International Journal of Cardiology 285 (2019) 65–71

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Acute effects of intravenous carvedilol versus metoprolol on baroreflex-mediated sympathetic circulatory regulation in rats☆

Hiromi Yamamoto [a,d,*], Toru Kawada [b], Shuji Shimizu [b], Yohsuke Hayama [b], Toshiaki Shishido [c], Yoshitaka Iwanaga [a], Kanji Fukuda [d], Shunichi Miyazaki [a], Masaru Sugimachi [b]

[a] Division of Cardiology, Department of Medicine, Faculty of Medicine, Kindai University, Osaka 589-8511, Japan
[b] Department of Cardiovascular Dynamics, National Cerebral and Cardiovascular Center, Osaka 565-8565, Japan
[c] Department of Research Promotion, National Cerebral and Cardiovascular Center, Osaka 565-8565, Japan
[d] Department of Rehabilitation Medicine, Kindai University, Osaka 589-8511, Japan

ARTICLE INFO

Article history:
Received 15 December 2018
Received in revised form 19 February 2019
Accepted 25 February 2019
Available online 4 March 2019

ABSTRACT

Aims: To compare the effects of metoprolol and carvedilol on baroreflex-mediated sympathetic circulatory regulation.

Methods: In anesthetized Wistar–Kyoto rats, carotid sinus baroreceptor regions were isolated. Changes in sympathetic nerve activity (SNA), arterial pressure (AP), heart rate (HR), and aortic flow (AoF) in response to a staircase-wise pressure input were examined before (control) and after intravenous injection of low-dose metoprolol (2 mg/kg), high-dose metoprolol (10 mg/kg), or carvedilol (0.67 mg/kg) ($n = 6$ each). Peripheral vascular resistance (PVR) was calculated from mean AP divided by mean AoF.

Results: Low-dose metoprolol had limited effect on sympathetic AP regulation compared to control [operating-point AP (drug vs. control): 88.7 ± 7.1 vs. 98.3 ± 3.3 mm Hg, not significant] despite a significant bradycardic effect. Although high-dose metoprolol showed central sympathoinhibition, it increased PVR at a given SNA as a peripheral effect. Consequently, high-dose metoprolol decreased the operating-point AP slightly (96.1 ± 2.7 vs. 101.9 ± 2.7 mm Hg, $P < 0.01$). Carvedilol showed no significant central sympathoinhibition at the dose examined in this study, but significantly reduced PVR at a given SNA, leading to a marked reduction in the operating-point AP (71.9 ± 8.2 vs. 112.6 ± 7.6 mm Hg, $P < 0.05$).

Conclusion: Low-dose metoprolol has limited hypotensive effect despite blockade of sympathetic HR regulation. Although high-dose metoprolol induces central sympathoinhibition, it also induces peripheral vasoconstriction that antagonizes the hypotensive effect. In contrast, carvedilol exhibits hypotensive effect mainly through peripheral vasodilation. Although carvedilol is frequently classified as a β-blocker, its vasodilatory effect via α_1-adrenergic blockade plays an important role in AP reduction or heart failure treatment.

1. Introduction

β-Blockers have long been used to treat cardiovascular diseases such as hypertension, arrhythmia, and ischemic heart disease [1–3]. Although β-blockers are no longer recommended as the first-line therapy for primary hypertension [4], they are still widely used as add-on therapy with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and/or diuretics. The peripheral effects of β-blockers may be divided into cardiac and vascular effects. Regarding the cardiac effect, reduction of cardiac output due to β_1-adrenergic blockade is one of the primary mechanisms of antihypertension [4,5]. Although the cardioinhibitory effect was initially thought to be a contraindication for heart failure, β-blockers have been shown to be cardioprotective against excess sympathoexcitation [6] partly because these agents improve the balance of oxygen supply and demand in the failing heart [2]. Regarding the vascular effect, β-blockers can be vasoconstrictive because they block vascular smooth muscle relaxation mediated by β_2-adrenergic receptors. Second-generation β-blockers such as metoprolol are characterized by higher affinity to β_1- than to β_2-adrenergic receptors, which may be beneficial for avoiding β_2-adrenoceptor-related adverse effects including bronchospasms [7]. Moreover, third-generation β-blockers such as carvedilol reduce peripheral vascular resistance [6,7]. Aside from these peripheral effects, β-blockers also exert central effects. For instance, intracerebroventricular administration of β-blockers prevents the increase in renal sympathetic nerve activity (SNA) in response to air-jet

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Division of Cardiology, Department of Medicine, Faculty of Medicine, Kindai University, Osaka 589-8511, Japan.
E-mail address: hiromi@med.kindai.ac.jp (H. Yamamoto).

https://doi.org/10.1016/j.ijcard.2019.02.062
0167-5273/

stress in rats [8]. Chronic intracerebroventricular administration of metoprolol attenuates the progression of left ventricular remodeling in a rat model of heart failure [9].

Although the above-mentioned cardiac, vascular, and central effects of β-blockers are well documented individually, how these effects are integrated in the baroreflex-mediated arterial pressure (AP) regulation remains to be clarified. The potential difficulties in assessing drug effect on SNA reside in the fact that any change in AP induced by systemic administration of a test drug inevitably affects SNA via the arterial baroreflex. As an example, intravenous metoprolol acutely increases muscle SNA in humans, but the study could not answer whether it is a direct central effect or an indirect reflex effect [10]. Likewise, the peripheral effect can be modified under in vivo conditions by baroreflex-mediated changes in SNA. To solve this problem, we have developed a framework of open-loop systems analysis of the carotid sinus baroreflex [11,12]. The present study aimed to quantify and compare the effects of intravenous metoprolol and carvedilol, two commonly prescribed β-blockers, on baroreflex-mediated sympathetic circulatory regulation.

