Influence of Age on Inotropic Response to Insulin and Insulin-Like Growth Factor I in Spontaneously Hypertensive Rats: Role of Nitric Oxide (44383)

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Abstract. **Insulin-like growth factor-1 (IGF-1) and insulin stimulate cardiac growth and contractility. Recent evidence suggests a relationship between essential hypertension, left ventricular hypertrophy, and circulating IGF-1 levels. Advanced age alters cardiac function in a manner similar to hypertension. The aim of this investigation was to evaluate the effects of IGF-1 and insulin on the force generating capacity of cardiac muscle in hypertension and the influence of age on this response. Contractile responses to IGF-1 and insulin were examined using papillary muscles from Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR) at 10 and 25 weeks of age. Muscles were electrically stimulated at 0.5 Hz, and contractile properties, including peak tension development (PTD), time-to-peak tension, time-to-90% relaxation, and the maximal velocities of contraction and relaxation, were evaluated. PTD was similar in WKY and SHR myocardium at both age groups. At 10 weeks of age, IGF-1 (1–500 ng/ml) caused a dose-dependent increase in PTD in WKY but not SHR myocardium, whereas insulin (1–500 n*M*) had no effect on PTD in either group. At 25 weeks of age, the positive inotropic effect of IGF-1 was attenuated in the WKY group, and IGF-1 exerted no inotropic action in the SHR group. Pretreatment with the nitric oxide synthase inhibitor, N-ω-nitro-L-arginine methyl ester (L-NAME, 100 μ*M*), did not alter the IGF-1-induced positive inotropic response in 10-week-old WKY myocardium, whereas it unmasked a positive inotropic action in muscles from age-matched SHR animals. At 25 weeks of age, L-NAME abolished IGF-1-induced a positive inotropic response in WKY myocardium, and did not unmask an IGF-induced inotropic response in SHR myocardium. Our results suggest that alterations in nitric oxide modulation of IGF-1-induced contraction may underlie resistance to this inotropic peptide with advancing age, and/or hypertension.** [P.S.E.B.M. 1999, Vol 221]

Hypertension is a major risk factor for both stroke and myocardial infarction. The primary adaptive response of the heart to sustained hypertension is cardiac hypertrophy accompanied by electromechanical abnormalities such as prolonged action potential and contraction duration (1). Advanced or increased age is often associated with myocardial alterations similar to those seen in hypertension, including a thickened left ventricular wall and prolonged contraction duration (1–3).

The spontaneous hypertensive rat (SHR) is a model of essential hypertension that results in left ventricular hypertrophy and increased total peripheral resistance (4). The hypertensive state in these animals is also associated with defects in insulin and insulin-like growth factor-1 (IGF-1) responsiveness, similar to that observed in persons with essential hypertension (5, 6). Moreover, the ventricular dysfunction seen in the SHR increases with age and/or the duration of hypertension (1, 7–9).

Insulin has been reported to exert various inotropic actions on myocardial tissue *in vitro* (10–12), suggesting that it may contribute to changes in cardiac mechanical function.

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IGF-1, which is structurally and functionally similar to insulin, is synthesized in the heart (13, 14) and may act as an autocrine/paracrine factor exerting both inotropic and growth effects (15). IGF-1 has been shown to stimulate cardiac protein synthesis (16), increase inositol-1,4,5 triphosphate levels (17), stimulate nitric oxide (NO) production (6, 18), and enhance myocardial contraction and intracellular free Ca^{2+} levels (11, 19, 20). Clinical and experimental investigations have shown an association between insulin resistance, hyperinsulinemia, and hypertension (5, 21). IGF-1 resistance also occurs in states of insulin resistance and hyperinsulinemia (6, 22). Clinical studies related to the role of IGF-1 in hypertension are extremely limited, but significant data from animal studies indicate a role for IGF-1 as a mediator of hypertrophic/hyperplastic responses in hypertension (23, 24). However, the underlying mechanism of action has not been elaborated.

This study was designed to investigate the myocardial inotropic action of IGF-1 as well as insulin in hypertension and to determine the influence of age on these responses. As IGF-1 is known to stimulate NO production (6, 18), and the latter has been considered a physiological modulator of cardiac excitation-contraction coupling (25), we also examined the role of NO in IGF-1-induced inotropic responses in hypertension at 10 and 25 weeks of age. In pursuing these aims, we used isolated left ventricular papillary muscles from SHR and age-matched normotensive Wistar-Kyoto (WKY) rats.

