Modulation of Left Ventricular Iodine-125-MIBG Accumulation in Cardiomyopathic Syrian Hamsters Using the Renin-Angiotensin System

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Genetically inbred cardiomyopathic hamsters were examined to investigate the mechanism of reduced myocardial accumulation of metaiodobenzylguanidine (MIBG) in the cardiomyopathic heart. **Methods:** Bio 14.6 Syrian hamsters (hypertrophic stage: n = 15, early heart failure stage: n = 17) and control F1b strain golden hamsters (n = 36) were injected with 296 kBq of [^{125}I] MIBG and killed 30 min or 4 hr later. Thirty-three of these hamsters were pretreated with 10 mg/kg of desipramine to determine non-neuronal MIBG accumulation. To evaluate the nonexocytotic MIBG release from nerve endings, desipramine was administered to four Bio 14.6 hamsters 15 min after [^{125}I]MIBG injection. To determine the role of the activated renin-angiotensin system (RAS) in MIBG washout from sympathetic nerve terminals in cardiomyopathy at early heart failure stage, 10 mg/kg/day cilazapril, an angiotensin-converting enzyme inhibitor, was given orally to 7 controls and 16 cardiomyopathic hamsters for 16 wk. **Results:** In the absence of desipramine pretreatment, left ventricular [^{125}I]MIBG accumulation 4 hr after injection was 0.376% ± 0.015 %kg dose/g (mean ± s.e.m.) in the hypertrophic hamsters (versus 0.418 ± 0.019 in controls of the same age; ns), and 0.195 ± 0.025 in early heart failure hamsters. Treatment with cilazapril partially restored MIBG accumulation in the Bio 14.6 hamsters but did not affect the controls. **Conclusion:** Decreased [^{125}I]MIBG accumulation in cardiomyopathic hamsters during the early heart failure stage is caused by neuronal release which is partially modulated by the activated RAS.

Key Words: iodine-123-metaiodobenzylguanidine; cardiomyopathy; angiotensin-converting enzyme inhibitor

Radioiodinated metaiodobenzylguanidine (MIBG), an analog of guanethidine, has been used to detect myocardial sympathetic denervation after myocardial infarction (*1–5*) and heart transplantation (*6,7*), as well as to identify ab-

normal adrenal medullary tissue (*8*) or various neuroectodermal tissues (*9,10*). Decreased cardiac accumulation and accelerated washout have also been reported in patients with cardiomyopathy (*11–15*). In addition, it has been reported that MIBG uptake 4 hr after injection is the best noninvasive predictor of survival of patients with congestive heart failure, including patients with cardiomyopathy (*16*); little is known, however, about the mechanism of reduced MIBG accumulation in the cardiomyopathic heart. It is widely known that the sympathetic nervous system and the renin-angiotensin system (RAS) are activated in patients with heart failure (*17–20*). Since angiotensin II facilitates cardiac sympathetic activation by increased neurotransmitter release from sympathetic nerve terminals (*21,22*), RAS activation may influence MIBG accumulation in failing hearts.

Bio 14.6 Syrian hamsters represent a useful hereditary model for cardiomyopathy (*23*). These animals develop progressive cardiac myocytolytic necrosis, which begins at about 30 days of age and worsens over the next 4 mo. Subsequent cellular hypertrophy is followed by congestive heart failure and death within 1 yr (*24,25*). Using this animal model, we investigated: (a) the relationship between cardiac [^{125}I]MIBG accumulation and the cardiomyopathic stage of the animals; (b) whether decreased [^{125}I]MIBG accumulation is primarily neuronal or non-neuronal; (c) whether the washout is due to exocytotic or nonexocytotic release from sympathetic nerve terminals, and (d) whether the administration of an angiotensin-converting enzyme inhibitor (ACE) can improve cardiac MIBG accumulation.