2. Materials and methods

2.1. Surgical preparation

Animals were cared for in strict accordance with the *Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences* as approved by the Physiological Society of Japan. Experimental protocols were reviewed and approved by the Animal Subject Committee of the National Cerebral and Cardiovascular Center.

Male adult Wistar–Kyoto rats (340–400 g) were anesthetized by intraperitoneal injection (2 ml/kg) of a mixture of α-chloralose (40 mg/ml) and urethane (250 mg/ml). AP was measured from the right femoral artery. Heart rate (HR) was determined from body surface electrocardiogram. SNA was recorded from a postganglionic branch of the left splanchnic nerve. The electrical signal was amplified with a band-pass filter between 150 and 1000 Hz and was full-wave rectified and low-pass filtered at 30 Hz to quantify SNA [12]. Bilateral carotid sinus regions were isolated [13], and carotid sinus pressure (CSP) was controlled externally. Bilateral vagal and aortic depressor nerves were sectioned to avoid confounding reflex effects. An ultrasound transit-time flow probe was placed around the ascending aorta to measure aortic flow (AoF).

2.2. Protocols

The effects of low-dose metoprolol, high-dose metoprolol, and carvedilol were examined. In the low-dose metoprolol protocol ($n = 6$), metoprolol tartrate salt (Sigma-Aldrich, USA, dissolved in physiological saline to a concentration of 2 mg/ml) was injected at a dose of 2 mg/kg. In the high-dose metoprolol protocol ($n = 6$), metoprolol (a concentration of 10 mg/ml) was injected at a dose of 10 mg/kg. In the carvedilol protocol ($n = 6$), carvedilol (Sigma-Aldrich, USA) was first dissolved in dimethyl sulfoxide (DMSO) (2 mg in 20 μl) and then diluted with 980 μl of polyethylene glycol 200. The solution was further diluted with physiological saline to a final concentration of 0.67 mg/ml of carvedilol, and injected at a dose of 0.67 mg/kg. The relative concentration of carvedilol to low-dose metoprolol was one-third based on a past report [14].

Open-loop static characteristics of the carotid sinus baroreflex were assessed using a staircase-wise CSP input protocol [12,15]. CSP was first set at 60 mm Hg for 5 min, followed by an increment of 20 mm Hg every minute up to 180 mm Hg. The staircase-wise CSP input was repeated and labeled as S1 through S5. The test drug was injected 1 min after completion of S2. A ganglionic blocker hexamethonium bromide (60 mg/kg) was administered intravenously at the end of the protocol to assess the noise level of SNA.

2.3. Data analysis

Data were stored at 1000 Hz using a 16-bit analog-to-digital converter. The data obtained after drug administration (S5) were compared with those obtained before drug administration (S2). In each input sequence, AP, SNA, HR, and AoF were averaged for the last 10 s of each CSP level. Based on the 10-s averaged values, peripheral vascular resistance (PVR) and stroke volume (SV) were derived from AP/AoF and AoF/HR, respectively. AoF was also normalized to body weight and presented as AoF/BW. The measured SNA values were normalized by treating the SNA obtained at CSP of 60 mm Hg in S2 as 100% and that after hexamethonium administration (noise level) as 0%. We use the term "total reflex arc" to refer to the CSP–AP relationship, "neural arc" to the CSP–SNA relationship, and "peripheral arc" to the SNA–AP relationship [11].

A four-parameter logistic function [16] was used to quantify an inverse sigmoidal input–output relationship:

$$y = \frac{P_1}{1 + \exp[P_2(CSP - P_3)]} + P_4 \quad (1)$$

where y is the output (AP, HR, or SNA); P_1 is the response range; P_2 is the slope coefficient; P_3 is the input pressure that gives the midpoint of the sigmoid curve; and P_4 is the lower asymptote of the sigmoid curve.

