PPARβ/δ activation in adult hearts facilitates mitochondrial function and cardiac performance under pressure-overload condition

Jian Liu1,1, Peiyong Wang1,2,1, Jinwen Luo1,3, Yao Huang4, Lan He1, Huan Yang1,3, Qingbao Li1,5, Sijie Wu1,3, Olga Zhelyabovska1, and Qinglin Yang1,1

1Department of Nutrition Sciences, University of Alabama at Birmingham, 1675 University Blvd, Birmingham, AL 35294-3360
2Department of Pathophysiology & High Altitude Physiology, Third Military Medical University, Chongqing 400038, China
3Department of Cardio-thoracic surgery, the second Xiangya Hospital, Central South University, Changsha, China
4Cardiovascular Research Institute, Morehouse School of Medicine, Atlanta, GA
5Cardiac Surgery Department, Provincial Hospital Affiliated to Shandong University 324, Jingwu Road, Jinan, Shandong, China

Abstract

Peroxisome proliferator-activated receptor β/δ (PPARβ/δ) is an essential transcription factor in myocardial metabolism. This study aims to investigate the effects of PPARβ/δ activation in the adult heart on mitochondrial biology and oxidative metabolism under normal and pressure-overload conditions. We have investigated the effects of cardiac constitutively active PPARβ/δ in adult mice using a tamoxifen inducible transgenic approach with Cre-LoxP recombination. The expression of PPARβ/δ mRNA and protein in cardiomyocytes of adult mice was substantially increased after short-term induction. In these mice, the cardiac expression of key factors involved in mitochondrial biogenesis, such as PPARγ coactivator-1, endogenous anti-oxidants Cu/Zn-Superoxide dismutase and catalase, fatty acid and glucose metabolism such as carnitine palmitoyltransferase Ib, II and glucose transporter 4, were upregulated. Subsequently, myocardial oxidative metabolism was elevated concomitant with an increased mitochondrial DNA copy number and an enhanced cardiac performance. Moreover, activation of PPARβ/δ in the adult heart improved cardiac function and resisted to progression pathological development in mechanical stress condition. We conclude that PPARβ/δ activation in the adult heart will promote cardiac performance along with transcriptional upregulation of mitochondrial biogenesis and defense, as well as oxidative metabolism at basal and pressure-overload conditions.

Keywords

PPARβ/δ; myocardial oxidative metabolism; anti-oxidants; mitochondrial biogenesis; cardiac function; pressure-overload; cardiac hypertrophy

*Correspondence should be addressed to Qinglin Yang, M.D., Ph.D., Associate Professor, Department of Nutrition Sciences, University of Alabama at Birmingham, 1675 University Blvd, Webb 435, Birmingham, AL 35294-3360, USA, Phone: 205-996-6022; Fax: 205-934-7049; qyang@uab.edu.
#These authors contribute equally to this work.

Disclosures: None.
Introduction

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors with three subtypes (PPARα, γ and PPARδ/β), which mediate ligand dependent transcriptional regulation.1-6 The three PPAR subtypes are differentially expressed in cardiomyocytes. The essential roles of PPARδ/β in the heart have been documented.4, 7, 8 Long-term, postnatal, cardiomyocyte-restricted PPARδ/β deletion in mice perturbs myocardial fatty acid oxidation (FAO) and leads to cardiac dysfunction, bioenergetic defect, cardiac hypertrophy and lipotoxic cardiomyopathy.4, 9 We have recently discovered that PPARδ/β is essential for the adult heart to maintain mitochondrial capacity and oxidative metabolism.10 However, little is known about the gain-of-function effects of PPARδ/β activation in the adult heart.

Cardiac metabolic disorders, mitochondrial dysfunction and oxidation stress in the heart are among the main pathological developments in patients with cardiac hypertrophy and heart failure. Mitochondrial biogenesis and the endogenous anti-oxidant defense are essential in maintaining mitochondrial function. Important determinants of mitochondrial biogenesis include PPARγ coactivator-1α and β (PGC-1α and β),11-15 nuclear respiratory factor 1 (NRF1) and NRF2s (NRF2a and b)11-15 and mitochondrial transcription factor A (TFAM).11 Evidence has been emerging that PPARδ/β may be an essential determinant of mitochondrial biogenesis and anti-oxidant defense.10, 16, 17 In the adult heart, PPARδ/β is required for the full expression of mitochondrial proteins.10, 7, 8 Moreover, many important endogenous anti-oxidants such as Cu/Zn-Superoxide dismutase (SOD1),18 Manganese superoxide dismutases (SOD2)16 and catalase19, 20 contain functional PPAR response elements (PPRE) in their promoter and are PPAR target genes in various cells. PPARδ/β is essential for the full expression of at least some of these key anti-oxidants in the adult heart.10 However, evidence of PPARδ/β activation facilitating mitochondrial biogenesis and anti-oxidant expression in the adult heart remains lacking. While PPARδ/β-selective ligands are under active clinical trial for treating metabolic syndrome, the clinical implication of PPARδ/β activation to cardiac structure/function remains elusive.

