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Cardiac Function in Young and Old *Little* Mice

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Abstract

We studied cardiac function in young and old, wild-type (*WT*), and longer-living *Little* mice using cardiac flow velocities, echocardiographic measurements, and left ventricular (LV) pressure (P) to determine if enhanced reserves were in part responsible for longevity in these mice. Resting/baseline cardiac function, as measured by velocities, LV dimensions, $+dP/dt_{max}$, and $-dP/dt_{max}$, was significantly lower in young *Little* mice versus young *WT* mice. Fractional shortening (FS) increased significantly, and neither $+dP/dt_{max}$ nor $-dP/dt_{max}$ declined with age in *Little* mice. In contrast, old *WT* mice had no change in FS but had significantly lower $+dP/dt_{max}$ and $-dP/dt_{max}$ versus young *WT* mice. Significant decreases were observed in the velocity indices of old *Little* mice versus old *WT* mice, but other parameters were unchanged. The magnitude of dobutamine stress response remained unchanged with age in *Little* mice, while that in *WT* mice decreased. These data suggest that while resting cardiac function in *Little* mice versus *WT* mice is lower at young age, it is relatively unaltered with aging. Additionally, cardiac function in response to stress was maintained with age in *Little* mice but not in their *WT* counterparts. Thus, some mouse models of increased longevity may not be associated with enhanced reserves.

DWARF mice (1,2) and rats (3) have increased longevity under laboratory conditions and therefore are of interest in gerontology. However, many of these mice have complex lesions with multiple endocrine changes. For example, the Snell and Ames dwarf mice have hypothyroidism (1), which is well known to alter cardiac function (4,5).

The *Little* mouse is generated by a missense mutation in the growth hormone (GH)–releasing hormone receptor (*Ghrhr*) (6), but, importantly, the rest of its pituitary is intact and it has normal thyroid function (1). These mice have reduced levels of circulating insulin-like growth factor 1 (IGF-I) (7) and have about 1% of normal levels of circulating GH (1,2). As a result, the *Little* ($Ghrhr^{lit/lit}$) mice weigh about a third less (1) and live a third longer than their wild-type ($Ghrhr^{lit/+}$) littermates (2). It has been shown that *Little* mice, despite having significant deficiencies in GH, have normal hematopoiesis and normal thyroid function (8), but delayed immune and collagen aging (2). Although the anabolic effects of GH/IGF-I in general are well recognized, the specific effects of GH and IGF-I deficiency in isolation on mouse cardiac function are not well characterized. Studies in young dwarf rats showed reduced left ventricular

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(LV) weight and impaired cardiac performance in vitro with significantly impaired systolic function and reduced LV diastolic distensibility (9). Spontaneous dwarf rats have no detectable circulating GH levels and have IGF-I levels at <10% of normal rats (10). Impaired IGF-I signaling causes cardiomyocyte apoptosis in spontaneously hypertensive models of rats (11), and IGF-I–deficient mice have increased rates of apoptosis following myocardial infarction (12). In contrast, elevated levels of IGF-I augment myocardial contractility by sensitizing myofilaments to calcium in rat hearts (13) and retard apoptosis in heart failure models of mice (14) and in cultured rat cardiomyocytes (15). Cardiac-specific and supraphysiologic IGF-I levels in SIS2 mice produced enhanced function in youth and impaired function and hypertrophy in old age (16). In human adults with GH deficiency, GH replacement leads to augmentation of LV mass, intraventricular septum thickness, and stroke volume (17). These data would suggest that GH deficiency is associated with impairment in cardiac function and that correcting this deficiency by replacement of GH can improve cardiac function.

However, it is also known that GH and IGF-I–deficient animals live much longer than their wild-type (*WT*) counterparts (2,18–20), which may be in part due to maintenance of cardiac function with age in these animals. So, the following questions need to be answered: (i) Is cardiac function in dwarf mice different from that of *WT* mice? (ii) How does the cardiac function change with age in dwarf animals? and (iii) Are there augmented cardiac reserves available to the dwarf animals that could contribute to their extended longevity? To address these questions, we studied and compared cardiac function in young and old *Little* mice with that of their age-matched *WT* littermates.

Methods

Animal Preparation

Twenty-four young mice (aged 4 months; 11 *Little* and 13 *WT*) and 17 old mice (aged 30 months; 8 *Little* and 9 *WT*) were used in the study. Animals were kept in rooms with controlled temperature (24°C) and lighting (14:10 hour light/dark cycle) with free access to food and water. The diets of both groups of mice consisted of normal chow.