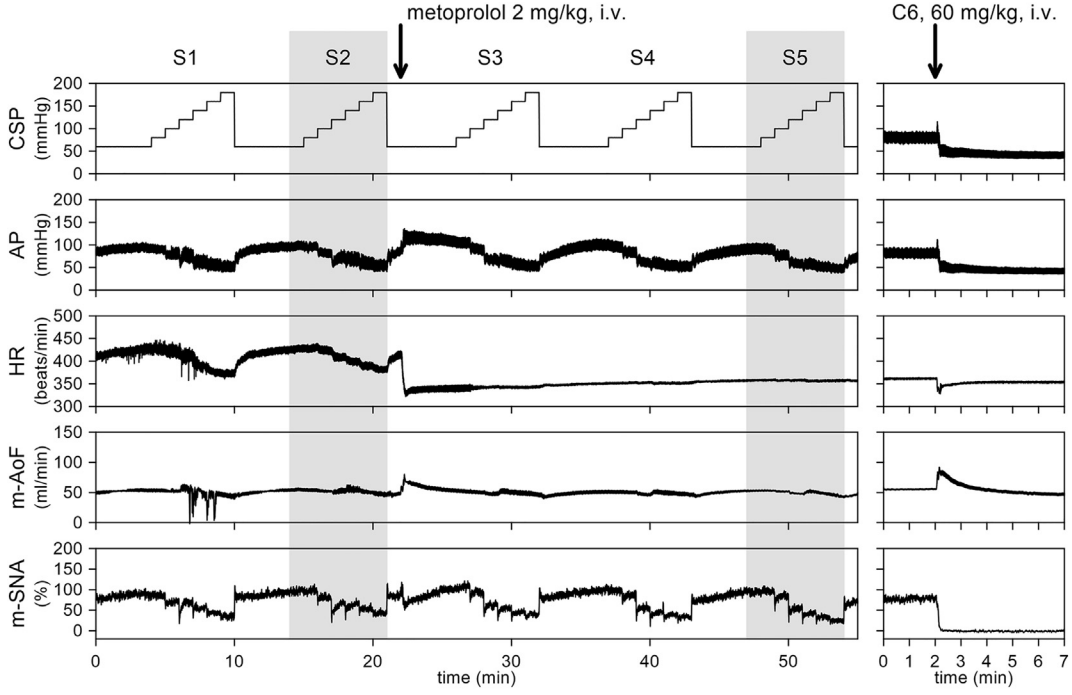

Fig. 1. Typical recordings of carotid sinus pressure (CSP), arterial pressure (AP), heart rate (HR), aortic flow (AoF), and sympathetic nerve activity (SNA) in the low-dose metoprolol protocol. The CSP, AP, and HR signals are displayed as 10-Hz resampled data. m-SNA and m-AoF represent 2-s moving averaged signals of SNA and AoF, respectively. In the left panels, baroreflex responses were examined using a staircase-wise CSP input. The baroreflex responses during S2 sequence served as control, and those assessed during S5 sequence were used to evaluate the drug effects. In the right panels, the SNA signal disappeared after an intravenous bolus injection of the ganglionic blocker hexamethonium bromide (C6).

After administration of metoprolol or carvedilol, the HR response to CSP was almost absent. Hence, HR measured at CSP of 180 mm Hg was regarded as P_4, and the difference in HR observed between CSP of 60 and 180 mm Hg was regarded as P_1. Parameters corresponding to P_2 and P_3 were not available for the CSP–HR relationship after test drug administration.

The relationship of AP or PVR versus SNA was analyzed by linear regression as follows:

$$y = b_0 + b_1 SNA \quad (2)$$

where y is AP or PVR; and b_0 and b_1 are the intercept and the slope, respectively.

The operating point of the carotid sinus baroreflex was calculated from a baroreflex equilibrium diagram, which is obtained by plotting the fitted CSP–SNA curve and SNA–AP line on a pressure–SNA plane [17].

2.4. Statistical analysis

Data are presented as mean ± SE. The data obtained after drug administration (S5) were compared with those obtained before drug administration (S2). This was because the effects of high-dose metoprolol and carvedilol on the baroreflex-mediated AP response (P_1 in the total reflex arc) reached a steady state only at S4 and thereafter (i.e., there was a difference between S3 and S4 but not between S4 and S5). The parameters were compared between before and after drug administration using a paired t-test. For AoF and SV, values averaged over all CSP levels were compared using a paired t-test. Differences were considered significant when $P < 0.05$ [18].

3. Results

Representative time series obtained from the low-dose metoprolol protocol are shown in Fig. 1. CSP, AP, and HR are displayed as 10-Hz resampled signals. m-AoF and m-SNA represent 2-s moving averaged signals of AoF and SNA, respectively. In the left panels, an increase in CSP decreased AP, HR, and m-SNA under control conditions (S1 and S2). Administration of low-dose metoprolol (depicted as a down arrow) initially decreased HR and m-SNA but increased AP and m-AoF. The transient increases in AP and m-AoF were probably due to volume loading during drug administration. While changes in AP, m-AoF, and m-SNA induced by metoprolol administration subsided with time elapsed, the decrease in HR persisted. In the right panels, CSP was adjusted to instantaneous AP via the servo pump system. Administration of hexamethonium bromide decreased m-SNA to the noise level.

Group-averaged data obtained from the low-dose metoprolol protocol are summarized in Fig. 2 and Table 1. Low-dose metoprolol shifted the CSP–AP relationship slightly downward (Fig. 2A) and decreased HR with the abolition of the HR response to CSP (Fig. 2B). Low-dose metoprolol had almost no effect on the SNA response to CSP (Fig. 2C). The effect of low-dose metoprolol on the averaged value was not significant for AoF/BW (Fig. 2D), AoF (Fig. 2E), or SV (Fig. 2F). Low-dose metoprolol tended to increase the intercept and decrease the slope of the AP response to SNA (Fig. 2G). No significant effect was observed in the PVR response to SNA (Fig. 2H). The operating-point AP and SNA were not changed significantly by low-dose metoprolol (Fig. 2G).

Group-averaged data obtained from the high-dose metoprolol protocol are summarized in Fig. 3 and Table 1. High-dose metoprolol narrowed the response range of AP without affecting the lower asymptote of AP (Fig. 3A), and lowered HR with the abolition of the HR response to CSP (Fig. 3B). In the neural arc, the lower asymptote of SNA was slightly decreased by metoprolol (Fig. 3C). The effect of high-dose metoprolol on the averaged value was significant for AoF/BW

