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RESPONSE TO COMMENT ON PRIOR ET AL.

Increased Skeletal Muscle Capillarization Independently Enhances Insulin Sensitivity in Older Adults After Exercise Training and Detraining. Diabetes 2015;64:3386–3395

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We thank Dr. Montero for his insightful comment (1) on our recent article (2). His comment raises two interesting questions regarding the finding that increases in skeletal muscle capillary density (CD) contribute to exercise training–induced increases in insulin sensitivity (M/I).

First, we address the question of whether the increases in HDL cholesterol (HDL-C) might affect the correlation between CD and M/I by presenting additional analyses. At each time point (baseline, 6-month exercise, and 2-week detraining), we found a moderate correlation between HDL-C levels and M/I (r = 0.37–0.47), but these did not reach statistical significance. We then incorporated the change in HDL-C (detraining − baseline) into our regression model as an additional variable predicting the change in M/I. We found only a weak relationship between the changes in HDL-C and M/I ($r = -0.26$, P = NS); however, the addition of HDL-C strengthened the overall model ($r = 0.90$, $P = 0.02$) and the partial correlation between the changes in CD and M/I ($r = 0.80$, $P = 0.01$). Thus, even after accounting for the variance in M/I attributable to changes in HDL-C, the strong, independent relationship between the increases in CD and M/I was maintained.

The second question is whether changes in interstitial space influenced our measurement of CD and whether different metrics of capillarization would yield similar results. While weight loss may reduce interstitial space (3), it is not clear whether the same occurs after exercise training or whether this affects M/I. Regardless, changes in interstitial space after exercise training or detraining did not affect CD in our study because individual fiber cross-sectional areas were measured and summed to derive the area used in the calculation of CD, exclusive of interstitial space. We did calculate capillary-to-fiber ratio (C:Fi) and capillary-to-fiber perimeter exchange index (CFPE), but we did not include these in the original article, primarily to avoid redundancy. Compared with baseline, C:Fi increased after 6-month exercise and the increase was maintained after detraining (1.42 ± 0.10 vs. 1.63 ± 0.10 vs. 1.61 ± 0.09 capillaries per fiber, respectively; $P < 0.05$) and CFPE similarly increased (5.08 ± 0.21 vs. 5.53 ± 0.19 vs. 5.67 ± 0.18 capillaries per mm fiber perimeter, respectively; $P < 0.05$). The increases in CFPE and M/I correlated ($r = 0.69$, $P < 0.05$); however, the correlation of C:Fi with M/I was weaker ($r = 0.42$) and did not reach statistical significance. This finding was not unexpected. Metrics accounting for fiber area or perimeter such as CD or CFPE may be more useful for predicting metabolic outcomes involving substrate flux into muscle. While C:Fi does indicate the number of capillaries around each muscle fiber, it does not account for the area perfused by those capillaries. This could, in part, explain

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the lack of relationship between C:Fi and M/I reported by Hedman et al. (4); however, it is difficult to directly compare our results to those of Hedman et al. as different insulin stimuli were used and M/I is expressed in different units.

We appreciate this opportunity to provide clarity and additional data in support of our finding that exercise training–induced increases in skeletal muscle capillarization independently contribute to increases in insulin sensitivity in older adults.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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