Exercise improves impaired ventricular function and alterations of cardiac myofibrillar proteins in diabetic dyslipidemic pigs

F. Steven Korte, Eric A. Mokelke, Michael Sturek, and Kerry S. McDonald

Department of Medical Pharmacology and Physiology, Center for Diabetes and Cardiovascular Health, University of Missouri School of Medicine, Columbia, Missouri; and Department of Cellular and Integrative Physiology, Indiana University School of Medicine, Indianapolis, Indiana

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Korte, F. Steven, Eric A. Mokelke, Michael Sturek, and Kerry S. McDonald. Exercise improves impaired ventricular function and alterations of cardiac myofibrillar proteins in diabetic dyslipidemic pigs. J. Appl. Physiol. 98: 461–467, 2005. First published October 1, 2004; doi:10.1152/japplphysiol.00551.2004.—Chronic diabetes is often associated with cardiomyopathy, which may result, in part, from defects in cardiac muscle proteins. We investigated whether a 20-wk porcine model of diabetic dyslipidemia (DD) would impair in vivo myocardial function and yield alterations in cardiac myofibrillar proteins and whether endurance exercise training would improve these changes. Myocardial function was depressed in anesthetized DD pigs (n = 12) compared with sedentary controls (C; n = 13) as evidenced by an ∼30% decrease in left ventricular fractional shortening and an ∼35% decrease in +dP/dt measured by noninvasive echocardiography and direct cardiac catheterization, respectively. This depression in myocardial function was improved with chronic exercise as treadmill-trained DD pigs (DDX) (n = 13) had significantly greater fractional shortening and +dP/dt than DD animals. Interestingly, the isoform expression pattern of the myofibrillar regulatory protein, cardiac troponin T (cTnT), was significantly shifted from cTnTα toward cTnTβ and cTnTγ in DD pigs. Furthermore, this change in cTnT isoform expression pattern was prevented in DDX pigs. Finally, there was a decrease in baseline levels of cAMP-dependent protein kinase-induced phosphorylation of the myofibrillar proteins troponin I and myosin-binding protein-C in DD animals. Overall, these results indicate that 20 wk of DD lead to myocardial dysfunction coincident with significant alterations in myofibrillar proteins, both of which are prevented with endurance exercise training, implying that changes in myofibrillar proteins may contribute, at least in part, to cardiac dysfunction associated with diabetic cardiomyopathy.

cardiomyopathy; diabetes mellitus; lipids; myocardium

DIABETES MELLITUS IS A DISEASE with wide prevalence in humans and is often associated with cardiovascular complications that represent the major cause of morbidity and mortality. Patients with diabetes have a high incidence of congestive heart failure, which may occur independent of coronary artery atherosclerosis, valvular heart disease, and hypertension (23). This deterioration of heart function is known as diabetic cardiomyopathy and is frequently associated with both systolic and diastolic left ventricular dysfunction (36). Much of what is known about the features of myocardial dysfunction has been obtained using rat models of diabetes. Rats treated with streptozotocin (STZ) develop diabetes mellitus associated with hypoinsulinemia, hyperglycemia, polyuria, weight loss, and myocardial dysfunction. The contractile dysfunction is due in part to contractile abnormalities of the myocyte, which are present within 4 days of diabetes (37). Myocytes isolated from diabetic rat hearts exhibit much slower contraction and relaxation rates (37). These contractile abnormalities are correlated with prolonged action potentials (22), depressed Ca2+ reuptake by the sarcoplasmic reticulum (14), a switch from α- to β-myosin heavy chain isoform (10), changes in the relative expression of cardiac troponin T (cTnT) isoforms (1, 21), and altered levels of troponin I (TnI) phosphorylation (27). Although the STZ-diabetic ratlet model is well characterized and has provided many insights into the basis of diabetic cardiomyopathy, it has limited relevance toward understanding human diabetic cardiomyopathy. For instance, the dietary habits and lipid metabolism of rodents prevent any signs of dyslipidemia, which is increasingly thought to be central in the etiology of cardiovascular complications in human diabetes (16). In contrast, a pig model of diabetes in combination with a high-fat diet yields lipid and lipoprotein profiles very similar to that found in human diabetic patients (12). Additionally, diabetic pigs with dyslipidemia [diabetic dyslipidemia (DD)] show early signs of vascular disease (11, 12, 25, 29, 30, 41), retinopathy (18), and exhibit weight gain (7) commonly associated with human diabetes (8, 23). At present, there have not been any animal model studies addressing whether DD alters the myocardium. Thus the main objective of this study was to determine if our porcine model of DD would depress in vivo myocardial function and/or alter specific cardiac myofibrillar proteins. In particular, we examined the expression of cTnT isoforms and the baseline level of protein kinase A (PKA)-induced phosphorylation of myofibrillar proteins, two alterations that have been implicated in rodent models of diabetes as well as during the progression of human heart failure (3, 5, 44). A second aim was to determine if endurance exercise training would attenuate any changes in myocardial function and/or alterations in relative cTnT isoform content associated with DD.