In the present study, we assess a conditional transgenic (TG) mouse model that a constitutively active PPARδ/β can be induced to express in cardiomyocytes of an adult mouse to elucidate how activation of PPARδ/β enhances mitochondrial capacities and cardiac performance under normal and pressure-overload conditions.

Methods and Materials

See online supplemental material at http://hyper.ahajournals.org.

Results

PPARδ/β activation in adult heart upregulates the expression of key proteins in fatty acid and glucose metabolism

As illustrated (Figure 1A), two VPD lines (line 1 and line 2) were established and the TMVPD heart from these two lines displayed ~2 and ~1.79 fold increases of the total PPARδ/β mRNA level with no significant change in PPARα and PPARγ mRNA levels compared with the TMCM heart (Figure 1B). In isolated cardiomyocytes from both lines of TMVPD, the abundance of VPD protein was about ~10 fold increased relative to the endogenous PPARδ/β protein, whereas the endogenous PPARδ/β level in the TMVPD hearts was similar to that of control hearts (TMCM) (Figure 1C). Cardiac expression of genes involved in FAO was significantly upregulated in TMVPD mice, including medium-,
long-, and very long-chain acyl-CoA dehydrogenase (ACADM; ACADL; and ACADvl, respectively), malonyl CoA Decarboxylase (MCD), Acyl-CoA oxidase 1 (ACOX1), carnitine palmitoyltransferase Ib (CPTIb), CPT-II, uncoupling protein (UCP) 2 and 3 (Figure 2A). Moreover, transcripts encoding important fatty acid uptake proteins such as CD36 and fatty acid transporting protein-1 (FATP-1) and acyl-CoA synthetase (ACS) were also upregulated in TMVPD hearts (Figure 2A). Genes involved in glucose metabolism including glucose transporters Glut1, Glut4, and phosphofructokinase (PFK) were upregulated (Figure 2A). Western blot analyses revealed that protein expression of CPT-Ib, CPTII and ACADM were correspondingly elevated in TMVPD compared with TMCM hearts (Figure 2B). Protein expression of GLUT4 was slightly upregulated in TMVPD vs TMCM hearts (Figure 2B).

**PPARβ/δ activation in adult heart enhances mitochondrial biogenesis and mitochondrial defense**

We investigate whether PPARβ/δ is a key determinant of oxidative metabolism by upregulate mitochondrial biogenesis. Transcripts of NRF-1, NRF-2a, NRF2b and PGC-1α, but not PGC-1β and TFAM, were increased in the TMVPD hearts compared with controls (Figure 3A). TMVPD hearts showed correspondingly elevated protein levels of PGC-1α, NRF-1, and NRF-2a (Figure 3B). The transcript expression of mitochondrial proteins, such as Cytochrome c oxidase subunit 2 (COX II), COXIV, COX7c, Cytochrome b5 (Cyt b), mitofusin (mfn)1, mfn2 and profission dynamin related protein 1 (DRP1) were also upregulated. The expression of Optic-nerve atrophy 1 (Opa1), cytochrome c1 (Cyt c) and mitochondrial fission 1 protein (Fis1) was not changed (Figure 3C). The mtDNA copy number was increased in TMVPD hearts (Figure 3D). TEM assessment further confirmed the elevated mitochondrial volume in TMVPD vs TMCM hearts (Figure 3E). Real time PCR revealed that the transcript levels of SOD1, SOD2, and catalase were significantly elevated in TMVPD compared with that of TMCM hearts (Figure 4A). Western blot analyses confirmed that protein level of SOD1 was increased by about 50% in TMVPD relative to TMCM hearts (Figure 4B). Protein expression of catalase was also upregulated by ~75% in TMVPD hearts relative to TMCM hearts, whereas SOD2 protein was not changed (Figure 4B). Together, these results demonstrate that PPARβ/δ is a key determinant of redox homeostasis of the heart.