MATERIALS AND METHODS

Animals

Cardiomyopathic Syrian hamsters (Bio 14.6) and normal healthy golden hamsters (F1b) were given a standard laboratory diet and water ad libitum. Experiments were undertaken after breeding in our laboratory for at least 2 wk.

Chemicals

Iodine-125-MIBG with a specific activity of 7.4 MBq/μg enabled reduction of the loading dose of MIBG to 0.4 μg/kg, which is considerably lower than the limiting dose causing neuronal saturation (26).

Effect of Desipramine on Myocardial MIBG Accumulation

Twenty-six F1b control hamsters, 160 days old, were used to determine the maximal effect of desipramine, a specific inhibitor of norepinephrine or MIBG neuronal uptake. Catheters were placed into the external jugular veins under light anesthesia induced by sodium pentobarbital (20 mg/kg i.p.). These venous catheters were inserted subcutaneously to emerge at the back of the neck. On the following day, these hamsters were injected intravenously with 0.4 ml of saline or desipramine solutions at doses of 0.1, 1.0, 5.0, 10.0 or 20.0 mg/kg body weight via the catheters after their complete recovery from anesthesia. Thirty minutes later they were injected with 296 kBq [^{125}I]MIBG and then killed by decapitation 4 hr later. Left ventricles were dissected and weighed, and their radioactivities were determined by an automated gamma counter. The inhibition of [^{125}I]MIBG accumulation by desipramine was expressed as a percent of the mean value of myocardial [^{125}I]MIBG in control saline-treated hamsters.

MIBG Accumulation in Normal and Cardiomyopathic Hearts

Eight Bio 14.6 hamsters at the hypertrophic stage (160-days-old 160), 10 control F1b strain hamsters (160-days-old), 9 Bio 14.6 hamsters at the early heart failure stage (220-days-old) and 8 F1b hamsters (220-days-old) were injected with 296 kBq [^{125}I]MIBG via the catheters. Animals were killed 30 min or 4 hr following the [^{125}I]MIBG injection and left ventricular radioactivity was counted. Left ventricular [^{125}I]MIBG accumulation was measured by multiplying kilograms per body weight by the percent injected dose/gram of tissue (% kg dose/g) (27).

Desipramine Pretreatment Studies

To determine non-neuronal left ventricular MIBG accumulation, 7 hypertrophic stage hamsters, 8 early heart failure stage hamsters and 18 control hamsters were injected intravenously with 10 mg/kg of desipramine 30 min prior to the [^{125}I]MIBG injection. The hamsters were killed 30 min or 4 hr following [^{125}I]MIBG and their left ventricles were weighed and counted. The neuronal component was calculated by subtracting the non-neuronal component (with desipramine pretreatment) from the total left ventricular MIBG accumulation (without desipramine). Either neuronal or non-neuronal washout rates from 30 min to 4 hr were calculated from these values.

Desipramine Post-Treatment Studies

Because desipramine is known as a potent inhibitor of nonexocytotic neurotransmitter release as well as an uptake-1 blocker (28-30), 10 mg/kg of desipramine were injected 15 min after [^{125}I]MIBG injection in 4 Bio 14.6 strain hamsters at 220 days of age. These hamsters were killed 4 hr after the [^{125}I]MIBG injection. Their left ventricles were counted and compared with the untreated hamsters.

Cilazapril Studies

To evaluate the effect of an ACE inhibitor on MIBG accumulation, cilazapril or the inactive vehicle was given orally once daily to control (n = 7) and cardiomyopathic hamsters (n = 16) from the age of 108 days to 220 days. Ten mg/kg/day of cilazapril in 0.4 ml of physiologic saline was given daily by gastric gavage to F1b hamsters for 16 wk (control) and to Bio 14.6 hamsters for 16 wk (long-term treatment). Alternatively, saline was given to Bio 14.6 hamsters for 15 wk and 4 days, and cilazapril for the last 3 days (short-term treatment). The hamsters in the control inactive vehicle group were given the same volume of saline for 16 wk. This dose of cilazapril has been reported to reduce plasma and tissue angiotensin-II levels significantly in Bio 14.6 hamsters (31). Body weights were measured every 2 wk. All hamsters were examined for myocardial [^{125}I]MIBG accumulation four hr after injection at an age of 220 days.

