Prediabetic insulin resistance is not permissive to the development of cardiac resistance to insulin-like growth factor I in ventricular myocytes

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Abstract

Resistance to insulin-like growth factor I (IGF-1)-induced cardiac contractile response has been reported in diabetes. To evaluate the role of prediabetic insulin resistance to cardiac IGF-1 resistance, whole body insulin resistance was generated with dietary sucrose and contractile function was evaluated in ventricular myocytes. Mechanical properties were evaluated using an IonOptix™ system and intracellular Ca2+ transients were measured as changes in fura-2 fluorescence intensity (ΔFFI). After 8 weeks of feeding, sucrose rats displayed euglycemia, hepatomegaly and normal heart size, and glucose intolerance, confirming the presence of insulin resistance. Myocytes from sucrose-fed rats displayed decreased peak shortening (PS), reduced resting FFI, increased intracellular Ca2+ clearing, associated with normal duration of shortening and relengthening compared to myocytes from starch-fed rats. IGF-1 (10^{-10}−10^{-6} M) caused a similar concentration-dependent decrease in PS in both groups. Only the highest concentration of IGF-1 elicited an inhibition on ΔFFI in sucrose myocytes. In addition, the IGF-1-induced response was abolished by the IGF-1 receptor antagonist H-1356 in both groups, and by the nitric oxide synthase inhibitor L-NAME in starch but not sucrose myocytes. These results indicated prediabetic insulin resistance alters cardiac contractile function at the myocytes level, but may not be permissive to cardiac contractile resistance to IGF-1.

Keywords: IGF-1; Insulin resistance; Ventricular myocyte; Cell shortening; Ca2+ transient

1. Introduction

Diabetic cardiomyopathy, a myopathic state independent of macrovascular abnormalities, often develops in the late stages of diabetes mellitus [1,2]. This cardiomyopathy is the leading cause of death in type 2 (non-insulin-dependent) diabetes and is characterized by impaired excitation–contraction coupling of the ventricular myocyte including prolonged action potentials, slowed cytosolic Ca2+ clearing and compromised contraction and relaxation [1–4]. The pathogenesis of
diabetic cardiomyopathy has not been clearly defined but may involve hyperglycemia, hyperinsulinemia, hyperlipidemia, and resistance to insulin or insulin-like growth factor I (IGF-1) [4–10].

IGF-1 is similar to proinsulin and has been used as a replacement for insulin to monitor blood glucose in diabetes, especially under insulin resistance. IGF-1, synthesized by various cell types, is capable of promoting cardiac growth and contraction, and to improve hemodynamics as well as energy metabolism [8]. We recently observed resistance to IGF-1 in myocardial contraction in diabetes of both chemically-induced [6] and genetically-predisposed origin [10]. An altered cardiac IGF-1/IGF-1 receptor level has also been reported in diabetic patients and experimental animals, suggesting a role of IGF-1 in diabetic cardiomyopathy [11,12].

Recently, an insulin resistant, prediabetic model was developed utilizing a high-sucrose diet to induce whole body insulin resistance that mimics early stages of non-insulin-dependent diabetes with only minor metabolic abnormalities such as elevated insulin and plasma triglycerides. This model is unique from other models of type 2 diabetes in that hypertension and obesity, which themselves can independently alter cardiac excitation–contraction coupling, are not present [13]. Therefore, the aim of this investigation was to characterize the single ventricular myocytes contractile properties and the IGF-1-induced cardiac contractile response under the sucrose-fed prediabetic insulin resistance.

2. Materials and methods

2.1. Animals

All animal procedure was in accordance with NIH animal care standards. Adult male Sprague–Dawley rats weighing 150–200 g were randomly divided into two groups and fed either a cornstarch (providing 68% of total energy) or sucrose (providing 68% of total energy) diet formulated by Research Diets Inc (New Brunswick, NJ) for 7–8 weeks.

2.2. Glucose tolerance test

After the 7–8 week feeding period, both starch and sucrose rats were fasted for 12 h and then given an intraperitoneal (i.p.) injection of glucose (2 g/kg bw). Blood samples were drawn from the tail 15 min and immediately before the glucose challenge, as well as 15, 60, and 120 min thereafter. Serum glucose levels were determined using an Accu-Chek III glucose analyzer (Accu-ChekII, Boehringer Mannheim Diagnostics, Indianapolis, IN).