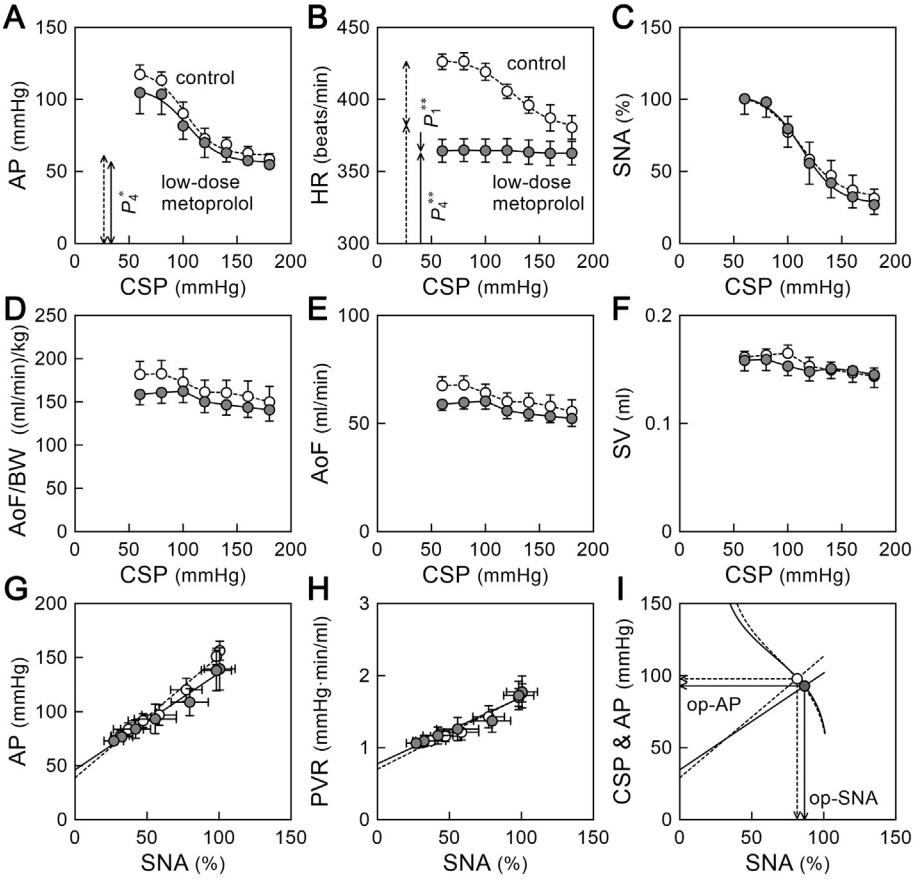

Fig. 2. Group-averaged results of the effects of low-dose metoprolol on baroreflex-mediated sympathetic circulatory regulation. Open and filled circles represent data points obtained before (control) and after low-dose metoprolol administration. The top row illustrates open-loop static characteristics of the total reflex arc (A), heart rate (HR) response curve (B), and the neural arc (C). CSP, carotid sinus pressure; AP, arterial pressure; SNA, sympathetic nerve activity; P_1, response range; P_4, lower asymptote of the fitted sigmoid curve. The second row illustrates aortic flow (AoF) relative to body weight (BW) (D) and in absolute values (E), and stroke volume (SV) (F) versus CSP. The bottom row illustrates the open-loop static characteristics of the peripheral arc (G), peripheral vascular resistance (PVR) versus SNA (H), and the baroreflex equilibrium diagram (I). op-SNA and op-AP, operating-point SNA and AP, respectively. Data are presented as mean ± SE. ** and * indicate $P < 0.01$ and $P < 0.05$, respectively. In panels A, C, D, E, and F, only one side of the error bar is displayed for legibility reasons.

Table 1
Effects of intravenous low-dose (2 mg/kg) and high-dose (10 mg/kg) metoprolol on parameters of static characteristics of the carotid sinus baroreflex.

	Control	Low-dose metoprolol	P value	Control	High-dose metoprolol	P value
CSP–AP (total reflex arc)						
P_1, mm Hg	60.8 ± 9.0	53.4 ± 17.1	0.528	71.8 ± 7.3	58.4 ± 7.3	*0.024*
P_2, mm Hg^{-1}	0.097 ± 0.028	0.107 ± 0.022	0.623	0.139 ± 0.019	0.144 ± 0.017	0.836
P_3, mm Hg	108.4 ± 4.9	114.0 ± 8.3	0.489	103.6 ± 1.1	99.3 ± 4.3	0.287
P_4, mm Hg	58.4 ± 3.7	53.0 ± 2.5	*0.015*	59.2 ± 4.3	58.3 ± 4.0	0.457
CSP–HR relationship						
P_1, beats·min^{-1}	46.9 ± 10.4	1.6 ± 1.1	*0.005*	32.4 ± 6.6	−3.1 ± 3.4	*< 0.001*
P_2, mm Hg^{-1}	0.079 ± 0.016	N/A	–	0.155 ± 0.037	N/A	–
P_3, mm Hg	121.1 ± 6.7	N/A	–	112.3 ± 5.5	N/A	–
P_4, beats·min^{-1}	380.9 ± 9.1	362.6 ± 8.2	*0.006*	399.8 ± 11.0	359.8 ± 4.6	*0.012*
CSP–SNA (neural arc)						
P_1, %	74.2 ± 9.0	77.1 ± 15.6	0.755	79.4 ± 4.1	68.0 ± 6.1	0.091
P_2, mm Hg^{-1}	0.087 ± 0.026	0.108 ± 0.024	0.457	0.163 ± 0.034	0.144 ± 0.008	0.567
P_3, mm Hg	119.8 ± 6.4	118.9 ± 7.6	0.853	109.7 ± 2.2	107.2 ± 2.2	0.151
P_4, %	28.0 ± 8.2	24.7 ± 6.9	0.440	22.5 ± 3.8	12.9 ± 3.4	*0.030*
SNA–AP (peripheral arc)						
b_0, mm Hg	31.2 ± 6.1	39.9 ± 3.0	0.074	37.1 ± 4.4	46.8 ± 3.4	*0.042*
b_1, mm Hg·%$^{-1}$	0.811 ± 0.068	0.599 ± 0.088	0.062	0.881 ± 0.086	0.790 ± 0.084	*0.046*
SNA–PVR relationship						
b_0, mm Hg·min·ml^{-1}	0.665 ± 0.121	0.869 ± 0.042	0.170	0.556 ± 0.051	0.789 ± 0.056	*0.007*
b_1, mm Hg·min·ml^{-1}·%$^{-1}$	0.0102 ± 0.0020	0.0083 ± 0.0015	0.452	0.0110 ± 0.0012	0.0126 ± 0.0012	*0.044*
Operating point						
AP, mm Hg	98.3 ± 3.3	88.7 ± 7.1	0.287	101.9 ± 2.7	96.1 ± 2.7	*0.002*
SNA, %	82.9 ± 5.9	83.0 ± 8.7	0.990	75.4 ± 5.2	64.6 ± 4.9	0.060

Data are expressed as mean ± SE ($n = 6$ each), because low-dose metoprolol and high-dose metoprolol were tested in separate animals. CSP: carotid sinus pressure, AP: arterial pressure, HR: heart rate, SNA: sympathetic nerve activity, PVR: peripheral vascular resistance, P_1 through P_4: parameters of the fitted logistic function. N/A: not available for fitted parameters due to the absence of significant HR response after metoprolol. *P* values <0.05 are italicized.