All studies (invasive and noninvasive) were performed on anesthetized mice. The mice were anesthetized with 1% isoflurane (in 100% oxygen) administered at a continuous flow rate of 20 mL/min (VetEquip, Inc., Pleasanton, CA) for noninvasive Doppler measurements. Pentobarbital cocktail (1.8 mL of pentobarbital sodium at 50 mg/mL, 4.0 mL of 200 proof ethyl alcohol, and 16.0 mL of 0.9% saline) administered intraperitoneally at 10 μL/g of body weight (BW) was used for the invasive LV pressure (LVP) measurements. The anesthetized mouse was placed on the electrocardiogram (ECG)/heater board with the board temperature adjusted to maintain mouse body temperature at 37 ± 1°C. The limbs of the mouse were taped to the four electrodes, the quality of ECG assessed, and the electrode contact optimized as needed. All animal protocols were approved by the Institutional Animal Care and Use Committee of Baylor College of Medicine in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (DHHS Publication No. 85-23, Revised 1985, Office of Science and Health Reports, Bethesda, MD).

Cardiac Doppler Measurement

Aortic and mitral blood flow velocities were measured with a 10 MHz pulsed Doppler probe in all mice. The probe was placed just below the sternum using minimal pressure and angled toward the ventricular inflow and outflow tracks, respectively (21). At each site, the sample volume depth and probe position were adjusted to record the maximum velocity with waveform, direction, and timing consistent with mitral or aortic velocity. We have verified in previous studies (22,23) that consistent and reproducible signals are obtainable from these sites

in mice without image guidance. Typical depth setting was 4–7 mm for transmitral recordings and 6–9 mm for transaortic recordings (23). Two-second segments of the Doppler signals along with ECG were acquired and stored using a Doppler signal processing workstation (DSPW; Indus Instruments, Houston, TX).

Echocardiography Measurement

Echocardiograph measurements were made in 21 young (11 *Little*, 10 *WT*) and in 11 old (5 *Little*, 6 *WT*) mice using an 8 MHz to 13 MHz probe (Sequoia C256; Acuson Siemens, Mountain View, CA). Short-axis M-mode was used for measurement of LV systolic and diastolic dimensions. Percent fractional shortening (%FS) was calculated as [(LVEDD − LVESD)/LVEDD)] × 100, where LVESD is LV end-systolic dimension and LVEDD is LV end-diastolic dimension.

LVP Measurement

We were able to measure LVP in 15 young (7 *Little*, 8 *WT*) and in 13 old (6 *Little*, 7 *WT*) mice using a 0.36-mm-diameter pressure catheter. The neck area of the anesthetized mouse was shaved, and using blunt surgical procedures, the right carotid artery was isolated. The artery was tied off distally, and the proximal end was temporarily closed. A small cut was made in the artery wall, and a modified RADI PressureWire^3 (RADI Medical Systems, Upsala, Sweden) was inserted and held in place with a suture tied over the artery–catheter overlap region (21). The proximal end of the artery was then opened, and the catheter was advanced into the ascending aorta and then into the LV. LVP was measured at baseline and after intraperitoneal administration of dobutamine (1.5 μg/g of BW as reported in Tanaka and colleagues, 24). Again, the signals were acquired using DSPW and stored for offline analysis.

Data Analysis

Noninvasive cardiac parameters such as peak and mean aortic flow velocities, mean aortic acceleration, peak early flow velocity, and isovolumic contraction (ICT) and relaxation (IRT) times were extracted from aortic and mitral flow velocity signals. Tei index was calculated as (ICT + IRT)/systolic ejection time (ET) as defined by Tei and colleagues (25). Maximal rate of LV contractility ($+dP/dt_{max}$; mmHg/s), maximal rate of LV relaxation ($-dP/dt_{max}$; mmHg/s), and τ (ms; time constant of −dP/dt) were calculated from the LVP signal. All the parameters are presented in the form of mean ± standard error (*SE*), and comparisons were made using paired and unpaired Student's *t* test using a significance level of .05.

Results

Little mice are clearly smaller. Both young and old *Little* mice weighed significantly less than their *WT* counterparts (*WT* vs *Little*—young: 22.8 ± 0.3 vs 13.3 ± 0.4 g, $p < .05$; old: 30.7 ± 0.8 vs 18.4 ± 0.8 g, $p < .05$), respectively. This difference in BW represented about 42% lower weight in young *Little* mice and 40% lower weight in old *Little* mice compared to their respective *WT* counterparts. No significant differences were observed between the baseline heart rates of the two groups with either of the anesthetics. The data are summarized in Table 1.

Doppler Studies

We studied systolic and diastolic function noninvasively with pulsed Doppler in *Little* mice and their *WT* littermates. Indices of systolic function such as peak and mean aortic flow velocities and mean aortic acceleration were significantly lower in the young *Little* mice than in the young *WT* mice. Also, peak early mitral velocity in young *Little* mice was significantly

lower than that of young *WT* mice, but no significant differences were observed either in ICT, IRT, or Tei index between young *Little* and *WT* mice (see Table 1).

We then examined the old *Little* mice compared to the old *WT* mice. Differences were found in systolic indices with significantly lower peak and mean aortic flow velocities and mean aortic acceleration in the old *Little* mice. No significant differences were observed in peak mitral flow velocity, ICT, IRT, or Tei index between the old *Little* and *WT* mice.