Myocardial Blood Flow

Four of the F1b and six of the Bio 14.6 hamsters were injected with 2.775 MBq of ^{201}T-Cl 30 min prior to killing to determine the myocardial blood flow, and the data were recorded as a percentage of the injected dose/g (% ID/g).

Statistical Analyses

Values are expressed as the mean ± s.e.m. for MIBG accumulation or the mean ± s.d. for body weight or desipramine dose-inhibition study. Data analyses were performed by ANOVA and probability values less than 0.05 were considered to be statistically significant.

RESULTS

Effect of Desipramine on Myocardial Iodine-125-MIBG Accumulation

As shown in Figure 1, desipramine caused dose-dependent inhibition of myocardial [^{125}I]MIBG accumulation in F1b hamsters. This inhibition reached a maximal plateau (72% inhibition) at a dose of 5 mg/kg of desipramine. The neuronal component of [^{125}I]MIBG accumulation therefore accounts for approximately 70% of the total [^{125}I]MIBG accumulation 4 hr after injection, and 10 mg/kg of desipramine is adequate to achieve near-complete inhibition of neuronal uptake.

Cardiac Neuronal Iodine-125-MIBG Accumulation in Normal and Cardiomyopathic Hamsters

Table 1 summarizes the [^{125}I]MIBG accumulation in the left ventricles of F1b hamsters (160 and 220 days) which served as controls, and of the Bio 14.6 hamsters at hypertrophic (160 days) and early heart failure (220 days) stages. The total left ventricular [^{125}I]MIBG accumulation 4 hr after injection was significantly lower in the Bio 14.6 and F1b hamsters at 160 days compared with F1b hamsters at 220 days. When compared with control hamsters of each age, [^{125}I]MIBG accumulation 4 hr after injection was significantly reduced in the Bio 14.6 hamsters at early heart failure stages (p < 0.01), but not in hamsters at hypertrophic stages. Since 10 mg/kg of desipramine almost completely blocks MIBG uptake by sympathetic nerve endings, [^{125}I]MIBG accumulation in desipramine-pretreated hamsters likely represents non-neuronal left ventricular [^{125}I]MIBG accumulation. The non-neuronal accumulation in the Bio 14.6 hamsters was significantly lower than in controls at 160 days. Then, a neuronal component in each group was calculated by subtracting the non-neuronal ac-
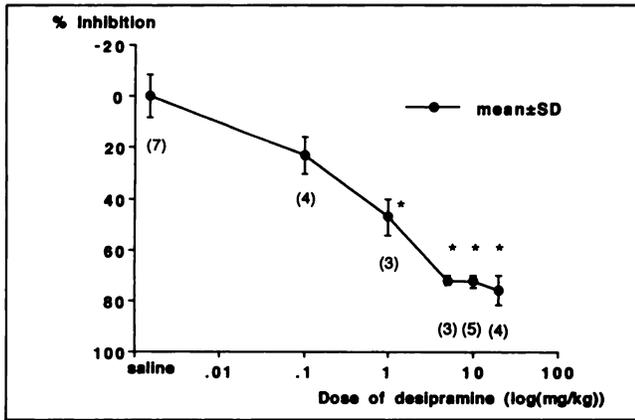
FIGURE 1. Dose-dependent inhibition of myocardial [^{125}I]MIBG accumulation by desipramine pretreatment. F1b hamsters of 160 days old were pretreated with saline or desipramine at doses of 0.1, 1.0, 5.0, 10.0 or 20.0 mg/kg of body weight 30 min prior to the injection of [^{125}I]MIBG. The inhibition is expressed in percent of the mean value of the saline-treated hamsters. Hamsters were killed 4 hr after [^{125}I]MIBG injection, and the left ventricular [^{125}I]MIBG counted by a gamma counter. * = significantly different from saline treated hamsters (p < 0.01).

