Cardiac Pacemakers Controlled by Autonomic Nervous System-Driven Sensor and Related Neurohumoral Aspects

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Summary

A sympathetic sensor-driven pacing system is an important means of physiological correction of chronotropic incompetence. The aim of this study was to evaluate the changes in heart rate provided by a sympathetically driven pacemaker compared with normal sinus function. Nine men and six women (age 37 – 80 years) with atrioventricular block and a pacemaker controlled by a closed-loop system were studied. Group I included eight patients with chronotropic incompetence, and group II included seven patients with normal sinus function. All patients underwent the Valsalva maneuver and head-up tilt table testing with measurements of plasma catecholamines and renin activity. Pacing was initially programmed in the DDD mode at a lower rate of 60 beats/min, with an upper rate limit of 0.85 x (220 – age/years) beats/min; the pacemakers were then programmed to DDD-CLS (DDDR) in group I and VVI-CLS (VVIR) in group II. The second phase of the study consisted of nitroglycerin and phenylephrine infusions, and the third phase involved physiological provocative maneuvers. The second and third phases were performed in three patients from each group with sensor activity On and Off. In group I, heart rate changed during tilt only in the DDD-CLS mode. In group II, heart rate changes were comparable in both modes. Catecholamine levels in group I were higher during DDD than during DDD-CLS pacing ($P < 0.05$). In group I, heart rate did not change during phases II and IV of the Valsalva maneuver in the DDD mode, but behaved nearly physiologically after sensor activation. A late and paradoxical response to nitroglycerin was observed in groups I and II, and a similar response to phenylephrine was observed in group I. During physiological maneuvers, significantly greater variations in heart rate were observed during DDD-CLS than during DDD pacing. Sympathetic sensor-driven pacing provides physiological modulations of the heart rate in patients with atrioventricular block and chronotropic incompetence.

Key Words

Chronotropic incompetence, heart rate response,Closed Loop Stimulation (CLS), circulating catecholamines

Introduction

Physiological chronotropism is modulated by the sympathetic and parasympathetic nervous systems, which facilitate cardiovascular adaptations to various situations such as rest, postural changes, and physical exertion. Reflex bradycardia and tachycardia, essential under these circumstances, are mainly triggered by arterial baroreceptors and the cardiopulmonary reflex. Changes in the intensity of adrenergic nerve impulses cause rapid modifications in cardiac contractility. Assuming a fixed stroke volume and a linear relationship between cardiac output and heart rate, changes in the heart rate are an important control mechanism of the cardiac output [1]. Among several rate adaptive artificial cardiac pacing systems currently in use, the performance of a physiological sensor capable of detecting changes in myocardial contractility as an indicator of sympathetic tone was evaluated [2].

The objectives of this study were:

- to closely examine the interaction between the physiological heart rate (HR) response and the blood pressure (BP) under several conditions during daytime in patients with chronotropic incompetence (CI) and advanced atrioventricular block (AVB); and
- to compare this physiological HR response with normal sinus function (NSF) [3].

Materials and Methods

The implanted cardiac pacing system was the Inos[2] CLS (Biotronik, Germany), a multiprogrammable pacemaker (PM) that evaluates the contraction dynamics of the heart to set the pacing rate (Closed Loop Stimulation: CLS), establishing a physiological closed-loop system based on variations in autonomic nervous system (ANS) activity detected as variations in impedance measured from the pacing electrode.

Study Design

Fifteen patients with advanced/complete AVB (37 – 80 years of age, mean 54.7) were prospectively studied between September 1997 and March 1999 at the time of PM implantation or replacement. Group I consisted of eight patients who had AVB plus CI, and group II consisted of seven patients with NSF and AVB. The follow-up of group I patients ranged between 14 and 31 months (mean 22.3 months), while the group II patients were followed for 2 months. All patients had a left ventricular ejection fraction > 0.60, except two patients in group II. The first phase of the study consisted of the evaluation of the performance of PMs programmed to the DDD mode at 30 days after implantation with a lower rate of 60 beats/min and an upper rate limit equal to 0.85 x (220 – age/years) beats/min. All patients underwent tilt table testing with plasma epinephrine (EP), norepinephrine (NE), and plasma renin activity (PRA) measured after 1 hour of rest in the supine position and after tilt to 60°. After completion of the head-up tilt table test, a Valsalva maneuver was performed. The PMs were then reprogrammed to DDD-CLS and VVI-CLS (DDDR and VVIR) modes in group I and group II patients, respectively. After 15 days of additional follow-up, the tests were repeated in the new pacing mode (i.e., after sensor activation). The second phase of the study (pharmacological tests) consisted of nitroglycerin and phenilephrine infusions. The third phase (physiological tests) consisted of physiological provocative maneuvers, including cough, postural changes, and physical exercise. The second and third phases were performed in three patients from each group with CLS activated and not activated.

Head-up Tilt Table Testing

During head-up tilt table testing the following variables were examined: degree of postural hypotension, HR response, circulating catecholamine levels by High Performance Liquid Chromatography [4], and PRA by radioimmunologic assay for angiotensin-1 in the presence of an angiotensinase inhibitor, both at baseline and during tilting at 60° to evaluate the sensor rate response in both groups.

Blood Sample Collection

After venous puncture, the patients remained in bed in a calm, dimmed environment. Blood specimens were collected in chilled tubes for baseline measurements of plasma EP, NE, and PRA. The collection of blood samples was repeated for identical measurements after 10 min of upright tilt.

Valsalva Maneuver

The Valsalva maneuver was performed with the patients in the supine position. After an average inhalation, the patients blew into a manometer to develop a pressure between 20 and 40 mmHg for 10 – 30 s to cause a reflexive drop in peripheral vasoconstriction. The Valsalva Index, the ratio of highest and lowest HR, was calculated [5].