Peak and mean aortic velocity and mean aortic acceleration were decreased significantly in old versus young *Little* mice. In *WT* mice, peak aortic velocity and peak early mitral velocity were decreased significantly in the old versus young mice. The Tei index was significantly higher in the old *WT* than in the young *WT* mice, which is consistent with overall dysfunction with age. In general, the values for the young *Little* mice were slightly lower but not significantly different from those in old *WT* mice (Table 1).

Echocardiography Studies

Echocardiograph measurements (Figure 1) showed that *Little* mice had significantly lower LV systolic and diastolic dimensions than their respective *WT* littermates, but %FS remained the same in *Little* and *WT* mice within each age group. Additionally, %FS did not change significantly with age in *WT* mice, but old *Little* mice had significantly higher %FS than did young *Little* mice.

Invasive Studies

The parameters of $+dP/dt_{max}$, $-dP/dt_{max}$, and τ (time constant of relaxation) were derived from the invasive LVP measurements. Both $+dP/dt_{max}$ and $-dP/dt_{max}$ were significantly lower in the young *Little* mice compared to their young *WT* littermates, but τ was similar. In old mice, however, the differences in $+dP/dt_{max}$ and $-dP/dt_{max}$ between *Little* and *WT* mice disappeared.

Both $+dP/dt_{max}$ and $-dP/dt_{max}$ were significantly lower in old *WT* mice compared to young *WT* mice (Table 1). However, aging did not diminish the heart function in old *Little* mice compared to young *Little* mice. We found no significant differences in τ between any of the groups.

Responses to Stress (Dobutamine)

Heart rate, $+dP/dt_{max}$, and $-dP/dt_{max}$ increased significantly, and τ decreased significantly, from their respective baseline values in the young *Little* and *WT* mice following the administration of dobutamine. Although the trend was similar in both groups of young mice in response to dobutamine, the percent change in magnitude from baseline showed that $+dP/dt_{max}$ increased by 98% in *WT* and by 76% in *Little* mice, $-dP/dtmax$ increased by 28% in *WT* and 40% in *Little* mice, and τ decreased by 28% in *WT* and 34% in *Little* mice. The absolute baseline and postdobutamine values of $+dP/dt_{max}$, $-dP/dt_{m}ax$, and τ in young mice are summarized in Figure 2. In old mice the percent change in magnitude from baseline showed that $+dP/dt_{max}$ increased by only 65% in *WT* and increased by 91% in *Little* mice, $-dP/dt_{max}$ increased by 37% in *WT* and 30% in *Little* mice, and τ decreased by 22% in *WT* and 31% in *Little* mice. The absolute baseline and post-dobutamine values of $+dP/dt_{max}$, and $-dP/dt_{max}$ in old mice are shown in Figure 3.

When compared for effects of aging within the groups, the magnitude of responses of young *WT* mice was significantly higher than that of the old *WT* mice, whereas the magnitude of responses of young and old *Little* mice was similar.

Discussion

Dwarf mice, including the *Little* mouse, live much longer than *WT* mice. This extended life span makes dwarf mice of interest in the field of geriatrics, but very little is known about the cardiovascular function of these mice and how it is altered as they age. Many of the available models of dwarfism have significant global pituitary dysfunction including loss of thyroid regulation and lack of prolactin in addition to the deficit in GH production (2). Thyroid hormone plays a fundamental role in cardiovascular homeostasis, and any alterations in thyroid function lead to altered cardiac function, including changes in heart rate (4,5). Therefore, it would be no surprise that altered cardiac function would occur in the Snell or Ames dwarf mice where very low thyroid hormone levels are part of the phenotype. The *Little* mouse model of dwarfism has no active GH-releasing hormone receptor, but the rest of its anterior pituitary is intact and has normal thyroid function (1). Therefore, we hypothesized that cardiac function in these mice might be robust and not deteriorate with age.

Body Weight

GH deficiency is associated with significant reduction in BW in humans (26,27), rats (9,28, 29), and mice (2,30,31). Our study confirmed that the young *Little* mice have significantly decreased BW compared to their *WT* littermates. The percent difference in BW with age is maintained in these mice (*WT* increased 35% and *Little* by 38%). Thus *Little* mice have aging-related obesity as do *WT* mice under normal dietary conditions. Miller and colleagues (30) reported that low BW at a young age is a significant predictor of prolonged life span in mice. We killed our animals after the invasive studies; therefore, we were unable to record either their life span or weight beyond 30 months.