Materials and Methods

Experimental Animals. Experimental procedures and protocols were approved by Wayne State University Animal Investigation Committee and have been previously described (9). Adult male SHR and their genetic controls, the normotensive WKY rats, were obtained at 4 weeks of age from Taconic Farms (Germantown, NY). The animals were housed individually in a temperature-controlled room under a 12:12-hr light:dark illumination cycle and were allowed access to standard rat chow and tap water *ad libitum*. While the rats were conscious, systolic blood pressures and body weights were obtained on a weekly basis by using the tail-cuff method and a standard laboratory balance, respectively. At the end of the experimental period, rats were euthanized under ketamine/xylazine sedation (3:1, 1.32 mg/kg i.p.), and the hearts were rapidly excised and immersed in oxygenated (95% O_2, 5% CO_2) Tyrode's solution (in m*M*: KCl 5.4, NaCl 136.9, $NaHCO_3$ 11.9, $MgCl_2$ 0.50, $CaCl_2$ 2.70, NaH_2PO_4 0.45, and glucose 5.6, pH 7.4) at 37°C. Left ventricular papillary muscles were dissected and mounted vertically in temperature-controlled 50-ml organ baths containing Tyrode's solution of the same ionic composition. The solution was continuously gassed with a mixture of 95% O_2/5% CO_2 through fine pores of glass bubblers.

Tension Measurement of Papillary Muscles. Tension development of papillary muscles was measured with a force transducer (F-30, Hugo Sachs, March-Hugstetten, Germany) as described previously (9). Preparations were allowed to equilibrate in Tyrode's solution for 60 min while being electrically driven by a stimulator (S-88, Grass Instrument Co., Quincy, MA) at a frequency of 0.5 Hz for establishment of baseline isometric peak tension development (PTD). Square-wave pulses of 4–8-ms duration and 50% suprathreshold were delivered through a pair of platinum electrodes in close contact with both ends of the muscle. Isometric tension was recorded at approximately 90% of L_{max}. Signals were amplified, differentiated, and displayed on a chart recorder (Grass 79, Quincy, MA). The output of the chart recorder was coupled to the input stage of an analog-digital board and later analyzed using a software program (Dasy Lab 3, Biotech Products, Greenwood, IN). PTD was normalized to respective control values and presented as percentage increase of isometric tension development to reduce any intermuscle variance.

Experimental Protocol. Following the equilibration period, the muscles were exposed to IGF-1 (1–500 ng/ml; Genentech, CA) or bovine insulin (1–500 n*M*, Sigma Chemicals, St. Louis, MO) for 5 min. These dose ranges were used previously for contractility studies (19, 20, 26). Agents were added cumulatively to compose a dose–response curve. Recovery was continuously monitored after removal of the drug from the organ baths. In some studies, N-ω-nitro-L-arginine methyl ester (L-NAME, 100 μ*M*, Sigma) was incubated with the muscles for 15 min prior to IGF-1 or insulin addition. The following parameters were measured: PTD; time- to-peak tension (TPT); time-to-90% relaxation (RT_{90}); and maximum velocity of tension development and decay (± VT). The inotropic response to both IGF-1 and insulin was maximal within 3 min of exposure and remained steady for more than 40 min. Therefore, all of the measurements were taken after a 5-min exposure to each hormone.

Data Analysis. Data are presented as mean ± SEM. Differences between and within groups were evaluated by two-way analysis of variance (ANOVA) with repeated measures (SYSTAT). A Tukey test was used as a follow-up for the multiple comparisons. To determine significant differences in the repeated measures factor (concentration of IGF-1), the "within subjects" MSerror and dferror terms from the parent ANOVA were used. To determine significant differences between strains at a given concentration of IGF-1, the "between subjects" MSerror and dferror terms from the parent ANOVA were used. Statistical significance was considered to be $P < 0.05$.