METHODS

Animal care and use. All procedures involving animals were approved by the Animal Care and Use Committee of the University of Missouri and complied fully with those approved by the American Veterinary Medical Association Panel on Euthanasia. Male Yucatan pigs (Sinclair Research Center, Columbia, MO) weighing 45–55 kg at 9–12 mo of age were housed in the Laboratory Animal Medicine Facility. Animals were randomly assigned to three groups: control (C; n = 13), DD (n = 12), and DD exercise trained (DDX; n = 13). DD

Address for reprint requests and other correspondence: K. S. McDonald, One Hospital Drive, MA415 MSB, Columbia, MO 65212 (E-mail: McDonaldKS@missouri.edu).

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and DDX animals received 125 mg/kg of alloxan in the superior vena cava through a surgically implanted vascular access port to induce diabetes (19). DD and DDX animals were maintained on a high-fat 2% cholesterol diet for 20 wk to induce dyslipidemia and cardiovascular disease as previously described (12). Blood glucose values were obtained using two different methods: 1) precision OID glucometers and strips (MediSense, Bedford, MA) and 2) YSI 2300 Stat Plus Analyzer (YSI, Yellow Springs, OH). High correlation of the instruments and reliability of the measures were documented (8). Plasma was directly assayed for total cholesterol and triglyceride levels using a standard enzymatic kit (Sigma-Aldrich, St. Louis, MO) (12, 13), and low-density lipoprotein and high-density lipoprotein levels were determined by separation of plasma samples with fast protein liquid chromatography (12, 13).

Before alloxan treatment, a vascular access port was surgically implanted into each pig via left external jugular vein catheterization (19). The vascular access port provided a nontraumatic and convenient means of serial venous blood sampling and intravenous drug administration. Accessing the venous circulation was accomplished by passing a 20-gauge 1-in. Huber point needle into the access dome of the port located subcutaneously on the left side of the neck. Blood samples were obtained between weeks 16 and 20 of the study for determination of glucose and lipids (Table 1).

Four weeks after alloxan treatment, DDX animals were acclimated to a motorized treadmill (Good Horsekeeping, Ash Grove, MO) for a 2-wk period during which the grade and speed were incrementally increased so that by the end of the 2 wk a moderate-intensity workload was reached that elicited a heart rate between 65 and 75% of maximum (7). The grade was adjusted during the remaining 14-wk exercise training regimen to maintain this target heart rate. The exercise protocol was followed 4 days/wk, which consisted of a 10-min warm-up period, followed by 30 min of walking at the target heart rate, followed by a 5-min cool-down period. The efficacy of the exercise program was tested by measuring resting heart rates (8) and citrate synthase activity from skeletal muscle homogenates of the right biceps muscle (39).

Cardiac catheterization. Cardiac catheterization was performed on anesthetized animals to assess cardiac hemodynamics. Anesthesia for surgery was induced with the following drugs administered intramuscularly (in mg/kg): 0.05 atropine, 6.6 telazol, and 2.2 xylazine; the level of anesthesia was maintained with isoflurane gas (2.5–4%). For arterial access, an 8-Fr sheath was inserted into the femoral artery and introduced into the aortic arch and then manipulated into the left common carotid artery (Cordis, Miami, FL) were inserted through the sheath and posterior wall are shown clearly. Commercially available soft-tipped guidewires (Cordis, Miami, FL) were inserted through the sheath and manipulated into the left ventricle (LV). The guidewire was removed, and in vivo hemodynamics were assessed by interfacing the catheter with a three-way pressure manifold, which allowed left ventricular pressure measurements. The use of a fluid-filled catheter likely reduces the fidelity of the pressure signal, and thus our measurements may underestimate the actual rates of pressure development. This underestimation, however, would have occurred in all groups and thus would not change our conclusions.