(Fig. 3D) and AoF (Fig. 3E) but not for SV (Fig. 3F). High-dose metoprolol increased the intercept and decreased the slope of the AP response to SNA (Fig. 3G), and increased the intercept with a slight increase in the slope of the PVR response to SNA (Fig. 3H). High-dose metoprolol decreased the operating-point AP slightly and tended to decrease the operating-point SNA (Fig. 3I).

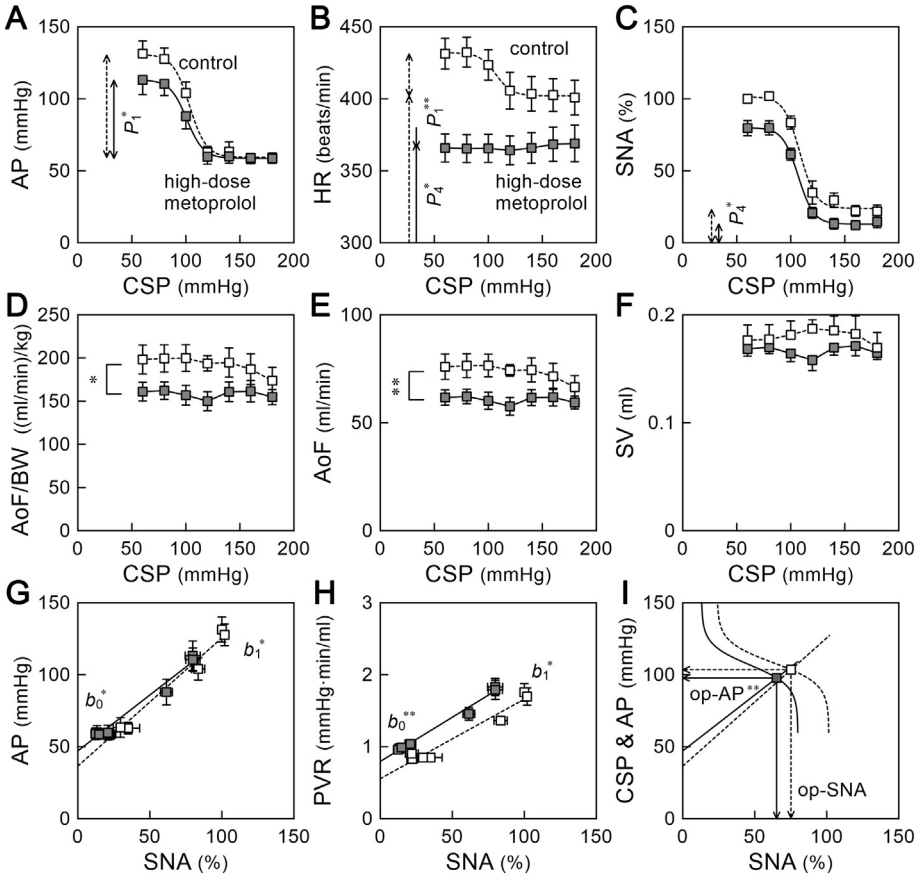

Fig. 3. Group-averaged results of the effects of high-dose metoprolol on baroreflex-mediated sympathetic circulatory regulation. Open and filled squares represent data points obtained before (control) and after high-dose metoprolol administration. The panel descriptions are the same as those in Fig. 2. ** and * indicate P < 0.01 and P < 0.05, respectively. In panels A and F, only one side of the error bar is displayed for legibility reasons.

Group-averaged data obtained from the carvedilol protocol are summarized in Fig. 4 and Table 2. Carvedilol decreased AP and markedly narrowed the response range of AP (Fig. 4A). Likewise, carvedilol decreased HR and abolished the HR response to CSP (Fig. 4B). On the other hand, carvedilol did not significantly affect the SNA response to CSP (Fig. 4C). The effect of carvedilol on the averaged value was significant for AoF/BW (Fig. 4D) and AoF (Fig. 4E) but not for SV (Fig. 4F). Carvedilol decreased the slope without affecting the intercept of the AP response to SNA (Fig. 4G). Carvedilol also decreased the slope and tended to increase the intercept of the PVR response to SNA (Fig. 4H). Carvedilol reduced the operating-point AP without a significant effect on the operating-point SNA (Fig. 4I).

4. Discussion

In all three protocols, the HR response to CSP was almost abolished after drug administration, suggesting complete blockade of sympathetic HR control mediated by β_1-adrenergic receptors. On the other hand, the effects on the baroreflex neural and peripheral arcs differed among three protocols, demonstrating differential impact of drugs or dosing regimens on baroreflex-mediated sympathetic circulatory regulation.

4.1. Comparison of low- versus high-dose metoprolol

Agents with higher degrees of lipid solubility are more likely to pass the blood–brain barrier. Metoprolol, which is moderately lipophilic, distributes into the cerebrospinal fluid (CSF) within 15 min after intravenous injection in rats [19]. Penetration of metoprolol into CSF has also been reported in humans [20,21] and may be responsible for central adverse effects such as sleepiness and nightmares [5]. Low-dose metoprolol, however, hardly affected the neural arc (Fig. 2C). The slope in the peripheral arc tended to decrease after metoprolol administration (Fig. 2G), which may have contributed to the reduction of the lower asymptote of AP (Fig. 2A). While β_1-adrenergic blockade exerts a negative inotropic effect, SV did not decrease after low-dose metoprolol (Fig. 2F), possibly because the ventricular filling pressure increases when circulation is retarded by bradycardia. An increase in the diastolic interval during bradycardia may have also contributed to the ventricular filling and the maintenance of SV. In sum, low-dose metoprolol has limited AP-lowering effect despite the significant HR reduction.