2.3. Cell isolation procedures

Ventricular myocytes were isolated using the method described [10]. Briefly, hearts were rapidly removed and perfused (37 °C) with Krebs–Henseleit bicarbonate (KHB) buffer containing (in mM): 118 NaCl, 4.7 KCl, 1.25 CaCl2, 1.2 MgSO4, 1.2 KH2PO4, 25 NaHCO3, 10 HEPES and 11.1 glucose. Hearts were subsequently perfused with a Ca2+-free KHB buffer containing 223 U/ml collagenase (Worthington Biochemical Corp., Freehold, NJ) and 0.1 mg/ml hyaluronidase (Sigma Chemical, St. Louis, MO). After perfusion, ventricles were removed and minced under sterile conditions, before being filtered through a nylon mesh (300 μm). Cells were initially washed with Ca2+-free Tyrode’s buffer to remove remnant enzyme and extracellular Ca2+ was added incrementally back to 1.25 mM. Myocytes with obvious sarcolemmal blebs or spontaneous contractions were not used.

2.4. Cell shortening/relengthening

Mechanical properties of ventricular myocytes were assessed using a SoftEdge video-based edge-detection system (IonOptix Corporation, Milton, MA) [10]. In brief, cells were placed in a chamber on the stage of an inverted microscope (Olympus, X-70) and superfused (25 °C) with a buffer containing (in mM): 131 NaCl, 4 KCl, 1 CaCl2, 1 MgCl2, 10 glucose, 10 HEPES, at pH 7.4. The cells were field stimulated at 0.5 Hz. An IonOptix soft-edge software was used to capture changes in cell length during shortening and relengthening.
2.5. Intracellular fluorescence measurement

Myocytes were loaded with fura-2/AM (0.5 μM) for 10 min and fluorescence measurements were recorded with a dual-excitation fluorescence photomultiplier system (Ionoptix) as described [10]. Myocytes were placed on an Olympus X-70 inverted microscope and imaged through a Fluor 40 × oil objective. Cells were exposed to light emitted by a 75 W lamp and passed through either a 360 or a 380 nm filter (+15 nm), while being stimulated to contract at 0.5 Hz. Fluorescence emissions were detected between 480–520 nm by a photomultiplier tube after first illuminating cells at 360 nm for 0.5 s then at 380 nm for the duration of the recording protocol (333 Hz sampling rate). The 360 nm excitation scan was repeated at the end of the protocol and qualitative changes in intracellular Ca$^{2+}$ concentration ([Ca$^{2+}$]) were inferred from the ratio of the fluorescence intensity at two wavelengths.

2.6. Statistical analyses

For each experimental series, data are presented as mean ± SEM. Statistical significance (P < 0.05) for each variable was estimated by analysis of variance (ANOVA) or t-test, where appropriate. A Dunnett’s test was used for post hoc analysis.

3. Results

3.1. General features of starch- and sucrose-fed rats

The body weight, heart and kidney weight/size, as well as plasma glucose level (shown in Fig. 1) are similar in starch- and sucrose-fed animals. Sucrose-fed rats exhibited hepatomegaly compared to the starch-fed rats (Table 1).

3.2. Glucose tolerance test

Following the intraperitoneal glucose challenge, the plasma glucose levels in the starch-fed rats started to decline after peaking at 15 min, and nearly returned to the baseline value after 120 min. However, the post-challenge hyperglycemia remained at a high level between 15 and 120 min in the sucrose-fed rats (Fig. 1), indicating the presence of glucose intolerance, an indicative of insulin resistance, in the sucrose-fed rats.

