeller et al. shows changes in ABI similar to those seen in our study²² wherein patients treated with femoropopliteal artery stenting had an improvement in resting ABI from 0.63 ± 0.20 to 0.94 ± 0.17 as well as post-exercise testing (0.44 ± 0.23 to 0.85 ± 0.21 , $p < 0.001$ for both). Although the ABI is used as a clinical marker of lower extremity blood flow, we did not observe an improvement in calf muscle perfusion measured by MRI. However, a recent study by Duerschmied et al.²³ used contrast ultrasound calf muscle perfusion imaging in patients at baseline and 3–5 months post-intervention, with an improvement in both ABI (0.60 to 0.85 , $p = 0.001$) and time-to-peak contrast enhancement (45 s to 24 s, $p = 0.015$). One of the challenges in using time-to-peak measurements is the inherent influence by volume status and hemodynamic function that may vary over time. Future studies comparing ultrasound and MRI methods to determine tissue perfusion appear warranted.

Measuring calf muscle perfusion with MRI using the technique developed by our group⁹ identifies peak exercise microvascular calf blood flow by indexing the local tissue perfusion indexed to the nearby arterial input. It is possible that by increasing bulk flow to the calf with proximal revascularization that our technique is not sensitive enough to measure the change in microvascular blood flow. Other techniques such as arterial spin labeling MRI allow for quantification of calf muscle blood flow without the use of exogenous contrast^{24,25} and may offer additional insight into changes in calf muscle perfusion. Alternatively, calf muscle microvascular blood flow may not significantly improve with revascularization. The post-exercise ABI in our study improved; however, it did not return to normal levels, suggesting that post-exercise calf blood flow remains impaired despite the proximal revascularization.

Limitations

The primary limitation of the study is the small sample size. This was a pilot study of 10 individuals scheduled for percutaneous lower extremity revascularization out of a larger cohort of 87 patients with PAD. This study is underpowered to examine the benefit of percutaneous revascularization on exercise measures and perfusion index. However, other larger studies have shown that there is an initial improvement in exercise capacity in patients treated with lower extremity percutaneous revascularization.^{21,22} It may take longer than 10 months for microvascular perfusion to improve. Another limitation is the lack of an untreated control group.

Given time constraints, we studied only the most symptomatic leg, which was scheduled for clinically indicated percutaneous revascularization, for calf muscle perfusion and energetics. However, exercise parameters are influenced by disease in both legs. Certainly some patients may have progression of their peripheral artery atherosclerosis in the non-intervened leg, which would impair their overall functional capacity. However, we did not find a significant decline in the contralateral ABI. We could not rule out instant stenosis in some cases due to stent-induced susceptibility artifact; however, rest ABI post-intervention was

higher in all subjects than at baseline, making significant in-stent restenosis unlikely. When we excluded the intervened upon segments from the MRA calculations, both at baseline and post-revascularization, there was no change in the other vascular territories. We did not measure the extent of collateral blood vessels seen on MRA, which could affect the relationship between macrovascular stenosis and calf muscle measures of perfusion and metabolism.

Conclusions

In patients with symptomatic PAD, treatment with percutaneous lower extremity revascularization improves calf muscle phosphocreatine recovery kinetics and ankle–brachial indices measured at rest and after exercise. Calf muscle tissue perfusion was unchanged, suggesting uncoupling of calf muscle perfusion and phosphocreatine recovery kinetics. However, the study was underpowered for the perfusion endpoint. Larger studies are needed to confirm our findings. With greater patient numbers, we may be able to show improvement in exercise capacity along with a change in the calf muscle phosphocreatine recovery time constant. Given the uncoupling of calf muscle perfusion and phosphocreatine recovery kinetics, new therapies aimed at improving tissue perfusion in PAD are needed. The MRI/MRS endpoints used in the present study may prove useful in future clinical trials comparing the benefits of established and novel therapies in PAD.

Acknowledgments

We would like to acknowledge the contributions of Jayne Missel RN, and the University of Virginia Vascular Lab.

Funding

Supported by National Heart, Lung, and Blood Institute R01 HL075792 (CMK), and National Institute of Biomedical Imaging and Bioengineering T32 EB003841 (JDA, AMW).