**PPARβ/δ activation in adult heart enhances cardiac performance and upregulates myocardial oxidative metabolism**

We further assessed the rates of myocardial palmitate and glucose oxidation in isolated working heart preparation. Both palmitate and glucose oxidation rates were significantly increased in TMVPD compared with TMCM hearts (Figure 5A and B) with augmented O2 consumption (Figure 5C). Myocardial glycogen content was markedly reduced in TMVPD hearts (Figure 5D) with elevated activity of pyruvate dehydrogenase complex (PDC) (Figure 5E). Interestingly, TMVPD hearts showed a reduced AMPK activity (Figure 5F). Isolated working heart study revealed that TMVPD hearts exhibited enhanced performance with greater maximal and minimal dP/dt, as well as contractility index (CI) than those of TMCM hearts at basal condition (Table 1).

**PPARβ/δ activation in adult heart protect against mechanical stress induced by pressure-overload**

TMVPD mice at 14 days post induction were subjected to TAC-induced left ventricular pressure-overload for 4 weeks. No difference in heart weight to body weight ratio, as well as the expression of molecular marker of cardiac hypertrophy (ie., Nppa and Nppb) could be detected between TAC-TMVPD and TAC-TMCM hearts (Figure 6A and B), whereas the mtDNA copy number remained higher in TAC-TMVPD than in TAC-TMCM hearts (Figure...
Echocardiography assessment revealed that TMVPD hearts exhibited comparable LV mass (Table 2) to TMCM hearts. However, TAC-TMCM hearts with substantially increased endocardial area at both diastolic and systolic phases were more dilated than TAC-TMVPD hearts (Table 2). As a result, TAC-TMCM hearts showed markedly depressed ejection fraction compared with TAC-TMVPD hearts (Table 2). In heart sections stained with H&E, cardiomyocyte in TAC-TMVPD hearts appeared to be less intense nuclear staining than those of TAC-TMCM hearts (Figure 6D). Heart sections stained with Trichrome blue revealed less pronounced fibrosis in TAC-TMVPD than in TAC-TMCM hearts (Figure 6D). TEM assessment revealed relatively normal mitochondrial structure in TAC-TMVPD heart sections, compared with abnormal ultrastructure such as swelling and loss of matrix in TAC-TMCM heart sections (Figure 6E). Therefore, these results implicate that the PPARβ/δ activation should post beneficial effects on hearts under pathological stress.

Discussion

The results of this study provide clear evidence that PPARβ/δ activation in the adult heart of an intact mouse facilitates mitochondrial oxidative metabolism and cardiac performance, yet avoiding oxidative damages.

The heart is an energy-demanding organ with active oxidative metabolism. Mitochondria play a pivotal role in oxidative metabolism. Accumulated evidence illustrates the importance of PPARβ/δ in regulating FAO in various tissues. However, it is not clear whether PPARβ/δ also regulates oxidative metabolism as a whole. Recently, the potential role of PPARβ/δ in mitochondrial biogenesis has been emerging. TG mice with VPD overexpression in skeletal muscle show signs of augmented mitochondrial biogenesis. Furthermore, we have demonstrated recently that PPARβ/δ is required in the adult heart to maintain normal mitochondrial biogenesis and function. However, a direct link of PPARβ/δ activation with mitochondrial biogenesis in the normal adult heart has not been established. The present study clearly demonstrated that a short-term induced hyper-expression of the constitutively active PPARβ/δ triggers modest mitochondrial biogenesis in the adult hearts. Since this short-term expression of the activated PPARβ/δ was not associated with overt cardiac dysfunction and cardiac pathology, it is not likely that the observed mitochondrial biogenesis is a part of the secondary response to hypertrophic growth signal. It is also noted that the degree of increased mitochondrial biogenesis in TMVPD hearts is not excessive to trigger pathological changes as those seen in PGC-1α overexpression hearts. Since PGC-1 is a known target gene of PPARβ/δ, it is plausible that PPARβ/δ activation directly upregulates PGC-1 to induce mitochondrial biogenesis. Therefore, PPARβ/δ appears to stimulate the mitochondrial gene expression by activating the PGC-1/NRF-1 regulatory pathway.