Table 1. Indicators of diabetic dyslipidemia

<table>
<thead>
<tr>
<th></th>
<th>C (n = 13)</th>
<th>DD (n = 12)</th>
<th>DDX (n = 13)</th>
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<tbody>
<tr>
<td>Blood glucose, mg/dl</td>
<td>65±5</td>
<td>326±14*</td>
<td>339±10*</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>54±2</td>
<td>337±43*</td>
<td>365±54*</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>28±2</td>
<td>75±6*</td>
<td>86±6*</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>18±1</td>
<td>219±41*</td>
<td>237±39*</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>0.68±0.06</td>
<td>2.98±0.52*</td>
<td>2.70±0.36*</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>32±4</td>
<td>85±27</td>
<td>48±8</td>
</tr>
</tbody>
</table>

Values are means ± SE. C, control; DD, diabetic dyslipidemia; DDX, DD-exercise trained; HDL, LDL, high- and low-density lipoprotein, respectively. *Significantly different from control, P<0.05.

Proper catheter placement was confirmed by injection of a small bolus of contrast media as well as by visual inspection of the pressure wave.

Echocardiography. Cardiac echocardiograms were recorded with an AU3 ultrasound system ( Biosound Esaote, Indianapolis, IN). A cardiac probe, adjusted to a sampling frequency of 2.0 MHz, was used to record two dimensionally guided M-mode images at the mid-papillary muscle level. Figure 1A shows the two-dimensional image from which the papillary (PM) was used as a landmark and M-mode images at the mid-papillary muscle level. Figure 1B shows the two-dimensional image from which the papillary (PM) was used as a landmark. Proper catheter position was confirmed by injection of a small bolus of contrast media as well as by visual inspection of the pressure wave.

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SDS-PAGE were similar to that previously described (17). Serially diluted myofibrillar suspensions (5.0–0.625 µg) were separated by SDS-PAGE using 12% polyacrylamide slab gels. Serial dilution of the muscle protein solution ensured that protein bands were in the linear range for densitometric analysis. Gels were then placed on a prewetted nitrocellulose membrane, and the gel-nitrocellulose combination was sandwiched between several sheets of 3MM chromatography paper (Whatman, Maidstone, UK). The protein samples were then transferred to nitrocellulose using a semidyblot apparatus at constant current (100 mA) for 30–45 min. The nitrocellulose blots were then placed in a blocking buffer consisting of 3% BSA in Tris-buffered saline plus Tween 20 (TTBS) and rocked overnight at 4°C. The blocking buffer was removed, and the blots were washed for 15 min in TTBS, followed by two subsequent 5-min washes in TTBS. Primary antibody (cTnT; Advanced Immunochemical, Long Beach, CA) 1:2,000 in 0.3% BSA in TTBS was allowed to react with blots for 2 h followed by the same washing protocol described above. Secondary antibody (SAM-hgG; Amersham, Piscataway, NJ) 1:2,500 in 0.3% BSA in TTBS reacted for 1 h followed by three washes using TTBS. On completion of the final wash, blots were coated for 1 min with enhanced chemiluminescent substrate (Amersham), which reacts with the secondary antibody. Blots were removed from the substrate and placed between two pieces of clear acetate. To detect relative amounts of cTnT isoforms, blots were exposed to photography film for ~1 min, followed by film development. Relative amounts cTnT isoforms were determined by measuring the areas under the peaks corresponding to the different cTnT isoforms using QuantiScan (Biosoft, Ferguson, MO) software and an Epson scanner.