![Fig. 1. Glucose tolerance test displaying serum glucose concentrations in response to intraperitoneal glucose challenge (2 g glucose/kg body weight) in starch- and sucrose-fed rats. The rats were fasted for 12-h before the tests were conducted. Values represent mean ± SEM. # P < 0.05 vs. starch group.](image)

Table 1
General feature of experimental animals

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Heart weight (g)</th>
<th>Heart wt/body weight (mg/g)</th>
<th>Liver weight (g)</th>
<th>Liver wt/body weight (mg/g)</th>
<th>Kidney weight (g)</th>
<th>Kidney wt/body weight (mg/g)</th>
<th>Serum glucose (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>439 ± 10</td>
<td>1.76 ± 0.08</td>
<td>4.02 ± 0.18</td>
<td>12.4 ± 0.3</td>
<td>28.3 ± 0.5</td>
<td>4.02 ± 0.18</td>
<td>5.56 ± 0.09</td>
<td>1.83 ± 0.20</td>
</tr>
<tr>
<td>Sucrose</td>
<td>417 ± 6</td>
<td>1.67 ± 0.06</td>
<td>3.99 ± 0.09</td>
<td>14.0 ± 0.2*</td>
<td>33.5 ± 0.8*</td>
<td>3.99 ± 0.09</td>
<td>5.72 ± 0.21</td>
<td>2.37 ± 0.40</td>
</tr>
</tbody>
</table>

Mean ± SEM, n = 5 animals/group.

* P < 0.05 vs. starch group.
Fig. 2. Contractile properties of cardiac ventricular myocytes isolated from starch- and sucrose-fed rat hearts. (A) Representative cell shortening traces from starch and sucrose group; (B) peak shortening amplitude (PS); (C) time-to-peak shortening (TPS); (D) time-to-90% relengthening (TR90); (E) maximal velocities of shortening (+ dl/dt); (F) maximal velocities of relengthening (− dl/dt). Mean ± SEM, n = 50 cells/group, *P < 0.05 vs. starch group.
Fig. 3. Concentration-dependent response of IGF-1 ($10^{-10}$–$10^{-6}$ M) on peak cell shortening in ventricular myocytes from starch- and sucrose-fed rat hearts. Data are presented as percent change from the respective control value. The number of myocytes is given in parentheses. Mean ± SEM *P < 0.05 vs. baseline.

3.3. Baseline cell shortening and relengthening from starch- and sucrose-fed rats

No obvious light microscopic morphological difference was noticed in ventricular myocytes from starch- and sucrose-fed rats. The average resting cell length (CL) was similar between the starch (160 ± 3 μm, n = 79) and the sucrose (168 ± 4 μm, n = 76) groups. The peak shortening amplitude (PS, normalized to CL) was significantly reduced in myocytes isolated from the sucrose-fed rat hearts, suggesting reduced myocyte contractile function under insulin resistance. Myocytes from both groups exhibited similar time-to-peak shortening (TPS), time-to-90% relengthening (TR90) and maximal velocities of shortening/relengthening ($\pm d/dt$) (Fig. 2).

3.4. Effect of IGF-1 on myocyte peak shortening (PS)

Acute application of IGF-1 ($10^{-10}$–$10^{-6}$ M) elicited a concentration-dependent decrease in PS with a threshold between $10^{-10}$ and $10^{-9}$ M in myocytes from both starch and sucrose-fed groups (Fig. 3). The effect of IGF-1 on cell shortening reached maximal within 5 min of exposure, therefore all the recording was taken 6 min after IGF-1 administration. The effect of IGF-1 was reversible upon washout (data not shown). IGF-1 also exerted a concentration-dependent depression on $\pm d/dt$ in myocytes from starch but not sucrose group, and had no effect on TPS and TR90 in myocytes from either group (Table 2). These data suggest that ventricular myocytes from starch and sucrose groups appeared to respond

Table 2: Effect of IGF-1 on duration of myocyte shortening (TPS) and relengthening (TR90) and maximal velocities of shortening and relengthening ($\pm d/dt$) in myocytes from starch and sucrose rat hearts