It is well known that reactive oxygen species (ROS), mediators of the oxidative stress, exert deleterious effects on myocardium. A role of PPARα and PPARγ in the transcriptional regulation of endogenous antioxidants such as SOD1, SOD2 and catalase has been reported and the promoters of all three of these antioxidants contain functioning PPAR response elements. A recent report demonstrated that PPARβ/δ activation protects H9C2 cardiomyoblasts from oxidative stress-induced apoptosis by inducing catalase expression. However, it is not clear if any of the above anti-oxidants are regulated by PPARβ/δ activation in the adult heart of an intact animal. The present study provides strong evidence supporting the in vivo role of PPARβ/δ as other PPAR family members in regulating cardiac expression of anti-oxidants, which may protect the heart from oxidative damage due to upregulated FAO. As a result, TMVPD hearts did not display elevated ROS and oxidative stress (data not shown), in which ROS could have been elevated with augmented constitutive oxidative metabolism.
As expected, hyperexpression of the constitutively active PPARβ/δ upregulated key factors of FAO and the actual myocardial FAO rate. Glucose oxidation rate was also enhanced with increased O₂ consumption. Evidence of a direct regulation of glucose utilization by PPARβ/δ has not been established. However, PGC-1 expression induced by PPARβ/δ activation appears to upregulate Glut4 expression as reported before. Together with the increased mitochondrial biogenesis and function, the upregulation of Glut4 and FFK II expression, and increased PDC activity should account for the increased glucose utilization in TMVPD hearts. The increased myocardial O₂ consumption is commensurate with the increased cardiac performance in the TMVPD hearts. Considering the increase of mitochondria and the enhanced cardiac performance in TMVPD hearts, the increased O₂ consumption should not be an indication of depressed cardiac efficiency. This point is further supported by the fact that prolonged TG expression of the constitutively active PPARβ/δ in the adult heart did not lead to overt pathological development (data not shown). Interestingly, mice with long-term cardiac-specific overexpression of a wild-type PPARβ/δ showed an increased myocardial glucose but not fatty acid utilization. Because the un-ligated PPARβ/δ could have quite different function than the activated PPARβ/δ, it is challenging to sort out functional changes derived from liganded- or un-ligated PPARβ/δ in this model with very high level of TG expression. The strategy used in the present study by TG hyperexpressing the constitutively active form of PPARβ/δ has help avoid this problem. The same strategy has been extensively used in the studies of nuclear receptors.

It has been reported that tamoxifen induced-Cre overexpression in the heart may exert adverse effects on gene expression and cardiac function. However, we did not detect overt phenotypic changes in the TMC heart as we reported before. On the cautious side, we used TMC mice as a control for even subtle effects of tamoxifen and Cre. The present results suggested that PPARβ/δ activation in the adult heart enhances cardiac performance not only under basal condition, but also under pressure-overload condition. PPARβ/δ activation eventually improved cardiac performance with a less dilated left ventricle, fibrosis and mitochondrial abnormalities. This result is in accordance with the previously reported beneficial effect of long-term PPARβ/δ overexpression in the heart with ischemia/reperfusion injury. However, the underlying mechanisms could have been different as the TMVPD heart demonstrated profound enhancement in mitochondrial biogenesis and function before pressure-overload stimuli. Future study should be warranted on the effects of PPARβ/δ activation during the development of pressure-overload induced cardiac hypertrophy.

Taken together, we conclude that activation of PPARβ/δ will promote cardiac performance with its transcriptional regulation of mitochondrial biogenesis and defense and therefore oxidative metabolism in the adult heart.

Perspectives

Hypertension associated left ventricular pressure-overload is one of the main causes of cardiac hypertrophy and heart failure. Cardiac metabolic derangement, mitochondrial dysfunction and oxidation stress in the heart are the main pathological developments in patients with cardiac hypertrophy and heart failure. Correcting myocardial metabolic derangement and improving mitochondrial function have been proposed as therapeutic strategy in treating cardiac pathological hypertrophy and heart failure. This study established the biological roles and effectiveness of PPARβ/δ activation in protecting the heart from pressure-overload induced pathological hypertrophy by improving mitochondrial oxidative metabolism and cardiac function. The conditional transgenic approach is a powerful tool to determine how PPARβ/δ activation in the adult heart with minimal non-activating PPARβ/δ effects. We documented that PPARβ/δ activation facilitated myocardial oxidative metabolism.
metabolism, mitochondrial biogenesis and antioxidative defense in the adult heart. Furthermore, PPARβ/δ activation improved cardiac performance with less fibrosis and mitochondrial abnormalities in mice subjected to left ventricular pressure-overload. Therefore, pharmacological development of specific activators and selective modulators of PPARβ/δ that specifically activate PPARβ/δ in the heart should be promising in combating cardiac hypertrophy and heart failure.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

We thank Drs. John Chatham and Timothy Garvey for helpful discussion and Kevin Yang for proofing and editing the manuscript.