Results

General Features of WKY and SHR Rats. The impact of sustained hypertension at 10 and 25 weeks of age on blood pressure and body, liver, and kidney weights is shown in Table I. As expected, SHR exhibited a significantly elevated systolic blood pressure and a lower body

Table I. General Features of WKY and SHR Rats at 10 and 25 Weeks of Age

Rat group	SBP (mmHg)	Body Wt (g)	Heart Wt (g)	HWt/Body Wt (mg/g)	LWt/Body Wt (mg/g)	KWt/Body Wt (mg/g)
WKY-10 (12)	122 ± 3	350 ± 12	1.07 ± 0.04	3.05 ± 0.06	42.6 ± 2.7	9.01 ± 0.18
SHR-10 (12)	177 ± 4*	259 ± 4*	0.95 ± 0.03*	3.66 ± 0.09*	41.2 ± 0.8	8.88 ± 0.23
WKY-25 (7)	131 ± 1	553 ± 20	1.45 ± 0.07	2.61 ± 0.09	31.0 ± 1.6	6.98 ± 0.32
SHR-25 (7)	176 ± 2*	376 ± 6*	1.41 ± 0.07	3.74 ± 0.20*	37.6 ± 0.5*	8.59 ± 0.42*

Note. SBP, systolic blood pressure; Wt, weight; H, heart; L, liver; K, kidney. Mean ± SEM, $*P < 0.05$ vs. respective WKY group. Animal number is given in parentheses.

weight compared to their WKY counterparts at both ages. Although the absolute heart weight was smaller in SHR at 10 weeks of age, both 10- and 25-week-old SHR showed cardiomegaly when assessed as a percentage of body weight. Older SHRs developed hepatomegaly and renal hypertrophy compared with their age-matched WKY and younger hypertensive counterparts.

Baseline Mechanical Properties. The hypertensive state had no significant effect on papillary muscle baseline PTD at either 10 or 25 weeks of age (10-week: 1.40 ± 0.15 vs. 1.26 ± 0.13 g; 25-week: 1.39 ± 0.13 vs. 1.47 ± 0.17 g; in WKY and SHR, respectively). When PTD was normalized to respective papillary muscle weight, preparations from 25-week-old SHR developed considerably greater tension, compared to their age-matched WKY (SHR: 129 ± 17 vs. WKY: 87 ± 11 g/g, $P < 0.05$). However, this difference was not noted at 10 weeks of age (WKY: 117 ± 16 vs. SHR: 126 ± 12 g/g; Fig. 1). The enhanced ability of 25-week-old SHR muscles (per gram weight) to develop tension was not associated with change in the maximal velocities of tension development and decline (± VT) (Table II). However, both hypertension and increased age prolonged contraction (TPT) and relaxation duration (RT_{90}), whereas 25-week-old SHR animals exhibited similar TPT and RT_{90} to those of 10-week-old SHR rats.

Inotropic Effects of IGF-1 on Papillary Muscle Isometric Tension Development. The acute inotropic effects of IGF-1 on myocardium from WKY and SHR at 10 and 25 weeks of age are shown in Figure 1. To avoid intermuscle variance, each PTD value in response to IGF-1 was normalized as a function of its respective control value. IGF-1 elicited a dose-dependent positive inotropic effect on myocardium from the WKY but not the SHR group. In papillary muscles from 10-week-old WKY rats, IGF-1 increased PTD by 2.0 ± 0.6%, 2.8 ± 1.0%, 8.6 ± 2.7%, and 11.9 ± 3.2% at doses of 1, 10, 100 and 500 ng/ml, respectively (Fig. 1A). The threshold of the positive inotropic effect of IGF-1 was between 10 and 100 ng/ml. However, this IGF-1-induced positive inotropic response was depressed in muscles from 25-week-old WKY animals, where only a 9.8% increase in PTD occurred, though significantly at the maximal dose of 500 ng/ml (Fig. 1B). Myocardium from SHR at either age group failed to respond to IGF-1 within the dose range tested. As mentioned, baseline TPT and RT_{90} were significantly longer in SHR myocardium, compared to their age-matched WKY counterparts. Similarly, baseline TPT and RT_{90} were also equally prolonged in muscles from animals at an older age, regardless of the blood pressure states. IGF-1 did not exert any effect on the TPT and RT_{90} or maximal velocity of tension development and decay (± VT) (Table III).