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>IGF-1 $10^{-10}$ M</th>
<th>IGF-1 $10^{-9}$ M</th>
<th>IGF-1 $10^{-8}$ M</th>
<th>IGF-1 $10^{-7}$ M</th>
<th>IGF-1 $10^{-6}$ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS (ms) starch</td>
<td>154 ± 5</td>
<td>158 ± 6</td>
<td>164 ± 5</td>
<td>157 ± 5</td>
<td>158 ± 5</td>
<td>162 ± 6</td>
</tr>
<tr>
<td>TPS (ms) sucrose</td>
<td>168 ± 7</td>
<td>165 ± 6</td>
<td>166 ± 6</td>
<td>167 ± 6</td>
<td>159 ± 6</td>
<td>155 ± 8</td>
</tr>
<tr>
<td>TR90 (ms) starch</td>
<td>506 ± 34</td>
<td>529 ± 38</td>
<td>533 ± 36</td>
<td>555 ± 41</td>
<td>583 ± 45</td>
<td>576 ± 52</td>
</tr>
<tr>
<td>TR90 (ms) sucrose</td>
<td>446 ± 37</td>
<td>499 ± 37</td>
<td>495 ± 43</td>
<td>535 ± 44</td>
<td>474 ± 37</td>
<td>502 ± 41</td>
</tr>
<tr>
<td>$\pm d/dt$ (μm/ms) starch</td>
<td>47 ± 4</td>
<td>43 ± 5</td>
<td>38 ± 4*</td>
<td>34 ± 3*</td>
<td>34 ± 4*</td>
<td>33 ± 4*</td>
</tr>
<tr>
<td>$\pm d/dt$ (μm/ms) sucrose</td>
<td>45 ± 5</td>
<td>42 ± 5</td>
<td>41 ± 6</td>
<td>42 ± 6</td>
<td>40 ± 5</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>$-d/dt$ (μm/ms) starch</td>
<td>-26 ± 4</td>
<td>-22 ± 4</td>
<td>-19 ± 3*</td>
<td>-17 ± 3*</td>
<td>-18 ± 4*</td>
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<tr>
<td>$-d/dt$ (μm/ms) sucrose</td>
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<td>-26 ± 5</td>
<td>-25 ± 6</td>
<td>-27 ± 6</td>
<td>-25 ± 6</td>
<td>-25 ± 6</td>
</tr>
</tbody>
</table>

Data represent mean ± SEM, n = 27 cells/group.

* P < 0.05 vs. baseline.
Fig. 4. Effect of IGF-1 on intracellular Ca$^{2+}$ transients in ventricular myocytes from starch- and sucrose-fed rat hearts. (A) Baseline intracellular Ca$^{2+}$ levels; (B) intracellular Ca$^{2+}$ transient decay rate; (C) concentration-dependent response of IGF-1 ($10^{-10}$–$10^{-6}$ M) on intracellular Ca$^{2+}$ changes (ΔFFI) in myocytes from starch and sucrose group. Actual data point in the concentration-dependent response curves were obtained by normalizing ΔFFI to the respective control value. Mean ± SEM, *P < 0.05 vs. baseline. Cell number is given in parentheses.

equally to IGF-1, although subtle difference may exist in the contractile response.

3.5. Effect of IGF-1 on intracellular Ca$^{2+}$ ([Ca$^{2+}$]) transients

Fluorescence dye fura-2 was used to estimate [Ca$^{2+}$], in the myocytes from both groups. The time course of the fluorescence signal decay (fluorescence decay time, $\tau$) was calculated to assess intracellular Ca$^{2+}$ clearing rate. Myocytes from the sucrose-fed rat hearts exhibited reduced baseline FFI (representing resting intracellular Ca$^{2+}$ levels) and faster intracellular Ca$^{2+}$ clearing rate compared to those from the starch group (Fig. 4A and B). Reduced intracellular Ca$^{2+}$ levels have been reported under diabetic state [6]. IGF-1 did not induce any noticeable effect on changes of intracellular Ca$^{2+}$ (ΔFFI = Peak FFI − Baseline FFI) in myocytes from both groups, except that $10^{-6}$ M IGF-1 significantly depressed ΔFFI in myocytes from the sucrose
group (Fig. 4C). Neither resting FFI nor τ was affected by IGF-1 in the concentration range tested (data not shown). The disparate response of IGF-1 on myocyte shortening and intracellular Ca\(^{2+}\) may suggest potential involvement of myofibril responsiveness to Ca\(^{2+}\) in IGF-1-induced myocyte contraction response.