cumulation from the total [^{125}I]MIBG accumulation, and the washout from either neuronal and nonneuronal components was also calculated. The cardiomyopathic hamsters at early heart failure stage had an extremely high neuronal washout rate (73.0%), while the neuronal washout was significantly lower for the other hamster groups (range: 17.0%–22.4%). On the other hand, the non-neuronal washout remains relatively stable (range: 67.2%–76.0%) in all four groups. The rapid neuronal washout seems to explain the reduction of total [^{125}I]MIBG accumulation in hamsters at early heart failure stage.

Body Weight and Left Ventricular Weight

Body weights and left ventricular weights in each F1b and Bio 14.6 hamsters at 160 and 220 days are shown in Table 2. Left ventricular weights did not significantly differ from each other in four groups, in spite of the significantly lower body weights in cardiomyopathic hamsters. The ratio of left ventricular weight to body weight was significantly higher in cardiomyopathic hamsters.

Blockade of Nonexocytotic Release

The left ventricular [^{125}I]MIBG accumulation was 0.196% ± 0.024 %kg dose/g (mean ± s.e.m., n = 4) in the hamsters treated with desipramine 15 min following [^{125}I]MIBG injection, and 0.195% ± 0.025 %kg dose/g (n = 4) in the untreated Bio 14.6 hamsters at 220 days of age. No significant increase in [^{125}I]MIBG accumulation was found following the blockade of nonexocytotic release with desipramine post-treatment.

Myocardial Blood Flow

The left ventricular accumulation of ^{201}T-Cl was 5.51 ± 0.78 (mean ± s.e.m., n = 4), 5.39 ± 0.05 (n = 3), and 5.28 ± 0.82 (n = 3) %dose/g in the F1b and Bio 14.6 hamsters at 160 days and 220 days of age, respectively. Therefore, no significant differences in myocardial blood flow were found between these three groups.

TABLE 1
Left Ventricular Accumulation of Iodine-125-MIBG in Control and Cardiomyopathic Hamsters

Interval to death	Untreated (Total accumulation)	Desipramine-treated (Non-neuronal compartment)	Neuronal accumulation (Neuronal compartment)	Neuronal washout	Non-neuronal washout
F1b strain, 160 days (control)					
30 min	0.825 ± 0.056 (5)	0.453 ± 0.012 (7)	0.372		
4 hr	0.418 ± 0.019* (5)	0.115 ± 0.010 (5)	0.303	18.5%	74.6%
Bio 14.6, 160 days (hypertrophic stage)					
30 min	0.693 ± 0.033 (3)	0.335 ± 0.020† (3)	0.358		
4 hr	0.376 ± 0.015* (5)	0.079 ± 0.013 (4)	0.297	17.0%	76.0%
F1b strain, 220 days (control)					
30 min	1.064 ± 0.111 (3)	0.390 ± 0.062 (3)	0.674		
4 hr	0.651 ± 0.089 (5)	0.128 ± 0.014 (3)	0.523	22.4%	67.2%
Bio 14.6, 220 days (early heart failure stage)					
30 min	0.682 ± 0.080* (5)	0.285 ± 0.050‡ (4)	0.397		
4 hr	0.195 ± 0.025§ (4)	0.088 ± 0.018 (4)	0.107	73.0%	69.0%

*Significantly different from F1b at 220 days with each interval (p < 0.05); †Significantly different from F1b at 160 days with each interval (p < 0.05); ‡Significantly different from F1b at 160 days with each interval (p < 0.01); §Significantly different from F1b at 220 days with each interval (p < 0.01). Data are shown in % kg dose/g (mean ± s.e.m.); number in parentheses represents the number of the animals.