Cardiac Function in Young *Little* Mice

Abnormalities in cardiac function have been a component of human and animal models deficient in GH. In GH-deficient humans, cardiac performance (as measured by ejection fraction and cardiac index) is significantly depressed (32), and several abnormalities in cardiac structure and function have been reported (33,34). Cardiac abnormalities in dwarf rats include reduced LV weight, smaller size of myocytes, impaired myocardial contractility and distensibility (9), reduced LV diastolic volumes (indexed to tibial length), depressed cardiac index, and abnormal stress-shortening relationships (34). Although the effects of GH deficiency are well established in dwarf mice (17), there are very few reports on cardiac function in these animals. Ren and Brown-Borg (31) reported that dwarf mice had lower heart weight and that excitation–contraction coupling in ventricular myocytes was impaired consistent with low levels of thyroid hormone. In our study, noninvasive cardiac Doppler indices showed significantly decreased systolic and diastolic function, and echocardiography studies showed decreased systolic and diastolic dimensions in young *Little* mice under light isoflurane anesthesia (baseline). The relative decreases in systolic and diastolic dimensions, however, kept the %FS similar in young *Little* and *WT* mice. Importantly, heart rates under these conditions were not different, consistent with the absence of thyroid differences between the two groups. These observations in *Little* mice at baseline were also confirmed by the reduced values of $+dP/dt_{max}$ and $-dP/dt_{max}$ obtained from LVP, despite slight decreases in heart rate under pentobarbital anesthesia. We acknowledge that anesthetics influence hemodynamic measurements; however, mouse heart rates of 350–400 beats/min were reported in sleeping mice when monitored using telemetry (35). While the heart rates with isoflurane were about 400 beats/min, they were slightly lower than with pentobarbital but still >350 beats/min. This would make the $\pm dP/dt$ values lower than those reported by others. The assumption that the effect of anesthesia is similar on both groups of mice allowed us to evaluate and compare the relative performance of the two groups of mice. The findings are consistent with studies in human and animal models of dwarfism that have shown that isolated GH deficiency

is associated with impairment in cardiac function (9,13,17,33), but are in contrast to the findings of Lembo and colleagues (36), who reported that "midi" mice with 30% of normal levels of IGF-I (total IGF-I=51 ng/mL) had better myocardial contractility perhaps enhanced due to elevated serum GH levels. Similarly, patients of Laron syndrome who have high levels of serum GH have normal LV contractile reserve (37). However, the levels of IGF-I in the *Little* mouse are even lower at 10% of normal (7) or 9%–23% of normal, as reported by Liang and colleagues (1) and have about 1% of normal levels of circulating of GH (1,2), thus resulting in diminished cardiac function in these mice.

On the basis of our findings, we considered that the lowered function at baseline in *Little* mice might permit enhanced physiologic reserves in later life for dealing with potential challenges. To test this hypothesis, we used dobutamine to maximally stimulate the heart (24) of young *Little* and *WT* mice. We found no differences in the relative peak responses of either systolic or diastolic function between the young *Little* and *WT* mice as measured by LVP (Figure 2). Thus, the young *Little* mice had neither enhanced nor decreased cardiac contractile reserve under stress when compared to their *WT* littermates.

Cardiac Function in Old *Little* Mice

The noninvasive cardiac Doppler indices of systolic function were lower in old *Little* mice at rest (baseline) compared to old *WT* mice. This finding was consistent with LV dimensions, but again the relative decreases in systolic and diastolic dimensions kept the %FS similar in young *Little* and *WT* mice. With age, however, %FS was significantly higher in *Little* mice than in *WT* mice (Figure 1). The findings of reduced dimensions and function with age as measured noninvasively were not confirmed by invasive studies ($+dP/dt_{max}$ and $-dP/dt_{max}$). Importantly, there were no age-related differences in $+dP/dt_{max}$ and $-dP/dt_{max}$ of *Little* mice from 4 months to 30 months of age, and the increase in %FS in old *Little* mice may support this finding that the cardiac contractility in these mice is unaltered if not improved. In contrast, $+dP/dt_{max}$ and $-dP/dt_{max}$ decreased significantly in *WT* mice with age (see Table 1). The significantly higher value of the Tei index in the old *WT* mice was consistent with the presence of cardiac dysfunction.

Despite the diminished baseline cardiac function in the young *Little* mice when compared to their *WT* littermates, their response to stress on a percentage or absolute basis did not change with age (see Figure 3). We speculated that the low levels of circulating IGF-I responsible for the diminished baseline cardiac function at a young age in *Little* mice could have played a cardioprotective role. Delaughter and colleagues (16) have shown that chronic expression of local IGF-I in the SIS2 transgenic mouse resulted in diminished systolic performance in old age, despite enhanced systolic performance at a young age. Although adults with Laron syndrome or Lembo and colleagues' (36) "midi" mouse live long perhaps due to high serum levels of GH, humans with GH and several other pituitary hormone deficiencies are known to have lived up to the age of 91 (38). It is reported that patients with adult onset of pituitary hormone deficiencies could have died early of complications from tumors, surgical procedures, or radiation treatments (37). While we can speculate that normal levels of IGF-I in the *WT* mouse may have caused its heart to hypertrophy with age and diminish systolic performance (see Figure 4), it is also known that IGF-I levels can decrease substantially from 4 months of age to 30 months of age in *WT* mice (39), and yet these mice have reduced contractility. It has been shown that serum IGF-I levels are decreased by as much as 50% in 80- to 90-year-old humans (40). Despite the reduction, the circulating levels of IGF-I are still high in *WT* mice compared to those in dwarf animals. Thus our hypothesis of Figure 4 may be valid; therefore, the role of the reduced circulating levels of IGF-I on the myocardial performance with age needs to be further investigated.