3.6. Effect of IGF-1 on PS in the presence of IGF-1 analogue and NO synthase inhibitor

To determine the membrane receptor(s) and post-receptor mechanism(s) involved in the IGF-1-induced cardiac contractile response, myocyte shortening in response to IGF-1 was re-examined in the presence of IGF-1 analogue, H-1356 (Bachem Bioscience, King of Prussia, PA) and nitric oxide synthase (NOS) inhibitor L-arginine methyl ester (l-NAME, Sigma Chemicals, St. Louis, MO). H-1356 inhibits the autophosphorylation of the IGF-1 receptor by IGF-1 and therefore serves as an IGF-1 receptor antagonist [14]. Pretreatment of l-NAME (100 μM) abolished the IGF-1-induced depression in myocyte shortening in starch (Fig. 5A) but not sucrose (Fig. 5B) group, indicating a disparate role of NO in IGF-1-induced contractile response. L-NAME alone had no effect on PS in either group (data not shown), as reported previously [6]. Not surprisingly, the IGF-1-induced myocyte contractile response was blunted by H-1356 (20 μg/ml) in myocytes from both starch and sucrose groups (Fig. 5C and D), indicating that the IGF-1-induced cardiac contractile response is mediated through the IGF-1 receptor.

Fig. 5. Effect of NOS inhibitor l-NAME (100 μM, Panels A and B) and IGF-1 analogue H-1356 (20 μg/ml, Panels C and D) on IGF-1-induced cardiac contractile response in myocytes from starch (A and C) or sucrose (B and D) group. Data are presented as percent change from the respective control value. The number of cells is given in parentheses. Mean ± SEM *P < 0.05 vs. baseline.
4. Discussion

IGF-1 promotes cardiac growth and function, facilitates glucose metabolism, increases insulin sensitivity and improves the lipid profile, suggesting both a physiological role and a therapeutic potential of the hormone [8]. IGF-1 and its binding proteins have been considered as markers for the presence of certain cardiac abnormalities. Altered IGF-1 responsiveness has been shown in diabetes [6,10], hypertension [15,16] and obesity [17], indicating that IGF-1 may increase the propensity of certain cardiac disorders [8]. Although several of the aforementioned disorders are characterized by the presence of insulin resistance, data from the present study does not favor the existence of insulin resistance alone as permissive to the development of full-blown cardiac excitation–contraction coupling abnormalities and IGF-1 resistance in cardiac contractile response, which can be seen in diabetes.

The most significant mechanical impairments in diabetic cardiomyopathy include prolonged duration and reduced maximal velocities of cardiac contraction and relaxation, which are often associated with reduced intracellular Ca$^{2+}$ clearing rate [1,2,6]. However, results from the current investigation revealed normal duration and velocity of cardiac contraction/relaxation associated with a rather enhanced intracellular Ca$^{2+}$ extrusion under prediabetic insulin resistance condition, supporting the notion that the development of diabetic cardiomyopathy occurs at late stage of diabetes mellitus. This is consistent with the euglycemic condition and normal heart as well as body mass in sucrose-fed rats, since full-blown diabetes often displays body weight loss, cardiac hypertrophy and hyperglycemia. Nevertheless, prediabetic insulin resistance has uncovered certain degree of abnormality manifested by reduced cardiac contractility (PS), decreased intracellular Ca$^{2+}$ level and hepatomegaly. The impact of insulin resistance on cardiac contractile function is largely unknown. We may speculate that insulin resistance or hyperinsulinemia may affect the abundance and/or function of certain cardiac enzymes (e.g. creatine kinase) for energy expenditure and metabolism, contributing to the decreased cardiac contraction and liver dysfunction. The reduced intracellular Ca$^{2+}$ level observed in this study is consistent with earlier reports in insulin-dependent diabetes mellitus [2,18], however contrary to the trend of an elevated intracellular Ca$^{2+}$ level under non-insulin-dependent diabetes mellitus [18]. Therefore, it is possible that the impaired Ca$^{2+}$ regulation may be different between the prediabetic insulin resistance and type 2 diabetes. Although the mechanism responsible for the reduced intracellular Ca$^{2+}$ level under prediabetic insulin resistance is still unknown, it may be speculated that depressed sarcoplasmic reticulum (SR) Ca$^{2+}$ store, which is seen in diabetes [18], may contribute to the reduced intracellular Ca$^{2+}$ and depressed myocyte contraction. In addition, alterations in Ca$^{2+}$ binding and phospholipid composition of the sarcolemmal membrane may also affect the transmembrane Ca$^{2+}$ flux and lower the Ca$^{2+}$ uptake. Diabetes is often associated with reduced rate of intracellular Ca$^{2+}$ clearing due to impaired sarco(endo)plasmic reticulum Ca$^{2+}$-ATPase and Na$^+$/Ca$^{2+}$ exchanger [1,2].