TABLE 2
Body Weight and Left Ventricular Weight in Control and Cardiomyopathic Hamsters during the Experiments

Strain/Age (n)	Body weight (kg)	LV weight (g)	LV/BW (%)
F1b strain (control)/160 days (22)	0.135 ± 0.003	0.295 ± 0.005	0.220 ± 0.005
Bio 14.6 (hypertrophic stage)/160 days (15)	0.108 ± 0.012*	0.286 ± 0.028	0.267 ± 0.008*
F1b strain (control)/220 days (14)	0.140 ± 0.004	0.306 ± 0.006	0.220 ± 0.005
Bio 14.6 (early heart failure stage)/220 days (17)	0.109 ± 0.009*	0.306 ± 0.011	0.281 ± 0.010*

*Significantly different from F1b 160 days and F1b 220 days (p < 0.05) by ANOVA.
Data are shown in mean ± s.e.m.; number in parentheses represents the number of the animals.

Cilazapril and Myocardial Iodine-125-MIBG Accumulation

Control (F1b) hamsters gradually gained body weight during the 16-wk period of the treatment, whereas no significant increase was observed in the cardiomyopathic hamsters (Fig. 2). At the time of the experiment, the heart-to-body weight ratio was significantly greater in the Bio 14.6 hamsters than in the F1b hamsters (0.28% vs. 0.20%).

As shown in Figure 3, either 16 wk or 3 days of treatment with cilazapril significantly improved the [125I]MIBG accumulation in cardiomyopathic hamsters at 220 days of age, when compared to inactive vehicle-treated hamsters (p < 0.05); cilazapril, however, did not increase [125I]MIBG accumulation in the F1b control hamsters at 220 days of age.

DISCUSSION

Non-neuronal myocardial MIBG accumulation has been reported to be relatively low in humans (7,32); however, it is also reported to reach 30% to 50% of total cardiac accumulation in rats and dogs studied 3 to 4 hr after MIBG injection (33–35). We conducted a desipramine dose-inhibition study and found that the non-neuronal component reaches approximately 30% in the hamsters 4 hr postinjection, and more than 5 mg/kg of desipramine is necessary to maximally inhibit neuronal MIBG uptake. Ten milligrams/kilogram of desipramine was used to separately evaluate the neuronal and non-neuronal accumulation and washout of MIBG. This dose is comparable to doses used in previous studies (36,37).
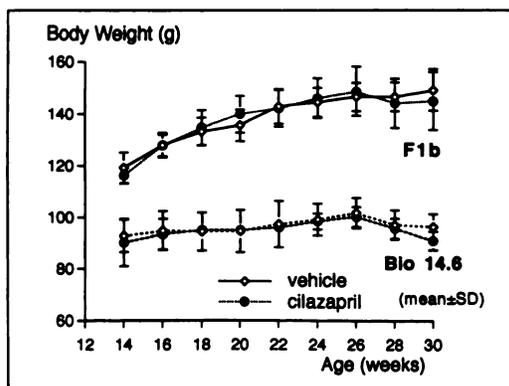
At 30 min postinjection, the total [125I]MIBG accumulation in Bio 14.6 was significantly lower than F1b strain hamsters at the age of 220 days, and the non-neuronal accumulation was also decreased in cardiomyopathic hamsters compared with controls. As shown in Table 2, Bio 14.6 hamsters had lower body weights than controls, although their left ventricular weights remain equivalent. This may be one of the reasons for less [125I]MIBG accumulation in cardiomyopathic hamsters than in controls, although this lower body weight cannot explain the more significant reduction at 4 hr postinjection in the cardiomyopathic hamsters in the early heart failure stage than in the hamsters in the hypertrophic stage, because there was no significant difference between the two groups in both body weight and initial [125I]MIBG accumulation. Bio 14.6 hamster hearts have been shown to develop hypertrophy (4 to 6 mo), followed by cardiac insufficiency over 6 mo, however, it is reported that congestive heart failure becomes significant after 9 mo of age (25). In the present study, hamsters at both hypertrophic and early heart failure stages showed no signs of overt heart failure, such as pleural effusion, ascites, or liver congestion. There was no significant difference in the myocardial perfusion estimated by [201]T-Cl accumulation. Reduced [125I]MIBG accumulation 4
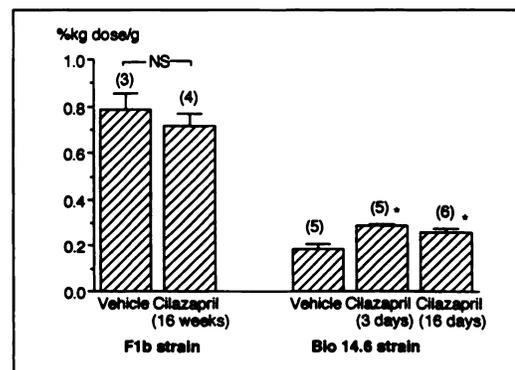