References

1. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004; 292:453–461. [PubMed: 15280343]
2. Pernow B, Zetterquist S. Metabolic evaluation of the leg blood flow in claudicating patients with arterial obstruction at different levels. *Scand J Clin Lab Invest*. 1968; 21:277–287. [PubMed: 5708696]
3. Pipinos II, Judge AR, Selsby JT, et al. The myopathy of peripheral arterial occlusive disease: Part I. Functional and histomorphologic changes and evidence for mitochondrial dysfunction. *Vasc Endovasc Surg*. 2008; 42:481–489.
4. Anderson JD, Epstein FH, Meyer CH, et al. Multifactorial determinants of functional capacity in peripheral arterial disease: uncoupling of calf muscle perfusion and metabolism. *J Am Coll Cardiol*. 2009; 54:628–635. [PubMed: 19660694]
5. Isbell DC, Berr SS, Toledano AY, et al. Delayed calf muscle phosphocreatine recovery after exercise identifies peripheral arterial disease. *J Am Coll Cardiol*. 2006; 47:2289–2297. [PubMed: 16750698]
6. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Prediction of claudication pain from clinical measurements obtained at rest. *Med Sci Sports Exerc*. 1992; 4:163–170. [PubMed: 1549004]
7. Gardner AW, Killewich LA. Lack of functional benefits following infra-inguinal bypass in peripheral arterial occlusive disease patients. *Vasc Med*. 2001; 6:9–14. [PubMed: 11358164]
8. Goodney PP, Beck AW, Nagle J, Welch HG, Zwolak RM. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. *J Vasc Surg*. 2009; 50:54–60. [PubMed: 19481407]

9. Isbell DC, Epstein FH, Zhong X, et al. Calf muscle perfusion at peak exercise in peripheral arterial disease: measurement by first pass contrast-enhanced magnetic resonance imaging. *J Magn Reson Imaging*. 2007; 25:1013–1020. [PubMed: 17410566]
10. Ouwendijk R, de Vries M, Pattynama PMT, et al. Imaging peripheral arterial disease: a randomized controlled trial comparing contrast-enhanced MR angiography and multi-detector row CT angiography. *Radiology*. 2005; 236:1094–1103. [PubMed: 16020559]
11. Peterkin GA, Manabe S, LaMorte WW, Menzoian JO. Evaluation of a proposed standard reporting system for preoperative angiograms in infrainguinal bypass procedures: angiographic correlates of measured runoff resistance. *J Vasc Surg*. 1988; 7:379–385. [PubMed: 3346951]
12. Haskell, W.; Durstine, J. Coronary heart disease. In: Skinner, J., editor. *Exercise testing and exercise prescription for special cases*. Philadelphia, PA: Lea & Febiger; 1993. p. 251-274.
13. Hedberg B, Angquist KA, Sjostrom M. Peripheral arterial insufficiency and the fine structure of the gastrocnemius muscle. *Int Angiol*. 1998; 7:50–59. [PubMed: 3385269]
14. Marbini A, Gemignani F, Scoditti U, Rustichelli P, Bragaglia MM, Govoni E. Abnormal muscle mitochondria in ischemic claudication. *Acta Neurol Belg*. 1986; 86:304–310. [PubMed: 3811830]
15. Hou XY, Green S, Askew CD, Barker G, Green A, Walker PJ. Skeletal muscle mitochondrial ATP production rate and walking performance in peripheral arterial disease. *Clin Physiol Funct Imaging*. 2002; 22:226–232. [PubMed: 12076351]
16. Hiatt WR, Wolfel EE, Regensteiner JG, Brass EP. Skeletal muscle carnitine metabolism in patients with unilateral peripheral arterial disease. *J Appl Physiol*. 1992; 73:346–353. [PubMed: 1506390]
17. Pipinos I, Shepard AD, Anagnostopoulos PV, Katsamouris A, Boska MD. Phosphorus 31 nuclear magnetic resonance spectroscopy suggests a mitochondrial defect in claudicating skeletal muscle. *J Vasc Surg*. 2000; 31:944–952. [PubMed: 10805885]
18. West AM, Anderson JD, Epstein FH, et al. LDL lowering does not improve calf muscle perfusion, energetic or exercise performance in peripheral arterial disease. *J Am Coll Cardiol*. 2011; 58:1068–1076. [PubMed: 21867844]
19. Zatina MA, Berkowitz HD, Gross GM, Maris JM, Chance B. ³¹P nuclear magnetic resonance spectroscopy: noninvasive biochemical analysis of the ischemic extremity. *J Vasc Surg*. 1986; 3:411–420. [PubMed: 2936903]
20. Schunk K, Romaneehsen B, Rieker O, et al. Dynamic phosphorus-31 magnetic resonance spectroscopy in arterial occlusive disease: effects of vascular therapy on spectroscopic results. *Invest Radiol*. 1998; 33:329–335. [PubMed: 9647444]
21. Afaq A, Patel JH, Gardner AW, Hennebry TA. Predictors of change in walking distance in patients with peripheral arterial disease undergoing endovascular intervention. *Clin Cardiol*. 2009; 32:E7–E11. [PubMed: 19645033]
22. Zeller T, Saratzis N, Scheinert D, et al. Non-randomized, prospective, multi-centre evaluation of the ABSOLUTE 0.035 peripheral self-expanding stent system for occluded or stenotic superficial or proximal popliteal arteries (ASSESS trial) acute and 30 day results. *J Cardiovasc Surg*. 2007; 48:719–726. [PubMed: 17947929]
23. Duerschmied D, Maletzki P, Freund G, Olschewski M, Bode C, Hehrlein C. Success of arterial revascularization determined by contrast ultrasound muscle perfusion imaging. *J Vasc Surg*. 2010; 52:1531–1536. [PubMed: 20843628]
24. Chan-Wen W, Mohler E, Ratcliffe SJ, Wehrli FW, Detre JA, Floyd TF. Skeletal muscle microvascular flow in progressive peripheral arterial disease: assessment with continuous arterial spin-labeling perfusion magnetic resonance imaging. *J Am Coll Cardiol*. 2009; 53:2372–2377. [PubMed: 19539149]
25. West AM, Meyer CH, Epstein FH, et al. Arterial spin labeling MRI reproducibly measures peak-exercise calf muscle perfusion in peripheral arterial disease. *JACC Cardiovasc Imaging*. 2012 (in press).