It is possible that the enhanced intracellular Ca$^{2+}$ clearing under prediabetic insulin resistance may be a compensatory mechanism against the progressing impaired intracellular Ca$^{2+}$ handling in full-blown type 2 diabetes. Further investigations are warranted to elucidate the intracellular Ca$^{2+}$ homeostasis under insulin resistance.

IGF-1 has been shown to enhance myocardial contractility [6,10,15–17]. Several mechanisms have been postulated including IGF-1-induced IP$_3$ accumulation, leading to increases in intracellular Ca$^{2+}$ concentration [19], and IGF-1-induced increase in intracellular Ca$^{2+}$ sensitivity [20]. Interestingly, the present study exhibited for the first time a decreased cardiac contractile response elicited by IGF-1. This negative cell shortening effect was not paralleled by similar response in intracellular Ca$^{2+}$ transients. The mechanism underlying IGF-1-induced negative contractile effect and disparate response between cell shortening and intracellular Ca$^{2+}$ transient is not clear, although several possible explanations are worthy of consideration. (i) Rat recombinant IGF-1 was used in the current study (Sigma) whereas all our earlier investigations were conducted using human re-
combinant IGF-1; (ii) the control rats were chronically fed with cornstarch-enriched diet but not the regular lab chow, it is not known at this point whether this feeding regime may interfere with the IGF-1 signaling pathway; (iii) the fact that IGF-1 at the concentration depressed cell shortening exerted no effect on intracellular Ca^{2+} level may indicate a reduced myofibril intracellular Ca^{2+} sensitivity, which has been reported in diabetes [2,21]. The results from the current study showed similar pattern of IGF-1 response between the starch- and sucrose-fed rats, different from our previous reports in full-blown diabetes where cardiac IGF-1 resistance was observed [6,10]. This data indicates that the existence of prediabetic insulin resistance is not permissive to the development of IGF-1 resistance in cardiac myocytes. It is worthy to point out that insulin resistance may have predisposed resistance to IGF-1 in certain cardiac contractile elements as indicated by the discrepancy in the effect of IGF-1 on d/dt between the starch and sucrose groups (Table 2). Decreased IGF-1 message has been demonstrated in diabetes [11,12], but not in non-diabetic insulin resistant model [17]. It is possible that altered intrinsic autocrine/paracrine effects of IGF-1 may contribute to the changed contractile response seen in the diabetic state.

The cardiac contractile effect of IGF-1 was blocked by the IGF-1 receptor antagonist H-1356, suggesting that IGF-1-induced cardiac response is mediated through the IGF-1 receptor but not the insulin receptor. This also adds to the notion that IGF-1-induced cardiac response is independent of the receptor/post-receptor mechanism involved in insulin resistance. The fact that IGF-1-induced cardiac contractile response was abolished by NOS inhibitor L-NAME in starch but not sucrose groups indicated either IGF-1 uses different mechanism (i.e. NO dependent vs. independent) to inhibit cardiac contraction or there is a substantial tonic NO level under prediabetic insulin resistance. Since NO is known to directly inhibit influx of Ca^{2+} through Ca^{2+} channel and cardiac contraction [22], the blockade of IGF-1-induced contractile depression by L-NAME in starch myocytes suggests that IGF-1 is likely to elicit its cardiac depression through increase of NO production in isolated ventricular myocytes (Ren, unpublished data). In conjunction with the fact that the activity of heart NOS may be compensatorily increased in diabetes [23], IGF-1 may stimulate a greater NO production in sucrose-fed insulin resistant myocytes, which cannot be completely blocked by L-NAME, accounting for our observation.

IGF-1 acts as an endogenous regulator of cardiac contraction. The nature of rapid onset, durable effect, and the relatively modest magnitude compared with other endogenous substances, all makes IGF-1 an important cardiac hormone. With our finding not favoring the development of cardiac IGF-1 resistance solely due to the presence of prediabetic insulin resistance, how cardiac IGF-1 resistance develops under diabetes would be intriguing to explore.

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References