FIGURE 3. Cilazapril treatment and myocardial [125I]MIBG accumulation in control and cardiomyopathic hamsters. Left ventricular [125I]MIBG accumulation was 0.185 ± 0.022, 0.288 ± 0.008, and 0.258 ± 0.022 %kg dose/g in vehicle-treated, 3-day, and 16-wk cilazapril-treated cardiomyopathic hamsters, respectively. NS = not significant; * = significantly different from vehicle-treated animals by ANOVA analysis (p < 0.05); number in parentheses represents the number of animals.

FIGURE 2. Body weights in the control and the cardiomyopathic hamsters treated with control inactive vehicle or cilazapril.

hr after injection therefore appears to be associated with the progression of cardiomyopathy or the severity of any "latent" heart failure which had developed. Considerable variation in MIBG accumulation is often seen in patients with hypertrophic cardiomyopathy (12,13,15), and this may correlate with differences in the degree of heart failure.

Rapid washout has been reported previously in patients with cardiomyopathy (11,13,14); however, it is not clear whether increased washout is primarily neuronal or non-neuronal. In the present study, the non-neuronal washout rates were similar in the four groups, and the neuronal washout rates were similar in the three groups, except for a high washout rate of 73.0% in Bio 14.6 group at early heart failure stage. We report here that reduced [^{125}I]MIBG accumulation in cardiomyopathic hamsters at an early heart failure stage is mainly due to increased washout from the neuronal component. Additionally, the washout rates of MIBG are useful to estimate the sympathetic activity independently from the initial accumulation or differing body weights.

Two mechanisms have been proposed for the increased presynaptic norepinephrine release (32,38): one is enhanced exocytosis by a hyperstimulated sympathetic nervous system, and the other is nonexocytotic release with the uptake-1 carrier in the reverse of its usual transport direction. Schömig et al. examined this nonexocytotic release in perfused rat heart and mentioned that desipramine inhibits both inward and outward transport of cathecholamines and effectively suppresses nonexocytotic noradrenaline release (28,29). Desipramine is considered to block this transport by inhibiting the same carrier for both uptake-1 and nonexocytotic release. As shown in the present paper, the uptake of MIBG was significantly depressed by desipramine. Therefore, it is potentially able to block the carrier-mediated nonexocytotic release, if the facilitated washout was due to this type of release; however, no significant increase was observed in the desipramine post-treatment study. This suggests that nonexocytotic release does not play a major role in the increased washout of [^{125}I]MIBG in this model, and that the facilitated exocytotic release due to increased firing of the sympathetic nerves may account for it. Sole et al. have demonstrated that there is a progressive and possibly specific increase in cardiac sympathetic tone that leads to a concomitant decrease in cardiac norepinephrine (which is the result of the increased norepinephrine turnover rate) in the late stages of hamster cardiomyopathy (39). In addition, increased neuronal release and preserved neuronal uptake have been reported in patients with congestive heart failure (40). Our data are consistent with these results and suggest that MIBG washout can be used as a suitable index for cardiac sympathetic tone in the failing heart. Rabinovitch et al. studied the accelerated washout of MIBG in mechanical overload hypertrophy and failure, and concluded the enhanced rate of loss was from nonvesicular sites (41); however, their subjects differ from ours. Although our animal