High-dose metoprolol significantly decreased SNA (Fig. 3C), confirming the central sympathoinhibitory effect [8]. Despite the significant reduction of AoF (Fig. 3E), AP at a given SNA was well maintained (Fig. 3G) possibly due partly to the significant increase of PVR at a given SNA (Fig. 3H). Although metoprolol is selective for β_1-adrenergic receptors, high-dose metoprolol may also block vascular smooth muscle relaxation mediated by peripheral β_2-adrenergic receptors. The results conform to the idea that cardioselectivity of β-blockers can be lost at high doses [5], although a conflicting view also exists [22]. The important finding is that peripheral vasoconstriction cannot be ignored at metoprolol doses that induce central sympathoinhibition. While central sympathoinhibition can be beneficial [9], the peripheral vasoconstrictive effect may be undesirable for the treatment of hypertension and heart failure.

4.2. Comparison of metoprolol versus carvedilol

Although carvedilol has moderate lipophilic properties, radioligand of carvedilol hardly enters the brain after intravenous injection, probably due to extensive binding to plasma proteins [23]. Carvedilol did not

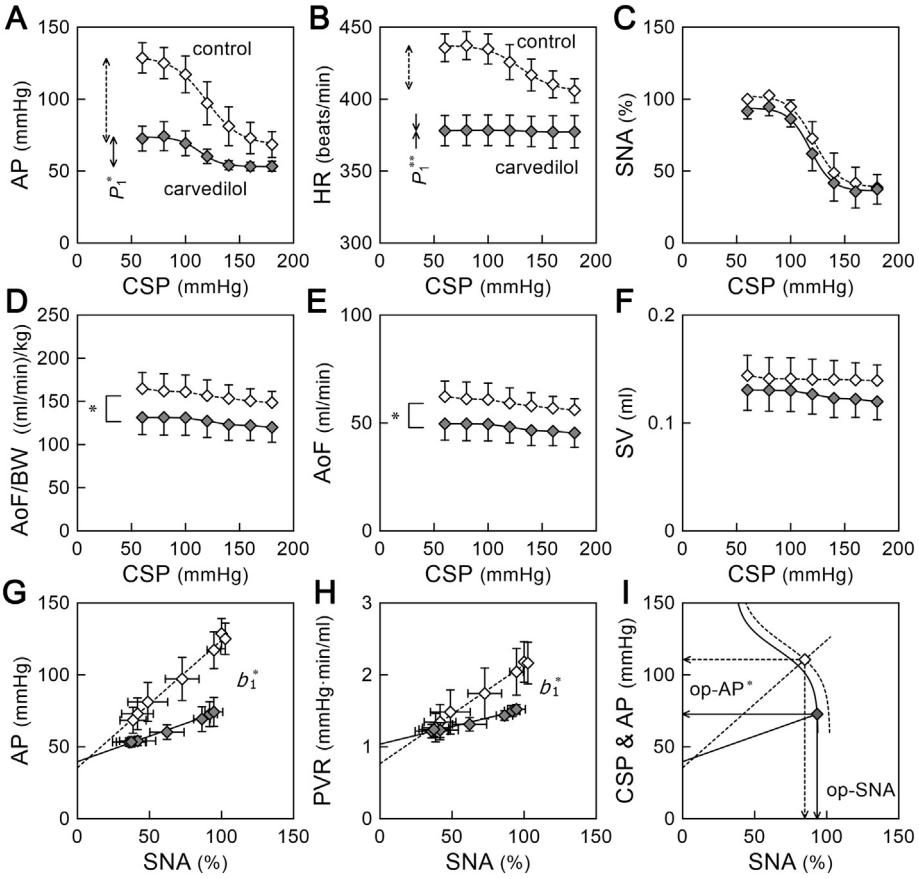

Fig. 4. Group-averaged results of the effects of carvedilol on baroreflex-mediated sympathetic circulatory regulation. Open and filled rhombuses represent data points obtained before (control) and after carvedilol. The panel descriptions are the same as those in Fig. 2. ** and * indicate $P < 0.01$ and $P < 0.05$, respectively. In panels C, D, E, and F, only one side of the error bar is displayed for legibility reasons.

Table 2
Effects of intravenous carvedilol (0.67 mg/kg) on parameters of static characteristics of the carotid sinus baroreflex.

	Control	Carvedilol	P value
CSP–AP (total reflex arc)			
P_1, mm Hg	63.9 ± 9.6	21.5 ± 6.6	*0.013*
P_2, mm Hg^{-1}	0.094 ± 0.019	0.109 ± 0.016	0.197
P_3, mm Hg	122.2 ± 7.2	124.1 ± 6.9	0.459
P_4, mm Hg	65.2 ± 9.3	52.3 ± 3.4	0.229
CSP–HR relationship			
P_1, beats·min^{-1}	33.0 ± 6.2	0.8 ± 1.0	*0.003*
P_2, mm Hg^{-1}	0.109 ± 0.020	N/A	–
P_3, mm Hg	130.4 ± 7.7	N/A	–
P_4, beats·min^{-1}	404.0 ± 8.5	377.3 ± 11.2	0.080
CSP–SNA (neural arc)			
P_1, %	69.1 ± 8.9	62.2 ± 12.3	0.534
P_2, mm Hg^{-1}	0.108 ± 0.020	0.118 ± 0.016	0.388
P_3, mm Hg	129.7 ± 7.3	125.7 ± 6.7	0.444
P_4, %	32.9 ± 9.3	31.5 ± 10.7	0.902
SNA–AP (peripheral arc)			
b_0, mm Hg	30.1 ± 7.4	40.8 ± 7.8	0.124
b_1, mm Hg·%$^{-1}$	0.917 ± 0.137	0.349 ± 0.070	*0.016*
SNA–PVR relationship			
b_0, mm Hg·min·ml^{-1}	0.423 ± 0.262	0.968 ± 0.148	0.067
b_1, mm Hg·min·ml^{-1}·%$^{-1}$	0.0168 ± 0.0051	0.0060 ± 0.0014	*0.048*
Operating point			
AP, mm Hg	112.6 ± 7.6	71.9 ± 8.2	*0.025*
SNA, %	89.6 ± 3.9	90.7 ± 6.5	0.842