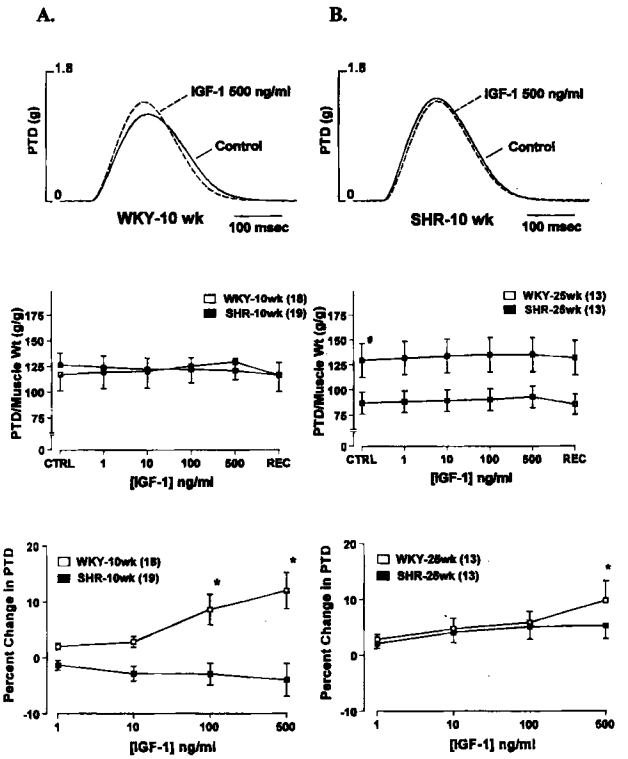

Figure 1. Inotropic response to IGF-1 (1–500 ng/ml) on PTD in papillary muscles from WKY (open square) and SHR (filled square) animals at 10 (A) and 25 (B) weeks of age. (Upper panels) Typical experiments showing the effect of IGF-1 (500 ng/mL) on myocardial contraction of papillary muscles isolated from 10-week-old WKY(left) and SHR (right) rat. The middle panels show the inotropic response to IGF-1 when PTD was normalized to respective papillary muscle weight (g/g). The lower panels show the inotropic response to IGF-1 when PTD was presented as the percentage change from the respective control value. The number of muscles is given in parentheses. Mean ± SEM $*P < 0.05$ vs. Control, $^{\#}P < 0.05$ vs. WKY group.

Influence of Insulin on Papillary Muscle Isometric Tension Development. For comparison, the inotropic response of insulin was also tested in myocardium from WKY and SHR, at 10 and 25 weeks of age. A comparable range of doses of insulin (1–500 n*M*) had no effect on myocardium from both 10- and 25-week-old rats (Fig. 2A). Moreover, insulin did not alter the duration and veloc-

Table II. Baseline Mechanical Properties of WKY or SHR Myocardium at Different Age

Muscle group	TPT (msec)	RT_{90} (msec)	+VT (g/sec)	−VT (g/sec)
WKY-10wk (18)	83.7 ± 1.5	122.0 ± 5.3	23.0 ± 1.9	−14.5 ± 1.2
SHR-10wk (19)	96.2 ± 2.2*	150.4 ± 10.9*	18.6 ± 1.8	−12.5 ± 1.4
WKY-25wk (13)	96.5 ± 5.9#	142.3 ± 6.3#	20.5 ± 1.7	−13.1 ± 1.0
SHR-25wk (13)	96.5 ± 2.8	146.9 ± 5.2	20.0 ± 2.1	−14.2 ± 1.5

Note. Time-to-peak tension (TPT), time-to-90% relaxation (RT_{90}), and maximal velocity of tension development (+VT) and decay (−VT). Data represent mean ± SEM. *$P < 0.05$ vs. respective WKY. #$P < 0.05$ vs. 10-week-old counterpart. Muscle number if given in parentheses.

Table III. Influence of IGF-1 on Baseline Contraction and Relaxation Duration (TPT, RT_{90}) and Velocity of Tension Development or Decline (±VT) in WKY or SHR Myocardium