Figure 1. Post-exercise calf muscle perfusion. First pass, contrast-enhanced calf muscle perfusion at baseline (A) and post-revascularization (B) in the same patient. Increased signal intensity is seen in the anterior tibialis (arrow) and soleus muscles (double arrow) at both time points (perfusion index: A = 0.35, B = 0.63).

Figure 2. Phosphocreatine recovery (PCr) plots at baseline (A) and post-revascularization (B) in a patient with PCr recovery time constants of 76 s and 35 s, respectively.

Table 1

Patient characteristics at enrollment

Characteristic	
Age, years	57 ± 9
Ankle-brachial index	0.62 ± 0.17
Body mass index	31 ± 9
Male sex (%)	7 (70)
Prior lower extremity revascularization	2 (20)
Involving study leg (%)	1 (10)
Race (%)	
White	6 (60)
Black	2 (20)
American Indian	2 (20)
Risk factors (%)	
Tobacco use	7 (70)
Diabetes mellitus	3 (30)
Hypertension	8 (80)
History of CAD	5 (50)
Hypercholesterolemia	8 (80)
Medications (%)	
Aspirin/clopidogrel	5 (50)
ACE-inhibitor	4 (40)
ARB	2 (20)
β-Blocker	1 (10)
Cilostazol	0 (0)

CAD, coronary artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin type-1 receptor blocker.

Table 2

Exercise parameters over time

	Pre-intervention	Post-intervention	Change score	<i>p</i> -value
Treadmill exercise time, s	579 ± 303	599 ± 310	18 ± 181	NS
Treadmill claudication time, s	321 ± 200	340 ± 243	17 ± 297	NS
Six-minute walk distance, feet	931 ± 256	1104 ± 242	173 ± 310	NS
Six-minute claudication distance, feet	466 ± 250	731 ± 426	245 ± 427	= 0.10
VO ₂ , ml/kg/min	11.6 ± 2.5	12.5 ± 3.1	0.7 ± 2.3	NS
Resting ABI	0.62 ± 0.17	0.93 ± 0.25	0.32 ± 0.23	< 0.003
Post-exercise ABI	0.33 ± 0.15	0.67 ± 0.37	0.33 ± 0.33	< 0.02
Contralateral leg ABI	0.87 ± 0.22	0.79 ± 0.27	0.06 ± 0.26	NS

ABI, ankle-brachial index.

Values are listed as mean ± SD.