model develops heart failure after hypertrophy, the hamsters may differ from other models of hypertrophy. Sole et al. reported that hamsters exhibit an increase (rather than a decrease) in cardiac tyrosine hydroxylase activity, unlike other models of hypertrophy (42). Wakasugi et al. recently reported that desipramine post-treatment restored the cardiac MIBG accumulation in the rat model with adriamycin cardiomyopathy at the advanced heart failure stage and not at the earlier stage, although the MIBG accumulation was already significantly lower in nontreated cardiomyopathies at the earlier stage than controls at the earlier stage (30). The mechanism of MIBG release from sympathetic nerve might therefore be different between the stages or models of heart failure. In the present study, we focused on the early or "latent" stage of the heart failure because cardiac imaging with MIBG is most useful to detect "compensated" or earlier stages of heart failure.

Since the plasma and left ventricular tissue angiotensin II levels have been reported to be markedly elevated in cardiomyopathic hamsters (31), we hypothesized that activated RAS may modulate the facilitated washout of MIBG. In the present study, cilazapril, an ACE inhibitor, significantly improved MIBG accumulation in the cardiomyopathic hamsters 4 hr after injection, although it caused no significant changes in the control hamsters. This suggests that cilazapril suppressed the presynaptic MIBG release, which was enhanced by the activated RAS in cardiomyopathic hamsters at early heart failure stage. This is consistent with several reports that suggest RAS modulates presynaptic norepinephrine release in several tissues, including the heart (17,18,21,22,43). Indirect mechanisms, such as myocardial remodeling or vasodilatation, may also act on this improvement. Recently, Davidson et al. reported that the chronic treatment of Syrian hamsters with ACE inhibitors resulted in myocardial remodeling by reducing scar tissue (44); however, there was no significant difference in the [^{125}I]MIBG accumulation between the hamsters treated for 16 wk and 3 days in our study. This indicates that the action of remodeling on the sympathetic tone via central nervous system may not be as great as the direct action by RAS inhibition in this model. Because only 3 days of treatment might cause vasodilatation (which may improve the sympathetic acceleration), the increase of [^{125}I]MIBG accumulation facillitated by ACE inhibitors may partially reflect this indirect action on sympathetic tone; however, the inhibition of the direct action of RAS on neurotransmitter release seems to be a major mechanism for increased MIBG accumulation, because ACE-I also markedly reduces norepinephrine release in the perfused heart with activated RAS (45). Recently ACE inhibitors have been reported to improve not only the signs and symptoms of heart failure, but also to prolong life (46–48). One of the proposed mechanisms of this cardioprotection is its effect on resting sympathetic tone (49). As shown in the present study, cardiac MIBG accumulation is useful to assess this beneficial effect of ACE inhibitors.

CONCLUSION

Reduced left ventricular [^{125}I]MIBG accumulation has been demonstrated in Bio 14.6 cardiomyopathic hamsters at the early heart failure stage and is caused mainly by rapid neuronal washout. The activated RAS can partially explain this facilitated washout, since the administration of cilazapril, an ACE inhibitor, improved [^{125}I]MIBG accumulation in cardiomyopathic hamsters' hearts. We suggest that MIBG washout is useful for the detection of cardiomyopathy in latent heart failure. In addition, MIBG accumulation can be utilized to assess the effect of ACE inhibitors on the activity of the RAS.

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