A basic mechanism of aging is the accumulation of oxidative damage. It has been reported that *Little* mice have increased stress resistance indices as observed through the up-regulation of several genes involved in reactive oxygen species detoxification (41). In *Little* mice, this could slow the aging of cardiac tissue through the reduction in the cumulative effect of oxidative damage caused by the presence of toxic free radicals that are generated from normal metabolism. Thus, dwarf mice may have enhanced antioxidative defense systems, especially if they live in a relatively stress-free environment (17,42), but may not have enhanced physiologic reserves to respond to environmental challenges. Also, higher measures of hematopoetic stem cells in *Little* mice (8) means that the damaged blood cells may be more readily replaced with new ones (albeit less efficiently in old age) to maintain function. All these potentially protective mechanisms may contribute to longevity in *Little* mice observed in laboratory environments.

Conclusion

Dwarf mice, which live much longer than their wild-type counterparts, might be aided by maintenance of cardiac function with age. We studied and compared the cardiac function in young and old *Little* (dwarf) mice to that of their *WT* littermates. Our results show that Doppler-derived systolic and diastolic measurements, Echocardiograph measurements of systolic and diastolic dimensions, and LVP-derived $+dP/dt_{max}$ and $-dP/dt_{max}$ at baseline were decreased in the young *Little* mice compared to their *WT* littermates. Although cardiac function in young *Little* mice is diminished, further deterioration did not occur with age (unlike that in *WT* mice). Stress-induced changes in LVP were similar in young *Little* and *WT* mice when compared to their respective baseline values. In the old *Little* and *WT* mice, the changes in $-dP/dt_{max}$ to stress were similar when compared to their respective baseline values. However, with aging, the increase in $+dP/dt_{max}$ to stress was slightly enhanced in *Little* mice and slightly diminished in *WT* mice. Neither of our hypotheses—(i) enhanced baseline function in *Little* mice or (ii) increased reserve in *Little* mice—proved to be correct. Instead, we found that the status of cardiac function at baseline and under stress, although reduced, was maintained with age in *Little* mice but not in their *WT* counterparts. This maintenance of cardiac function with age suggests that some models of increased longevity may not be associated with enhanced reserves.

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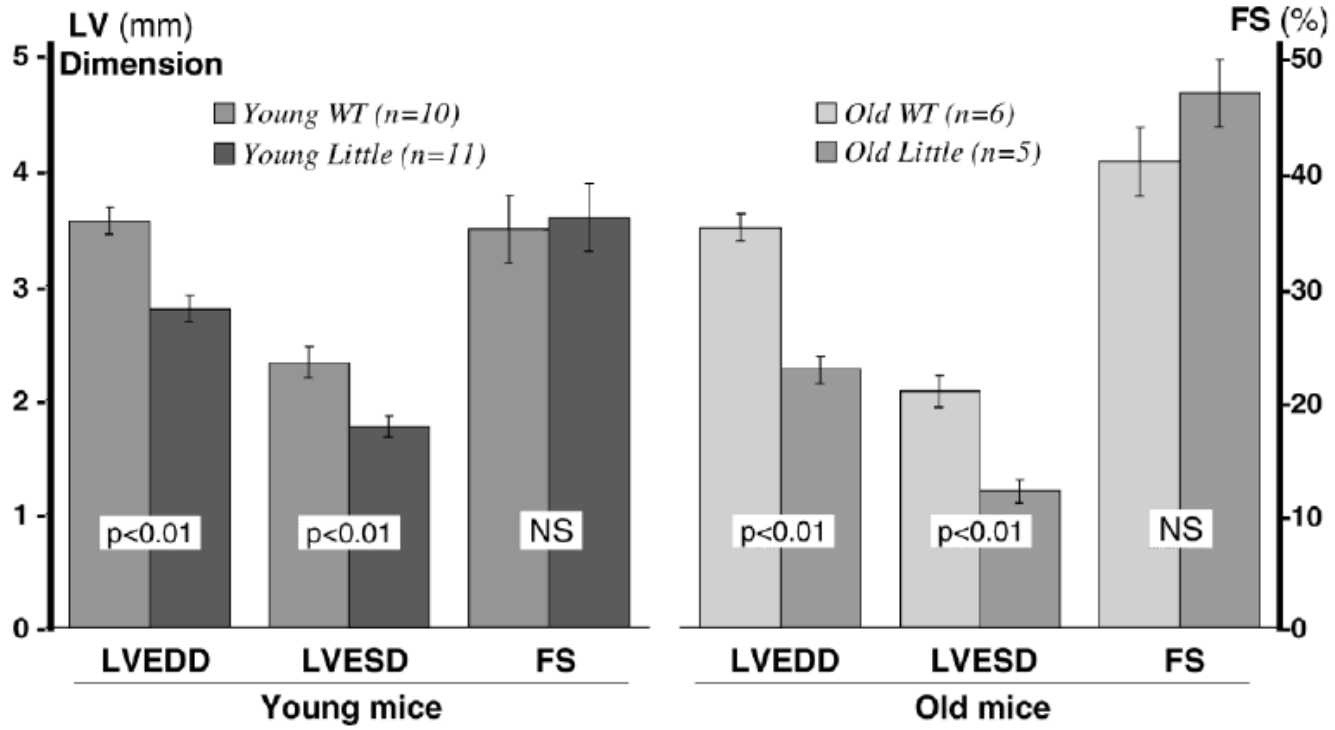