**Source of Funding:** This work was supported by grants from National Institute of Health (1R01HL085499, 1R01HL084456 and R21 AT003734).

**References**


_Hypertension. Author manuscript; available in PMC 2012 September 11._


Hypertension. Author manuscript; available in PMC 2012 September 11.
Figure 1. Generating cardiomyocyte-restricted PPARβ/δ hyperexpression (TMVPD) mice and cardiac PPARβ/δ expression

A) TG constructs and Cre-mediated recombination event. The structures of the target gene (CAG-CAT-PPARβ/δ) and their recombined allele are shown. B) Real time PCR results of PPARα, PPARβ/δ and PPARγ mRNA levels on RNA samples extracted from ventricular tissues of TMCM and TMVPD mice 14 days after the end of tamoxifen treatment (n=4, *p<0.05). C. Western blotting results of PPARβ/δ protein levels in nuclear proteins from ventricular tissues of TMCM and TMVPD mice 14 days after the end of tamoxifen treatment (n=4, *P<0.05).
Figure 2. Elevated expression levels of key proteins involved in fatty acid and glucose metabolism in TMVPD hearts

A) Real Time PCR analyses of transcript levels of fatty acid and glucose metabolic genes on samples from ventricular tissues of TMCM and TMVPD mice 14 days after the end of tamoxifen treatment (n=4-7, *P<0.05).

B) Protein levels of CPT-Ib, CPT2, ACADM and GLUT4 in samples from ventricular tissues of TMCM and TMVPD mice 14 days after the end of tamoxifen treatment (n=4-6, *P<0.05).
Figure 3. Elevated expression of key determinants of mitochondrial biogenesis in TMVPD hearts

A) Real-time PCR measurements of transcript levels of PPARγ coactivator 1 (PGC-1α and -1β), nuclear respiratory factor -1 (NRF-1), NRF2 (a and b), and TFAM on samples from TMVPD and TMCM hearts. B) Western blot analysis of protein expression of PGC-1α, NRF1 and NRF-2 (n=4, *P<0.05). C) Real-time PCR measurement of transcript levels of Cytochrome c oxidase subunit II, IV and Cytochrome c oxidase subunit 7c (Cox7c), Cytochrome c and b (Cyto c, and b), mitofusin 1 (Mfn1), mitofusin 2 (Mfn2), optic atrophy 1 (Opa1, nuclear gene encoding mitochondrial protein), Dynamin related protein 1 (DRP1) and mitochondrial fission 1 protein (FIS1, mitochondrial outer membrane) on samples from TMVPD and TMCM hearts (n=4, *P<0.05). D) Real-time PCR measurement of mtDNA to nuclear DNA copy number in cardiac tissues from TMVPD and TMCM mice (n=6, *P<0.05). E) TEM assessment of TMCM and TMVPD hearts (9800X). Show is the representative images and quantification results of mitochondrial volume (%) of TMCM and TMVPD heart sections.
Figure 4. Elevated expression of endogenous anti-oxidants in TMVPD hearts
A) Real time PCR analyses of transcript expression of SOD1, SOD2, and catalase on samples extracted from ventricular tissue of TMVPD and TCMC mice (n=4, *P<0.05).  
B) Western blotting analyses of protein level of SOD1, SOD2 and catalase (n=6, *P<0.05).
Figure 5. Elevated rates of oxidative metabolism in TMVPD hearts
A) Palmitate oxidation rate (n=6-8, *P<0.05). B) Glucose oxidation rate (n=6-8, *P<0.05).
C) Myocardial O$_2$ consumption (MVO2) (n=6, *P<0.05). D) Glycogen content (n=6, *P<0.05). E) PDC activity (n=6, *P<0.05). F) AMPK α subunit phosphorylation (n=4-6, *P<0.05).
Figure 6. Effects of TAC-induced pressure-overload
A) Heart weight/body weight ratio in TMVPD and TMCM mice 4 weeks post induction (n=15-16, *P<0.05), respectively. B) Real time PCR assessment of Nppa and Nppb transcripts (n=4-6, *P<0.05 vs Sham). C) Real-time PCR measurement of mtDNA to nuclear DNA copy number in cardiac tissues from TMVPD and TMCM mice with TAC (n=5, *P<0.05). D) Images of heart sections stained with H&E and Trichrome blue from TAC-TMVPD and TAC-TMCM mice (200X). E) Representative images of TEM images (9800X).
Table 1
Hemodynamic measurement of isolated working heart