**RESULTS**

Effects of DD on heart size and hemodynamics. Table 1 provides indicators of DD. As expected, DD animals had marked (4- to 6-fold) elevations in both blood glucose and cholesterol compared with controls. Triglycerides in DD were increased 2.7-fold over control, but this did not reach statistical significance due to the high variability. Both glucose and cholesterol remained elevated in DDX animals that underwent 14 wk of endurance exercise training as noted previously (29, 42). This was predicted given the hyperglycemia-induced insulin resistance (34) and high-fat/cholesterol diet. This aspect of the experimental design enables one to determine more directly the effects of exercise on the myocardium, largely independent of blood glucose and lipids. The overall efficacy of the exercise program was confirmed, though, by testing both central and peripheral adaptations commonly associated with endurance exercise training. Specifically, DDX animals had significantly lower conscious resting heart rates (Table 2) and higher citrate synthase activity of skeletal muscle homogenates from the right biceps muscle (citrate synthase activity: C = 14 ± 3; DD = 9 ± 1; DDX = 18 ± 3 µmol.min⁻¹.g wet wt⁻¹). Table 2 summarizes the heart dimensions and hemodynamics of the animals. The rate of pressure development was significantly lower in DD animals (500 ± 57 mmHg/s) compared with C (768 ± 110 mmHg/s) and DDX (812 ± 84 mmHg/s), implying compromised myocardial function in response to DD and exercise improved the impaired function. Fractional shortening was calculated from LV diameter changes between systole and diastole, measured from parasternal M-mode echocardiograms in anesthetized animals (Fig. 1B). Fractional shortening under basal conditions was significantly lower in DD animals compared with controls (P < 0.05) (Table 2). This difference represented an ~30% reduction in fractional shortening in DD pigs, which provides further evidence of impaired myocardial function in association with DD. Interestingly, the functional improvement in response to exercise occurred independent of blood glucose and cholesterol levels, which remained elevated in exercised trained animals.

**Changes in myofibrillar proteins in response to DD.** Because changes in cTnT isoforms have been implicated in rodent models of diabetes and human heart failure (1–4), we first examined whether relative cTnT isoform content changed in DD pigs. Figure 2A shows representative cTnT Western blots of cardiac myofibrillar proteins from C, DD, and DDX animals. Three distinct isoforms of cTnT were expressed (so named cTnT1, cTnT2, and cTnT3 in accordance with each isoform’s SDS-PAGE migration pattern). The relative content of cTnT isoforms shifted in response to DD, whereby there was a significant reduction in the relative content of cTnT1 (62 ± 7% in controls vs. 51 ± 10% with DD) coincident with a significant increase in the relative amount of cTnT2 (28 ± 6% in controls vs. 35 ± 9% with DD) and cTnT3 expression (10 ± 4% in controls vs. 14 ± 5% in DD; Fig. 2B). Chronic exercise prevented these cTnT isoform shifts, with cTnT isoform con-

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**Table 2. Characteristics of animals, heart dimensions, and in vivo myocardial function**

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>DD</th>
<th>DDX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body wt, kg</strong></td>
<td>54±3</td>
<td>63±3</td>
<td>61±3</td>
</tr>
<tr>
<td>Heart wt, g</td>
<td>215±9</td>
<td>215±14</td>
<td>257±5*</td>
</tr>
<tr>
<td>Heart wt/body wt</td>
<td>4.2±0.3</td>
<td>3.3±0.2*</td>
<td>3.9±0.2</td>
</tr>
<tr>
<td><strong>Conscious</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76±5</td>
<td>75±3</td>
<td>62±2*†</td>
</tr>
<tr>
<td>Peak systolic pressure, mmHg</td>
<td>113±4</td>
<td>117±4</td>
<td>116±3</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>79±2</td>
<td>76±4</td>
<td>74±3</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>90±2</td>
<td>90±4</td>
<td>88±3</td>
</tr>
<tr>
<td><strong>Anesthetized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>82±4</td>
<td>71±5</td>
<td>76±7</td>
</tr>
<tr>
<td>LV peak systolic pressure, mmHg</td>
<td>79±3</td>
<td>79±3</td>
<td>94±6*†</td>
</tr>
<tr>
<td>LV end diastolic pressure, mmHg</td>
<td>8±4</td>
<td>6±3</td>
<td>4±2</td>
</tr>
<tr>
<td>+dP/dt, mmHg/s</td>
<td>768±110</td>
<td>500±57*</td>
<td>812±84*†</td>
</tr>
<tr>
<td>−dP/dt, mmHg/s</td>
<td>459±58</td>
<td>585±72</td>
<td>654±91</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>52±5*</td>
<td>35±5*</td>
<td>59±4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. (Heart weight and thus heart-weight-to-body weight ratios were only measured in 8 control hearts, 6 DD hearts, and 6 DDX hearts.) LV, left ventricular; +dP/dt and −dP/dt, maximal rate of pressure development and decline, respectively. *Significantly different from control, †significantly different from DD, P<0.05.
tent in DDX animals (62 ± 5% cTnT1, 29 ± 4% cTnT2, and 10 ± 3% cTnT3) being virtually indistinguishable from controls and significantly different from DD values. Figure 2C shows a scatterplot of relative cTnT1 expression vs. fractional shortening correlating myofibrillar protein changes with in vivo myocardial function. The amount of fractional shortening decreased in proportion to the amount of cTnT1 expression with regression analysis revealing a statistically significant correlation ($P < 0.0017$, $r^2 = 0.55$).