Figure 1.
Echocardiographic measurement of left ventricular (LV) dimensions (LV end-diastolic dimension [LVEDD] and LV end-systolic dimension [LVESD]) and percent fractional shortening (%FS) in young and old *Little* and wild-type (*WT*) mice.

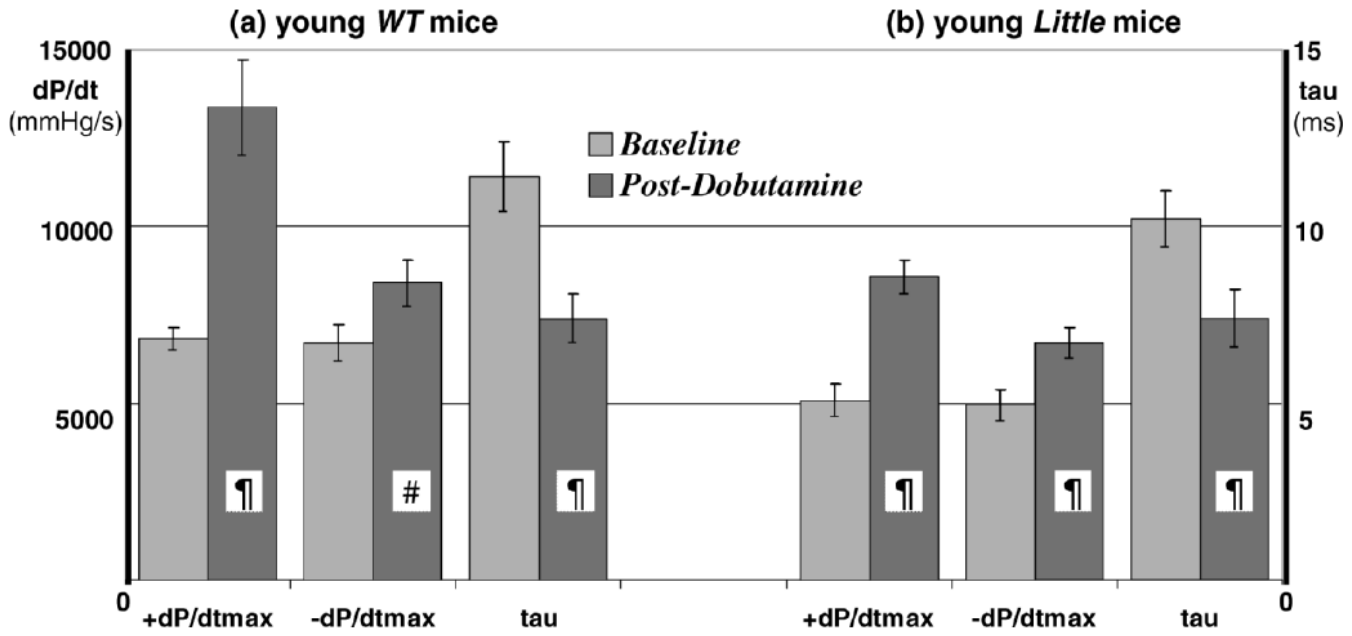

Figure 2.

Baseline and postdobutamine left ventricular pressure parameters in 8 young wild-type (*WT*) (**a**) and 7 young *Little* mice (**b**) ($^{¶}p < .01$, $^{\#}p < .05$ postdobutamine vs baseline). The heart rates at (*WT* vs *Little*) were 392 ± 18 versus 363 ± 32 beats/min at baseline and 541 ± 9 versus 535 ± 10 beats/min postdobutamine.