	TPT (msec)	RT_{90} (msec)	+VT (g/sec)	−VT (g/sec)
WKY-10wk-Basal (18)	83.7 ± 1.5	122.0 ± 5.3	23.0 ± 1.7	−14.5 ± 1.2
IGF-1 1 ng/ml	83.8 ± 1.3	123.1 ± 4.6	23.1 ± 2.0	−14.5 ± 1.2
IGF-1 10 ng/ml	83.6 ± 1.0	124.5 ± 4.6	23.1 ± 2.0	−14.6 ± 1.2
IGF-1 100 ng/ml	84.6 ± 1.6	125.4 ± 4.0	23.8 ± 2.0	−14.9 ± 1.1
IGF-1 500 ng/ml	85.4 ± 1.4	125.0 ± 4.0	24.4 ± 2.0	−15.4 ± 1.2
SHR-10wk-Basal (19)	96.2 ± 2.2*	150.4 ± 10.9*	18.6 ± 1.8	−12.5 ± 1.4
IGF-1 1 ng/ml	97.1 ± 2.3	152.1 ± 12.1	18.5 ± 1.8	−12.5 ± 1.3
IGF-1 10 ng/ml	96.2 ± 2.4	150.0 ± 11.3	18.5 ± 1.8	−12.5 ± 1.3
IGF-1 100 ng/ml	96.5 ± 2.1	151.3 ± 11.3	18.6 ± 1.9	−12.6 ± 1.4
IGF-1 500 ng/ml	95.9 ± 2.2	154.0 ± 11.4	18.9 ± 2.0	−12.7 ± 1.5
WKY-25wk-Basal (13)	96.5 ± 5.9#	142.3 ± 6.3#	20.5 ± 1.7	−13.1 ± 1.0
IGF-1 1 ng/ml	97.1 ± 6.1	149.2 ± 6.7	21.0 ± 1.7	−13.5 ± 1.0
IGF-1 10 ng/ml	95.7 ± 5.8	150.0 ± 6.3	21.3 ± 1.7	−13.6 ± 1.1
IGF-1 100 ng/ml	93.4 ± 4.4	148.2 ± 6.8	21.6 ± 1.7	−13.8 ± 1.1
IGF-1 500 ng/ml	94.0 ± 4.9	145.7 ± 6.0	22.0 ± 1.8	−14.1 ± 1.2
SHR-25wk-Basal (13)	96.5 ± 2.8	146.9 ± 5.2	20.0 ± 2.1	−14.2 ± 1.5
IGF-1 1 ng/ml	94.9 ± 1.9	146.2 ± 5.4	20.2 ± 2.1	−14.1 ± 1.4
IGF-1 10 ng/ml	96.8 ± 3.0	144.2 ± 4.8	20.5 ± 2.1	−14.3 ± 1.4
IGF-1 100 ng/ml	95.4 ± 2.3	147.7 ± 5.5	20.7 ± 2.1	−14.3 ± 1.4
IGF-1 500 ng/ml	96.3 ± 2.8	149.9 ± 6.6	20.7 ± 2.1	−14.0 ± 1.6

Note. Time-to-peak contraction (TPT), time-to-90% relaxation (RT_{90}), and maximal velocity of tension development (+VT) and decay (−VT). Data represent mean ± SEM. *$P < 0.05$ vs. respective WKY. #$P < 0.05$ vs. 10-week-old counterpart.

ity of contraction and relaxation in all animal groups either (data not shown).

Effect of IGF-1 and Insulin on Myocardial Contraction in the Presence of L-NAME. To explore the role of NO as one possible mechanism of action of IGF-1 and insulin, the effect of IGF-1 and insulin was re-examined in the presence of the nitric oxide synthase (NOS) inhibitor, L-NAME (100 μ*M*). L-NAME alone did not modify any of the mechanical indices at the dose used over a duration of 30 min in myocardium from any group. As shown in Figure 3(A), the IGF-1-induced positive inotropic response seen in 10-week-old WKY myocardium was not affected by L-NAME. Interestingly, pretreatment with L-NAME unmasked a positive inotropic response to IGF-1 in 10-week-old SHR myocardium. By contrast, at 25 weeks of age, L-NAME completely blocked the positive inotropic response of IGF-1 (500 ng/ml) in WKY myocardium, whereas it failed to modify the action of IGF-1 on SHR myocardium (Fig. 3B). Unlike IGF-1, the myocardial response to insulin (1–500 n*M*) was not affected by the pretreatment of L-NAME (100 μ*M*). In the presence of L-NAME, insulin (500 n*M*) decreased PTD by 1.8 ± 3.4 and 5.5 ± 1.6 in WKY and SHR groups at 10 weeks of age, whereas it increased PTD by 4.8 ± 4.2 and 1.9 ± 2.4%, in WKY and SHR groups at 25 weeks of age ($P > 0.05$). These results are similar to the insulin-induced response in the absence of L-NAME. Furthermore, neither the IGF-1- nor the insulin-induced response on the duration and velocity of contraction and relaxation was affected by L-NAME in any of the animal groups studied (data not shown).