Data are expressed as mean ± SE (n = 6). CSP: carotid sinus pressure, AP: arterial pressure, HR: heart rate, SNA: sympathetic nerve activity, PVR: peripheral vascular resistance, P_1 through P_4: parameters of the fitted logistic function. N/A: not available for fitted parameters due to the absence of significant HR response after carvedilol. P values <0.05 are italicized.

exhibit central sympathoinhibition (Fig. 4C) at a dose that showed complete blockade of sympathetic HR control (Fig. 4B) and significant hypotensive effect (Fig. 4A). Redox signaling is an important determinant of SNA [24]. While carvedilol has been shown to scavenge free radicals [25], intravenous carvedilol may not have reached the brain with a sufficient concentration to suppress SNA via the antioxidant mechanism. Therefore, the acute hypotension induced by carvedilol is primarily attributed to the peripheral effects. In contrast to high-dose metoprolol, carvedilol significantly reduced the slope of the peripheral arc (Fig. 4G). The vasodilatory effect of carvedilol via α_1-adrenergic blockade may have exceeded the possible vasoconstrictive effect via β_2-adrenergic blockade. Whereas high-dose metoprolol reduced the operating-point AP through a change in the neural arc (Fig. 3I), carvedilol reduced the operating-point AP mainly via a change in the peripheral arc (Fig. 4I).

Central aortic pressure is a powerful and potentially more robust predictor of cardiovascular risk than brachial pressure [26]. Conventional β-blockers such as atenolol are less effective in reducing central aortic pressure [27,28]. Central aortic pressure increases in association with increasing PVR or aortic stiffness. In this study, high-dose metoprolol increased PVR at a given SNA. In contrast, carvedilol significantly decreased PVR at a given SNA. The results are consistent with the clinical observation of the hemodynamic differences between metoprolol and carvedilol in hypertensive patients [29]. Such differences in the effect on PVR may partly account for the superiority of carvedilol to metoprolol (metoprolol tartrate, short-acting) in the treatment of heart failure [30], although there is no conclusive difference in all-cause mortality between treatments with carvedilol and metoprolol (metoprolol succinate, extended release) [31].

4.3. Limitations

We recorded SNA from the splanchnic sympathetic nerve to represent systemic SNA. As we perturbed SNA via the carotid sinus baroreflex, systemic SNA might have changed in concert. Although we have no data that directly compared splanchnic and cardiac SNAs, the static CSP–SNA relationship is similar between cardiac and renal SNAs [32] and between splanchnic and renal SNAs [33].

As we performed acute experiments under baroreflex open-loop conditions in anesthetized animals, the results need to be verified in more physiological, baroreflex closed-loop conditions. Further, we examined the drug effect on normal rats. Future studies are required to examine whether the above discussions hold in animal models of hypertension or heart failure.

5. Conclusions

Low-dose metoprolol had limited effect on sympathetic AP regulation despite a significant bradycardic effect. Although high-dose metoprolol showed central sympathoinhibition, it increased PVR at a given SNA as a peripheral effect. Carvedilol did not show significant central sympathoinhibition at the dose examined in this study, but significantly reduced PVR at a given SNA. Although carvedilol is frequently classified as a β-blocker, its vasodilatory effect via α_1-adrenergic receptor blockade plays an important role in AP reduction or treatment of heart failure.

Acknowledgements

This study was partly supported by a Grant-in-Aid for Scientific Research (JSPS KAKENHI grants 26462774, 15K09110, 15H03101, 18K10695). The authors confirm that the funders had no influence over the study design, contents of the article, or selection of this journal.