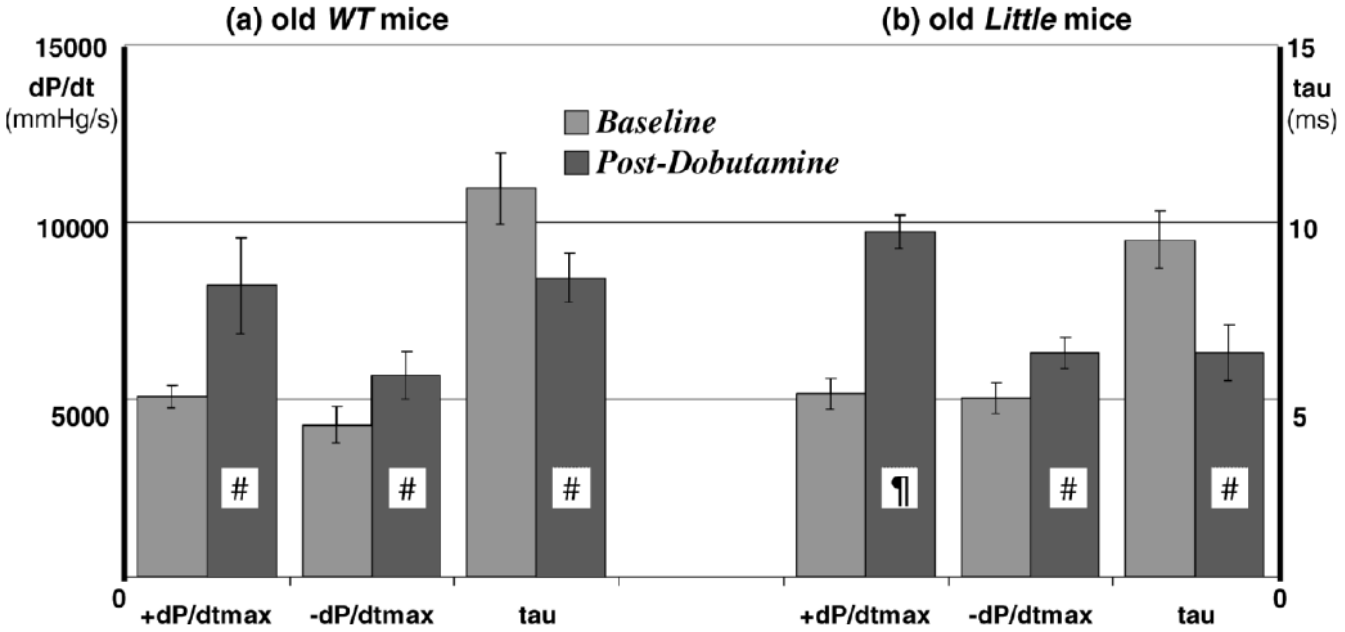

Figure 3.

Baseline and postdobutamine left ventricular pressure parameters in 7 old wild-type (*WT*) (**a**) and 6 old *Little* mice (**b**) ($^{¶}p < .01$, $^{\#}p < .05$ postdobutamine vs baseline). The heart rates at (*WT* vs *Little*) were 392 ± 8 versus 385 ± 6 beats/min at baseline and 559 ± 25 versus 515 ± 25 beats/min postdobutamine.