Discussion

Insulin resistance and hyperinsulinemia are both associated with hypertension and advanced age (6). Resistance to the actions of insulin have been reported in adipocytes and skeletal muscle tissues from rodent models of essential hypertension and advanced age (6, 27). It is believed that insulin resistance may be related to postreceptor defects in the mechanism of insulin-mediated glucose uptake in target tissue (28). Both IGF-1 and insulin exert positive inotropic effects on cardiac growth and myocardial contraction (11, 12, 19, 29). However, resistance to IGF-1-induced actions

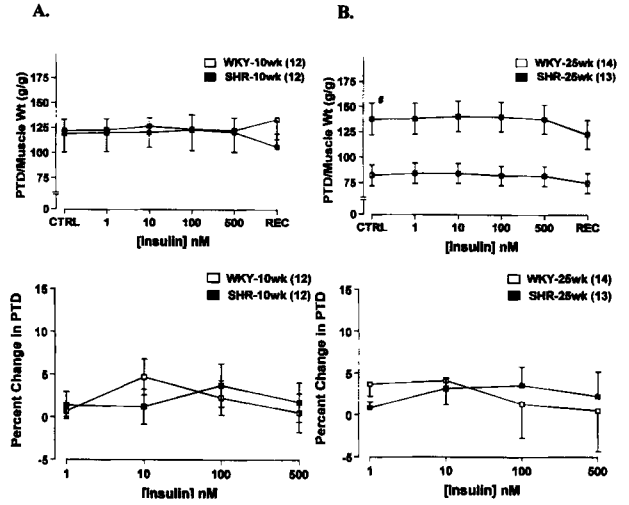

Figure 2. Inotropic response to insulin (1–500 n*M*) on PTD in papillary muscles from WKY (open square) and SHR (filled square) animals at 10 (A) and 25 (B) weeks of age. Upper panels: Inotropic response to IGF-1 when PTD was normalized to respective papillary muscle weight (g/g); Lower panels: Inotropic response to IGF-1 when PTD was presented as the percentage change from the respective control value. The number of muscles is given in parentheses. Mean ± SEM $^*P < 0.05$ *vs.* Control, $^\#P < 0.05$ vs. WKY group.

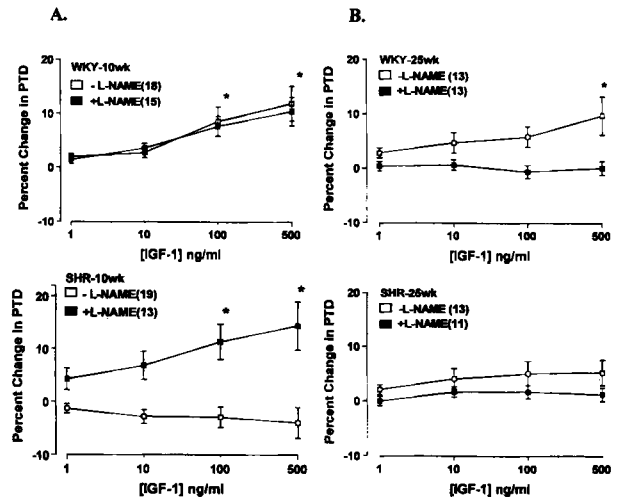

Figure 3. Effect of L-NAME on the IGF-1-induced inotropic response in papillary muscles from WKY (upper panels) or SHR (lower panels) animals at 10 (A) or 25 (B) weeks of age. Papillary muscles were pretreated with L-NAME (100 μ*M*) for 15 min, prior to application of IGF-1 (1–500 ng/ml). Data are presented as the percentage change from the respective control value. The number of muscles is given in parentheses. Mean ± SEM $^*P < 0.05$ vs. Control.

using experimental animal models of various insulin resistance states have been shown (6, 20, 22).