References

[1] H. Ishiguro, T. Ikeda, A. Abe, et al., Antiarrhythmic effect of bisoprolol, a highly selective beta1-blocker, in patients with paroxysmal atrial fibrillation, Int. Heart J. 49 (2008) 281–293.
[2] D.L. Pearle, Pharmacologic management of ischemic heart disease with beta-blockers and calcium channel blockers, Am. Heart J. 120 (1990) 739–742 (discussion 743-735).
[3] C.V. Ram, Beta-blockers in hypertension, Am. J. Cardiol. 106 (2010) 1819–1825.
[4] T.L. Ripley, J.J. Saseen, Beta-blockers: a review of their pharmacological and physiological diversity in hypertension, Ann. Pharmacother. 48 (2014) 723–733.
[5] M. Wehland, J. Grosse, U. Simonsen, M. Infanger, J. Bauer, D. Grimm, The effects of newer beta-adrenoceptor antagonists on vascular function in cardiovascular disease, Curr. Vasc. Pharmacol. 10 (2012) 378–390.
[6] V. Barrese, M. Taglialatela, New advances in beta-blocker therapy in heart failure, Front. Physiol. 4 (2013) 323.
[7] F.Y. Fisker, D. Grimm, M. Wehland, Third-generation beta-adrenoceptor antagonists in the treatment of hypertension and heart failure, Basic Clin. Pharmacol. Toxicol. 117 (2015) 5–14.
[8] J.P. Koepke, G.F. DiBona, Central beta-adrenergic receptors mediate renal nerve activity during stress in conscious spontaneously hypertensive rats, Hypertension 7 (1985) 350–356.
[9] A. Gourine, S.I. Bondar, K.M. Spyer, A.V. Gourine, Beneficial effect of the central nervous system beta-adrenoceptor blockade on the failing heart, Circ. Res. 102 (2008) 633–636.
[10] G. Sundlof, B.G. Wallin, E. Stromgren, C. Nerhed, Acute effects of metoprolol on muscle sympathetic activity in hypertensive humans, Hypertension 5 (1983) 749–756.
[11] T. Kawada, M. Sugimachi, Open-loop static and dynamic characteristics of the arterial baroreflex system in rabbits and rats, J. Physiol. Sci. 66 (2016) 15–41.
[12] H. Yamamoto, T. Kawada, S. Shimizu, A. Kamiya, S. Miyazaki, M. Sugimachi, Effects of cilnidipine on sympathetic outflow and sympathetic arterial pressure and heart rate regulations in rats, Life Sci. 92 (2013) 1202–1207.
[13] T. Sato, T. Kawada, H. Miyano, et al., New simple methods for isolating baroreceptor regions of carotid sinus and aortic depressor nerves in rats, Am. J. Physiol. 276 (1999) H326–H332.
[14] H. Yaoita, A. Sakabe, K. Maehara, Y. Maruyama, Different effects of carvedilol, metoprolol, and propranolol on left ventricular remodeling after coronary stenosis or after permanent coronary occlusion in rats, Circulation 105 (2002) 975–980.
[15] H. Yamamoto, T. Kawada, S. Shimizu, et al., Ivabradine does not acutely affect open-loop baroreflex static characteristics and spares sympathetic heart rate control in rats, Int. J. Cardiol. 257 (2018) 255–261.
[16] B.B. Kent, J.W. Drane, B. Blumenstein, J.W. Manning, A mathematical model to assess changes in the baroreceptor reflex, Cardiology 57 (1972) 295–310.
[17] T. Sato, T. Kawada, M. Inagaki, et al., New analytic framework for understanding sympathetic baroreflex control of arterial pressure, Am. J. Physiol. 276 (1999) H2251–H2261.
[18] S.A. Glantz, Primer of Biostatistics, 5th ed. McGraw-Hill, New York, 2002.

[19] P. Ylitalo, I.B. Linden, A. Penttila, H. Vapaatalo, Distribution of beta-adrenoceptor blocking drugs into cerebrospinal fluid in rats, Acta Pharmacol. Toxicol. (Copenh) 58 (1986) 84–87.
[20] G. Neil-Dwyer, J. Bartlett, J. McAinsh, J.M. Cruickshank, Beta-adrenoceptor blockers and the blood-brian barrier, Br. J. Clin. Pharmacol. 11 (1981) 549–553.
[21] A.J. Wood, Cerebrospinal fluid concentration of metoprolol in a hypertensive patient, Br. J. Clin. Pharmacol. 4 (1977) 240–241.
[22] D.G. McDevitt, Pharmacologic aspects of cardioselectivity in a beta-blocking drug, Am. J. Cardiol. 59 (1987) 10F–12F.
[23] P. Doze, P.H. Elsinga, B. Maas, A. Van Waarde, T. Wegman, W. Vaalburg, Synthesis and evaluation of radiolabeled antagonists for imaging of beta-adrenoceptors in the brain with PET, Neurochem. Int. 40 (2002) 145–155.
[24] T. Kawada, Y. Sata, S. Shimizu, M.J. Turner, M. Fukumitsu, M. Sugimachi, Effects of tempol on baroreflex neural arc versus peripheral arc in normotensive and spontaneously hypertensive rats, Am. J. Physiol. Regul. Integr. Comp. Physiol. 308 (2015) R957–R964.
[25] T.L. Yue, H.Y. Cheng, P.G. Lysko, et al., Carvedilol, a new vasodilator and beta adrenoceptor antagonist, is an antioxidant and free radical scavenger, J. Pharmacol. Exp. Ther. 263 (1992) 92–98.
[26] B. Williams, P.S. Lacy, Central aortic pressure and clinical outcomes, J. Hypertens. 27 (2009) 1123–1125.
[27] J. Polonia, L. Barbosa, J.A. Silva, S. Bertoquini, Different patterns of peripheral versus central blood pressure in hypertensive patients treated with beta-blockers either with or without vasodilator properties or with angiotensin receptor blockers, Blood Press. Monit. 15 (2010) 235–239.
[28] B. Williams, P.S. Lacy, S.M. Thom, et al., Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study, Circulation 113 (2006) 1213–1225.
[29] K. Weber, T. Bohmeke, R. van der Does, S.H. Taylor, Hemodynamic differences between metoprolol and carvedilol in hypertensive patients, Am. J. Hypertens. 11 (1998) 614–617.
[30] M. Metra, C. Torp-Pedersen, K. Swedberg, et al., Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial, Eur. Heart J. 26 (2005) 2259–2268.
[31] H. Frohlich, J. Zhao, T. Tager, et al., Carvedilol compared with metoprolol succinate in the treatment and prognosis of patients with stable chronic heart failure: carvedilol or metoprolol evaluation study, Circ. Heart Fail. 8 (2015) 887–896.
[32] T. Kawada, T. Shishido, M. Inagaki, et al., Differential dynamic baroreflex regulation of cardiac and renal sympathetic nerve activities, Am. J. Physiol. Heart Circ. Physiol. 282 (2001) H1581–H1590.
[33] T. Kawada, M. Li, A. Kamiya, et al., Open-loop dynamic and static characteristcis of the carotid sinus baroreflex in rats with chronic heart failure after myocardial infarction, J. Physiol. Sci. 60 (2010) 283–298.