We next examined if there were changes in baseline levels of PKA-induced phosphorylation of myofibrillar proteins with DD. Autoradiographic phosphoimaging analysis along with silver stain imaging revealed that two myofibrillar proteins were phosphorylated by PKA in control and DD myocardium [i.e., myosin binding protein-C (MyBP-C) and cardiac troponin I (cTnI; Fig. 3A)]. Backphosphorylation experiments indicated that there was a significant increase in the amount of PKA-induced phosphate incorporation of both MyBP-C and cTnI in samples from DD animals. Because this assay measured PKA-induced phosphorylation from baseline levels, the finding that phosphate incorporation was greater in DD myofibrils implies a significant reduction in the amount of baseline phosphorylation of myofibrillar PKA substrates as a result of DD. These results are summarized in Fig. 3B. We were unable to perform phosphorylation assays on DDX animals due to exhaustion of tissue supply.

**DISCUSSION**

This is the first study, to our knowledge, that tested the hypothesis that in vivo myocardial function will be impaired and cardiac myofibrillar proteins altered in a 20-wk porcine model of DD. We observed alterations in LV performance, the relative cTnT isoform content, and baseline levels of PKA-induced covalent modulation of myofibrillar proteins following 20 wk of DD. Moderate endurance exercise training improved the changes in ventricular function and prevented the cTnT isoform content shift in DD pigs. These findings may have important implications in determining myofibrillar defects associated with human diabetic cardiomyopathy, especially because our DD porcine model yields positive energy balance (7), lipoprotein profiles (12), and vascular adaptations (11) all
ALTERED IN VIVO MYOCARDIAL FUNCTION IN RESPONSE TO DD. Myocardial function was impaired in DD animals compared with control animals as evidenced by reduced rates of pressure development and depressed LV fractional shortening (as determined by conventional echocardiography). These results imply that DD animals exhibited early signs of cardiomyopathy, a condition that commonly develops in human diabetes (23, 36). In fact, fractional shortening has specifically been shown to be decreased in humans with diabetes mellitus (9). The impaired myocardial function in this porcine model most likely results from DD conditions per se as opposed to secondary effects of ischemic conditions because observed coronary atheroma was only in beginning stages and insufficient to be flow limiting (11). Interestingly, chronic exercise significantly improved myocardial performance in DD animals as evidenced by faster rates of isovolumic relaxation and greater fractional shortening. This is consistent with many studies reporting that exercise maintains or reverses many degenerative disease states, with individuals with diabetes among the largest beneficiaries of exercise (6, 31, 33). Although the exact factors that initiate and lead to depressed myocardial function with diabetes remain unknown and are, in fact, beyond the scope of this study, it appears that the exercise-induced improvement of depressed myocardial function is not due to reductions in elevated levels of blood glucose, cholesterol, and triglycerides, at least in our model, because these values were similar in DD and DX animals. In other words, the beneficial effects of exercise to maintain myocardial function were largely independent of blood glucose and lipids, thus suggesting direct actions of exercise on the myocardium.

