Supplemental Methods

Randomization and Blinding
Allocation concealment for enrollment of animals in TAC vs Sham surgical protocol for the next experimental phase of miRNA vs sham PBS delivery was implemented by having different laboratory staff other than surgeon randomize selection of post-surgical animals for division into the 2nd surgical protocol. Wherever possible tissue was provided to laboratory staff in a blinded manner and data was un-blinded by a different individual than who performed the assay.

Sample size and power calculations
Samples sizes within experimental groups (n) were determined by the necessary statistical power to obtain significance (5%) based on variability in previous studies. An additional 10% is added to the required experimental group number of animals to account for experimental loss during non-survival surgical procedures. Power calculation was performed using a downloadable tool (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).

Justification for the Use of Male patients/rodents
Published data indicates that hearts from male and female patients respond differently to both cardiac hypertrophy and the development of heart failure[1]. Additionally, the hypothesis that anaplerosis is a key mechanism in the maladaptive response to cardiac hypertrophy was originally identified in male rats and therefore we are following an established precedent[2]. Future study will work to expand our understanding of sex effects on the results observed in this study.

References

1. Kadkhodayan A, Lin CH, Coggan AR, Kisrieve-Ware Z, Schechtman KB, Novak E, Joseph SM, Davila-Roman VG, Gropler RJ, Dence, and Peterson LR. Sex affects mycardial blood flow and fatty acid substrate metabolism in humans with nonischemic heart failure. *J Nucl Cardiol*. 2017;24:1226-1235.

2. Sorokina N, O'Donnell JM, McKinney RD, Pound KM, Woldegiorgis G, LaNoue KF, Ballal K, Taegtmeyer H, Buttrick PM, and Lewandowski ED. Recruitment of compensatory pathways to sustain oxidative flux with reduced carnitine palmitoyltransferase I activity characterizes inefficiency in energy metabolism in hypertrophied hearts. 2007;115:2033-41.