<table>
<thead>
<tr>
<th>Parameters</th>
<th>TMCM</th>
<th>TMVPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>414±14</td>
<td>451±11</td>
</tr>
<tr>
<td>LVPsys (mmHg)</td>
<td>107.4±2.3</td>
<td>125.5±0.4</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>9.0±1.1</td>
<td>8.0±1.5</td>
</tr>
<tr>
<td>LVPdia (mmHg)</td>
<td>3.4±1.2</td>
<td>1.3±2.0</td>
</tr>
<tr>
<td>LVPamp (mmHg)</td>
<td>106.7±4.3</td>
<td>124.2±1.6</td>
</tr>
<tr>
<td>dLVPdtmax (mmHg/s)</td>
<td>556±605</td>
<td>863±559 *</td>
</tr>
<tr>
<td>-dLVPdtmin (mmHg/s)</td>
<td>-4546±515</td>
<td>-7446±349 *</td>
</tr>
<tr>
<td>CI</td>
<td>128.9±9.2</td>
<td>146.2±12.3 *</td>
</tr>
</tbody>
</table>

Data were expressed as mean±SEM,
* P<0.05, n=8.
Table 2
Echocardiography measurement in mice 14 days after the end of tamoxifen treatment followed by 4 weeks of TAC

<table>
<thead>
<tr>
<th>Parameters</th>
<th>TMCM</th>
<th>TAC</th>
<th>TMVPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham n=17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>419±5</td>
<td>431±8.06</td>
<td>417±8</td>
</tr>
<tr>
<td>Pressure grad. (mmHg)</td>
<td>NA</td>
<td>50.2±3.2</td>
<td>NA</td>
</tr>
<tr>
<td>IVS;d (mm)</td>
<td>3.79±0.05</td>
<td>4.37±0.08*</td>
<td>3.86±0.08</td>
</tr>
<tr>
<td>LVID;d (mm)</td>
<td>2.36±0.08</td>
<td>3.2±0.08*</td>
<td>2.3±0.08</td>
</tr>
<tr>
<td>EF (%)</td>
<td>70.5±1.5</td>
<td>52.4±1.9*</td>
<td>74.3±1.35</td>
</tr>
<tr>
<td>Endocardial area; d(mm²)</td>
<td>20.9±0.56</td>
<td>25.38±0.5*</td>
<td>22.1±0.6</td>
</tr>
<tr>
<td>FS (%)</td>
<td>39.7±1.45</td>
<td>26.8±1.2*</td>
<td>42.9±1.21</td>
</tr>
<tr>
<td>LV mass (mg)/bw</td>
<td>3.58±0.09</td>
<td>5.29±0.30*</td>
<td>3.72±0.05</td>
</tr>
<tr>
<td>IVS;s (mm)</td>
<td>0.82±0.02</td>
<td>1.05±0.05*</td>
<td>0.82±0.03</td>
</tr>
<tr>
<td>LVPW;d (mm)</td>
<td>1.17±0.04</td>
<td>1.43±0.05*</td>
<td>1.23±0.04</td>
</tr>
<tr>
<td>Endocardial area; s(mm²)</td>
<td>11.5±0.41</td>
<td>16.94±0.8*</td>
<td>12.4±0.52</td>
</tr>
<tr>
<td>LVID;s (mm)</td>
<td>0.82±0.02</td>
<td>1.05±0.05*</td>
<td>1.15±0.03*</td>
</tr>
<tr>
<td>LVPW;s (mm)</td>
<td>0.66±0.02</td>
<td>0.98±0.04*</td>
<td>0.72±0.03</td>
</tr>
<tr>
<td>EF (%)</td>
<td>74.3±1.35</td>
<td>63.5±1.98*†</td>
<td></td>
</tr>
<tr>
<td>FS (%)</td>
<td>34.3±1.43*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (mg)/bw</td>
<td>3.72±0.05</td>
<td>5.15±0.14*†</td>
<td></td>
</tr>
<tr>
<td>Endocardial area; s(mm²)</td>
<td>12.4±0.52</td>
<td>14.73±0.50*†</td>
<td></td>
</tr>
</tbody>
</table>

Data were expressed as mean±SEM, n=13-17, *P<0.05 (vs Sham), †P<0.05 (vs TMCM-TAC).

Hypertension. Author manuscript; available in PMC 2012 September 11.