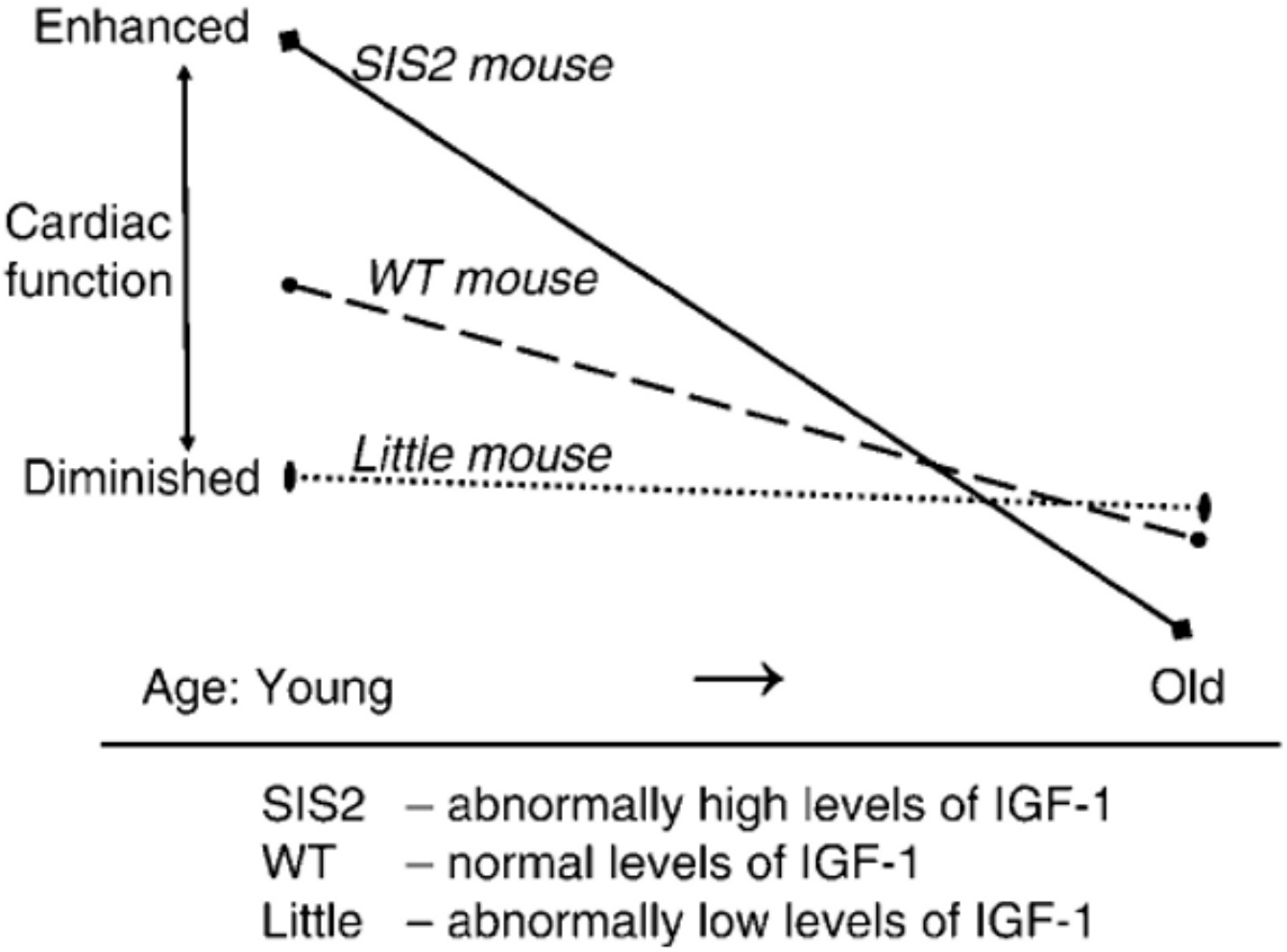

Figure 4.
Plot of hypothetical curves concerning cardiac function in mice with different levels of insulin-like growth factor 1 (IGF-I): SIS2 mouse (high), wild-type (*WT*) mouse (normal), and *Little* mouse (low).

Table 1

Baseline (Resting Values) Parameters Extracted From Noninvasive Cardiac Doppler Flow Velocity Signals and Invasive Left Ventricular (LV) Pressure

Parameters	Young Mice		Old Mice	
	***WT* (11)**	***Little* (10)**	***WT* (9)**	***Little* (8)**
General				
Heart rate (beats/min)	414 ± 12	380 ± 16	409 ± 14	371 ± 11
Body weight, g	22.8 ± 0.3	13.3 ± 0.4*	30.7 ± 0.8†	18.4 ± 0.8‡,§
Cardiac Doppler indices				
Peak aortic flow velocity, cm/s	88.5 ± 2.1	73.7 ± 3.0*	78.6 ± 3.2†	65.0 ± 2.5‡,§
Mean aortic flow velocity, cm/s	21.4 ± 0.6	17.6 ± 1.1*	19.8 ± 1.1	15.5 ± 0.6‡,§
Mean aortic acceleration, cm/s^2	7254 ± 257	5943 ± 434*	6714 ± 485	5304 ± 304‡,§
Peak E-flow velocity, cm/s	75.1 ± 1.6	61.4 ± 3.5	62.8 ± 5.4†	52.5 ± 3.7
Isovolumic contraction time, ms	12.3 ± 0.4	11.5 ± 0.7	13.5 ± 0.6†	12.0 ± 0.5
Isovolumic relaxation time, ms	18.4 ± 0.5	19.2 ± 1.2	20.5 ± 1.1	21.2 ± 1.0
Tei index	0.56 ± 0.01	0.55 ± 0.03	0.66 ± 0.11	0.61 ± 0.02
	WT (8)	*Little* (7)	*WT* (7)	*Little* (6)
LV pressure indices				
Heart rate, beats/min	392 ± 18	363 ± 32	392 ± 8	385 ± 6
Maximal +dP/dt, mmHg/s	6819 ± 319	5079 ± 449*	5062 ± 557†	5153 ± 375
Maximal −dP/dt, mmHg/s	−6708 ± 521	−4941 ± 434*	−4291 ± 501†	−5028 ± 601
Tau, τ, ms	11.6 ± 0.9	10.2 ± 0.8	11.0 ± 1.2	9.3 ± 1.8

Notes: All values are mean ± standard error.

Comparisons at $p < .05$:

*Young *WT* versus young *Little*.

†Young *WT* versus old *WT*.

‡Old *WT* versus old *Little*.

§Young *Little* versus old *Little*.

WT = wild-type.