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Diffferential effects of LDL Lowering on CMR measures of calf muscle perfusion and cellular metabolism in peripheral arterial disease

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Introduction

Evidence suggests lipid-lowering therapy may improve exercise performance in patients with peripheral arterial disease (PAD).

Purpose

We hypothesized that LDL reduction over two years would improve calf muscle perfusion and metabolism in PAD as measured by magnetic resonance imaging (CMR) and spectroscopy (MRS).

Methods

36 patients with mild-to-moderate symptomatic PAD (mean age 63 ± 11 years, ankle brachial index (ABI) 0.70 ± 0.14) were studied for two years after beginning lipid-lowering therapy. Statin-naïve patients were treated with simvastatin 40 mg or simvastatin 40 mg plus ezetimibe 10 mg and patients previously on a statin had ezetimbibe 10 mg added (total n = 36). Phosphocreatine recovery time constant (PCr) was measured using ^{31}P MRS at 1.5 T after symptom-limited calf muscle exercise. PCr was calculated using a monoexponential fit of phosphocreatine concentration versus time, beginning at peak exercise. Calf muscle perfusion (n = 28, excluding those with compromised renal function) was measured at 1.5 T with gadolinium (0.1 mM/kg) infused after patients used a pedal ergometer to exhaustion (Figure 1). Slope of the time intensity curve in the calf muscle region with the greatest signal intensity defined tissue perfusion and was divided by the arterial input slope to define perfusion index. Gadolinium enhanced MRA from the distal aorta to the foot was graded for location and degree of stenosis (MRA Index). Skinner-Gardner treadmill test with post-exercise ABI and 6 minute supervised walks were performed. Changes in parameters over time were compared by ANOVA.

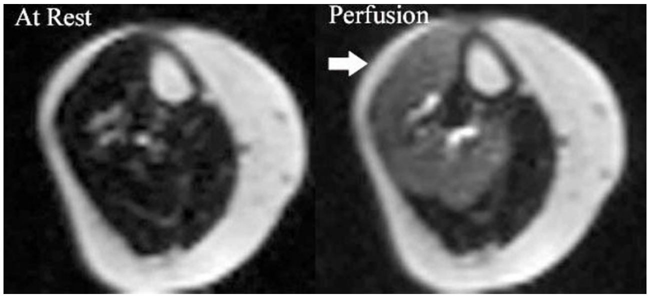

Figure 1
Left - prior to exercise. Right - first pass contrast-enhanced perfusion at peak exercise with increased signal in the anterior tibialis and soleus

Table 1: Changes in MRI, MRS and exercise parameters over time

	Baseline	One Year	Two Years	ANOVA p
Perfusion index	0.49 ± 0.18	0.57 ± 0.36	0.55 ± 0.46	0.96
PCr, sec	89.9 ± 64.8	76.4 ± 48.7	69.2 ± 55.0	0.07
MRA Index	0.78 ± 0.64	0.89 ± 0.76	0.89 ± 0.78	0.23
Treadmill exercise time, sec	548 ± 362	590 ± 370	536 ± 360	0.54
6 minute walk distance, ft	1075 ± 406	1176 ± 388	1131 ± 378	0.28
Post-exercise ABI	0.57	0.53	0.56	0.24

Results

In the group as a whole, LDL at baseline was 107 ± 34 mg/dl, decreasing at one year (77 ± 34, $p < 0.001$) while remaining stable (74 ± 27, p = ns) at two years. The total cholesterol at baseline was 178 ± 41 mg/dl, decreased significantly at one year (144 ± 38, $p < 0.001$) and was unchanged at two years at (142 ± 28, p = ns). Triglycerides and HDL were unchanged. There was a trend towards improvement in PCr. There was no significant change in perfusion index, MRA indices or exercise parameters over two years (see table 1). No between treatment group differences in MRI or MRS parameters were noted.

Conclusion

Lipid-lowering therapy was effective at lowering total and LDL cholesterol in patients with PAD. Despite this, neither tissue perfusion nor exercise parameters improved over 2 years. However, cellular metabolism trended towards improvement. Therefore, LDL lowering in PAD may improve calf muscle metabolism, but does not improve exercise performance or calf muscle perfusion.