ALTERATIONS IN CARDIAC MYOFIBRILLAR PROTEINS IN DD PIGS. Because any change in myocardial performance is ultimately mediated by changes in myocyte contractile properties, we investigated if there were changes in cardiac myofibrillar proteins in response to DD. We specifically examined the relative content of the thin filament regulatory protein cTnT, which has been shown to change under a variety of conditions (2–4) and whose alterations have been implicated in depressed myocardial function (1, 3, 4, 35) and, second, if there were changes in cAMP-dependent protein kinase (PKA)-induced phosphorylation of myofibrillar proteins, which have been observed in rodent models of diabetes and in failing human myocardium (27, 28). Alterations in both relative cTnT isoform content and PKA-induced baseline phosphorylation levels were observed in pigs after 20 wk of DD. Although the exact functional consequences of these changes are not known, it is noteworthy that similar changes have been observed in rodent models of diabetes and in the progression of heart failure in humans. For example, a shift in cTnT isoforms that resulted in the relative reduction of the larger cTnT isoform coincident with a relative increase in a smaller cTnT isoform has been observed in STZ-induced diabetic rats (1, 21). A similar switch in cTnT isoform expression has been observed in myocardium from failing human hearts, where there is a reexpression of the fetal isoform, cTnTα, and a downregulation in normal adult cTnT3 (3, 4). Again, it remains unclear as to the exact functional consequences of these changes in cTnT isoform content, although it appears that expression of the fetal isoform of cTnT does not alter either maximal Ca\(^{2+}\)-activated ATPase activity or calcium sensitivity in reconstituted myofilaments (40). It is known, however, that varied expression of cTnT isoforms correlates with Ca\(^{2+}\) sensitivity of isometric force in skinned cardiac muscle (32). Also, it has been speculated that early changes in cTnT isoform expression are necessary at the onset of changes in myofibrillar phenotype to optimize myofilament restructuring because cTnT serves as a molecular interface with tropomyosin, actin, titin, and the other troponin subunits. The potential importance of cTnT is underscored by our results that show that rates of pressure development and relative cTnT isoform content were similar between control animals and DD animals that had undergone chronic exercise training. Additional studies are needed to more directly assess if perhaps altered cTnT isoforms modulate rates of myocyte force development and relaxation, which may translate to compromised LV performance associated with diabetic cardiomyopathy.
Changes in cAMP-dependent PKA-induced phosphorylation have also been observed in rodent models of diabetes and in failing human myocardium (27, 28). Interestingly, baseline phosphorylation of cTnI was observed to be greater, not lesser, in diabetic rat hearts (27). However, the greater levels of cTnI phosphorylation may have arisen from elevated PKC activity as opposed to PKA activity. In fact, PKC activity has been shown to be elevated in experimental diabetes in rat (28). In human heart failure, however, there is direct evidence for decreased basal PKA-induced phosphorylation levels in cardiac myofibrillar proteins (44) and that these changes in PKA activity may be mediated by altered autophosphorylation and binding to A-kinase anchoring proteins (43). The similar reductions in baseline PKA-induced phosphorylation of cardiac myofibrillar proteins in our porcine model of DD are entirely consistent with changes in humans, although the exact functional consequences of these changes are not known. It is well established, however, that phosphorylation of cTnI by PKA results in reduced Ca\textsuperscript{2+} affinity of cTnC (38) and diminished Ca\textsuperscript{2+} sensitivity of force (15), which is thought to assist in ventricular relaxation (24). PKA-induced phosphorylation of myofibrillar proteins has also been shown to increase both force and power output-generating capacities of skinned cardiac myocytes (20). Thus reductions in baseline PKA-induced phosphorylation of cardiac myofibrillar proteins may contribute to attenuation of both systolic and diastolic function of the left ventricle. Future studies will be needed to determine if chronic exercise in DD animals results in a restoration of basal PKA-induced phosphorylation levels to control values.

In conclusion, myofibrillar regulatory proteins were altered in a porcine model of DD in a manner consistent with the myocardial dysfunction noted. In addition, changes in cTnI isoform content and depressed rates of ventricular pressure changes were not observed in DD animals that underwent endurance exercise training. It is not known if exercise in control animals would induce similar changes seen in DD animals, and this remains a question for future studies. Additionally, although exercise has been shown in this and in other studies to induce changes that would be beneficial to diabetic patients, there is evidence that suggests diabetic patients may not gain much benefit from exercise and could possibly even be putting themselves at risk when performing physical exercise (26). Overall, however, these results suggest that changes in cTnI isoform composition and covalent modulation of myofibrils may contribute, at least in part, to both the ventricular dysfunction associated with diabetic cardiomyopathy and the improvement of function with exercise training.

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