Myocardial inotropic actions of insulin have been studied extensively in states of normal insulin sensitivity, although its action has been somewhat contradictory. Studies have suggested that insulin exerts positive, negative, or no inotropic effects on cardiac growth and myocardial contraction (11, 12, 19, 30). IGF-1 has been shown to increase myocardial contraction, myocyte shortening, and intracellular Ca^{2+} transients (11, 19, 20). Results from this investigation showed that insulin exerts little inotropic action, whereas IGF-1 increases myocardial contraction in young normotensive animals (10 weeks old). However, this positive inotropic action of IGF-1 was not seen in SHR animals at the same age. The IGF-1-induced positive intropism in myocardium from normotensive animals was markedly reduced in 25-week-old animals. The attenuated responsiveness of IGF-1 in hypertension and/or increased age may be related to reduced number/effectiveness of IGF-1/insulin receptor or glucose transporters (6). Several observations have reported increased IGF-1 mRNA and protein levels in various models of hypertension, including human essential hypertension (24, 31, 32). It was reported that an elevation in vascular wall stress as a result of hypertension is an important predisposing factor for the over-expression of IGF-1 and growth hormone receptor mRNA (32). High circulating levels of IGF-1 or hyperinsulinemia, which is commonly seen in hypertension, may result in downregulation of IGF-1/insulin receptor number or affinity (24). However, some evidence has suggested an increased cardiac IGF-1 receptor expression in essential hypertension (33, 34). The reasons for the discrepancy between this increased IGF-1 receptor mRNA and the lack of response in hypertension observed in our study are not clear. The differential response between IGF-1 and insulin in SHR myocardium may be related to an altered expression of IGF-1/insulin hybrids found in insulin-resistance states such as hypertension (24). The response to high concentrations of IGF-1 may also be mediated through the insulin receptor, instead of the IGF-1 receptor alone.

Our data suggest that NO may modulate IGF-1-, but not insulin-induced, cardiac inotropic effects. Constitutive NOS (cNOS) as well as inducible NOS (iNOS) are present in cardiac myocytes (25). Although IGF-1 is known to stimulate NO production in various tissues or cell types (18, 26), there are no reports regarding cardiac tissues. A number of studies have indicated that a compensatory increase in cNOS activity occurs in hypertension (35), and a reduction in NO production/responsiveness occurs with advanced age (36). This alteration in cNOS activity may underlie the discrepancy in IGF-1-induced action between WKY and SHR groups at different ages. In 10-week-old WKY animals, IGF-1 caused a positive inotropic action, and NOS inhibition with L-NAME did not affect this response. This indicates that IGF-1 may be associated with a tonic NO production in young normotensive animals, a process that does not modulate myocardial contraction (37). However, in age-matched SHR animals, inhibition of NO production with L-NAME unmasked an IGF-1-induced positive inotropic response. This may be due to a high cNOS activity in hypertension associated with a substantial NO production induced by IGF-1. NO has been reported to exert a biphasic action on voltage-gated Ca^{2+} currents, including potentiation at lower concentrations and attenuation at higher concentrations (38). Mohan *et al.* (39) also reported that low concentrations of NO donor, S-nitroso-N-acetyl-D,L-penicillamine and cGMP (responsible in part for NO-induced action) exerts a positive inotropic effect, whereas

high concentrations display a negative inotropic response. It is possible that an optimal NO level may be required for normal myocardial responses to IGF-1. Thus, NOS inhibition shifts NO production from a compensatory high to a low normal level in young SHR myocardium, unmasking the IGF-1's intropic effect.

In our study, L-NAME abolished IGF-1 (500 ng/ml)-induced positive inotropism in 25-week-old WKY myocardium but had no effect on age-matched SHR myocardium. This suggests that NO modulated the inotropic effect of IGF-1 in 25-week-old normotensive, but not hypertensive, hearts. Several studies have indicated that advanced age may decrease NO production/responsiveness and differentially affect NOS activity in WKY versus SHR rats (36, 40). It is thus possible that the optimal NO level is not preserved with increased age. That L-NAME may completely abrogate the IGF-1-induced contraction in the 25-week-old WKY myocardium suggests the crucial role of NO in this response, which is expected to be at a lower level. However, in 25-week-old SHR myocardium, the reduced NO production/responsiveness may be compensated by the increased cNOS activity in hypertension. Thus, IGF-1 may stimulate a greater NO production in 25-week-old SHR animals that cannot be abolished by the concentration of L-NAME employed in these studies. Alternatively, the IGF-1 response in hearts from older hypertensive animals may be more dependent on other intermediate pathways than that of NO. Interestingly in this study, L-NAME did not alter the insulin-induced myocardial contractile response in any animal group. These data indicate that the difference between the effects of IGF-1 and insulin may be due, in part, to the difference in the modulation of NO.

Clinical and experimental studies examining the action of IGF-1 in the cardiovascular system in hypertension are limited. However, evidence has emerged for a role for IGF-1/NO as a mediator of hypertrophic/hyperplastic responses in hypertension. Future studies addressing the mechanisms whereby IGF-1 interacts with its receptor and binding proteins to produce its effects on NO and associated electromechanical coupling are required.

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