Pharmacological Tests

Tachycardia was induced by the infusion of a 100 µg bolus of intravenous nitroglycerin and bradycardia was induced by the infusion of a 100 µg bolus of phenilephrine. During these tests, baroreceptor sensitivity, defined as the coefficient between HR and systolic BP variations before and after the infusion of drugs, was measured [6].

Physiological Tests

Automatic measurements of HR and BP were performed (Cardiotens, Meditech – Medical Electronics, Hungary) every 5 min for 3 h, during which the patients were instructed to cough, defecate, change posture, perform handgrip maneuvers, and climb stairs [7,8]. Initial testing was performed with the sensor

	Inactive Sensor						Active Sensor					
	EP rest (au)	EP tilt (au)	NE rest (au)	NE tilt (au)	PRA rest (au)	PRA tilt (au)	EP rest (au)	EP tilt (au)	NE rest (au)	NE tilt (au)	PRA rest (au)	PRA tilt (au)
Group I	43*	74*	429*	525*	0.5	0.6	16*	40*	222*	397*	0.7	1.2
Group II	38*	58*	277*	467*	1.5	1.9	38*	131*	201*	501*	1.5	1.7

a

		Mode	Cough	Tilt	Evacuation	Handgrip	Effort
Group I	∆ SBP (mmHg)	DDD	0.59	9	17	8	20
		DDD-CLS	0	7	10	10	12
	∆ HR (beats/min)	DDD	0	0	0	0	3
		DDD-CLS	2	7	14	4	22
Group II	∆ SBP (mmHg)	DDD	3	2	15	9	24
		VVI-CLS	2	3	26	23	44
	∆ HR (beats/min)	DDD	2	8	7	6	24
		VVI-CLS	1	9	15	2	26

b

	VI Inactive Sensor	VI Active Sensor
Group I	1.1	1.4
Group II	1.3	1.3

c

*Table 1. Epinephrine (EP), norepinephrine (NE), and plasma renin activity (PRA) in arbitrary units (au) measured in groups I and II (panel a); changes in systolic blood pressure (D SBP = SBP pacing – SBP pre-pacing) and changes in heart rate (D HR= HR post-pacing – HR pre-pacing) during physiological tests before and during pacing (panel b); Valsalva Index (VI) calculated with sensor inactive (DDD) versus active (DDD-CLS and VVI-CLS) in groups I and II (panel c). * = statistical significant difference P < 0.05.*

activated, and all measurements were repeated 15 days later with the sensor off. The Hospital Ethics Committee approved the study and all patients granted their written, informed consent prior to the study.

Results

Head-up Tilt Table Testing

After activation of the PM sensor (DDD-CLS mode), more physiologically paced HR and BP responses were observed in group I. Mean HR and BP values remained unchanged during coughing and tilt table testing in group II. However, a greater increase in BP, but not in HR, was observed during defecation and exertion in the VVI-CLS than the DDD mode (Table 1b).

Plasma Catecholamine Measurements

Baseline plasma EP and NE levels in patients with CI paced in the DDD mode were significantly higher than in patients paced in DDD-CLS mode ($P < 0.05$). Furthermore, patients with CI programmed to DDD mode tended to have a lesser increase in NE level with upright tilt. Baseline NE levels in patients with NSF and PM programmed to VVIR were comparable to those of patients with CI and PM programmed to the DDD-CLS mode (Table 1a).

PRA Measurements

Baseline PRA measurements were within the normal range in both groups (DDD mode). With upright tilt, mean PRA tended to increase in patients whose PM were programmed to the DDD mode and in those programmed to DDD-CLS and VVI-CLS modes. A lesser increase in PRA was also measured in the group of patients with CI whose PM were programmed to the DDD mode.

Valsalva Maneuver

In patients with CI in the DDD mode (group I), phases II and IV of the Valsalva maneuver were not well defined. However, in the DDD-CLS mode, not only were all Valsalva maneuver phases clearly defined, but a physiological response was also observed in phases I – III (Figure 1a). Group II patients had a nearly physiological response to the Valsalva maneuver during each of its phases in VVI-CLS mode compared to the DDD mode. Although the curves were comparable under both conditions, it is noteworthy that, in this group, the two patients who had left-ventricular dysfunction showed an abnormal response to the Valsalva maneuver (square wave) that remained unchanged in both conditions (Figure 1b). A slight paradoxical HR response was noted at the start of phase IV in both groups.

Valsalva Index

In patients with IC (group I), the mean Valsalva Index was near 1.0 in the DDD mode, though it was higher in DDD-CLS mode (Valsalva Index 1.4). However, in group II the mean value was 1.3 during pacing in both DDD and VVI-CLS modes (Table 1c).

Pharmacological Tests

After phenilephrine infusion, the HR changed in three patients with CI who were being paced in the DDD-CLS mode, and no changes were observed in the other three patients with NSF in VVI-CLS. All patients developed subtle and delayed increases in HR in response to nitroglycerine injection. Group I patients (DDD-CLS mode) developed greater HR increases than group II patients in VVI-CLS mode (Figure 2).

Physiological Tests

Variations in BP and HR during physiological tests are shown in Table 1c. Under all conditions, HR was higher in group I (DDD-CLS), and further increased during defecation and isotonic exercise [9]. A lesser increase in BP was observed. During tilt table testing and hand grip maneuvers, the increase was comparable in both pacing modes, while no changes were observed with coughing. In group II, mean HR values were comparable during tilt table testing and exertion in the DDD

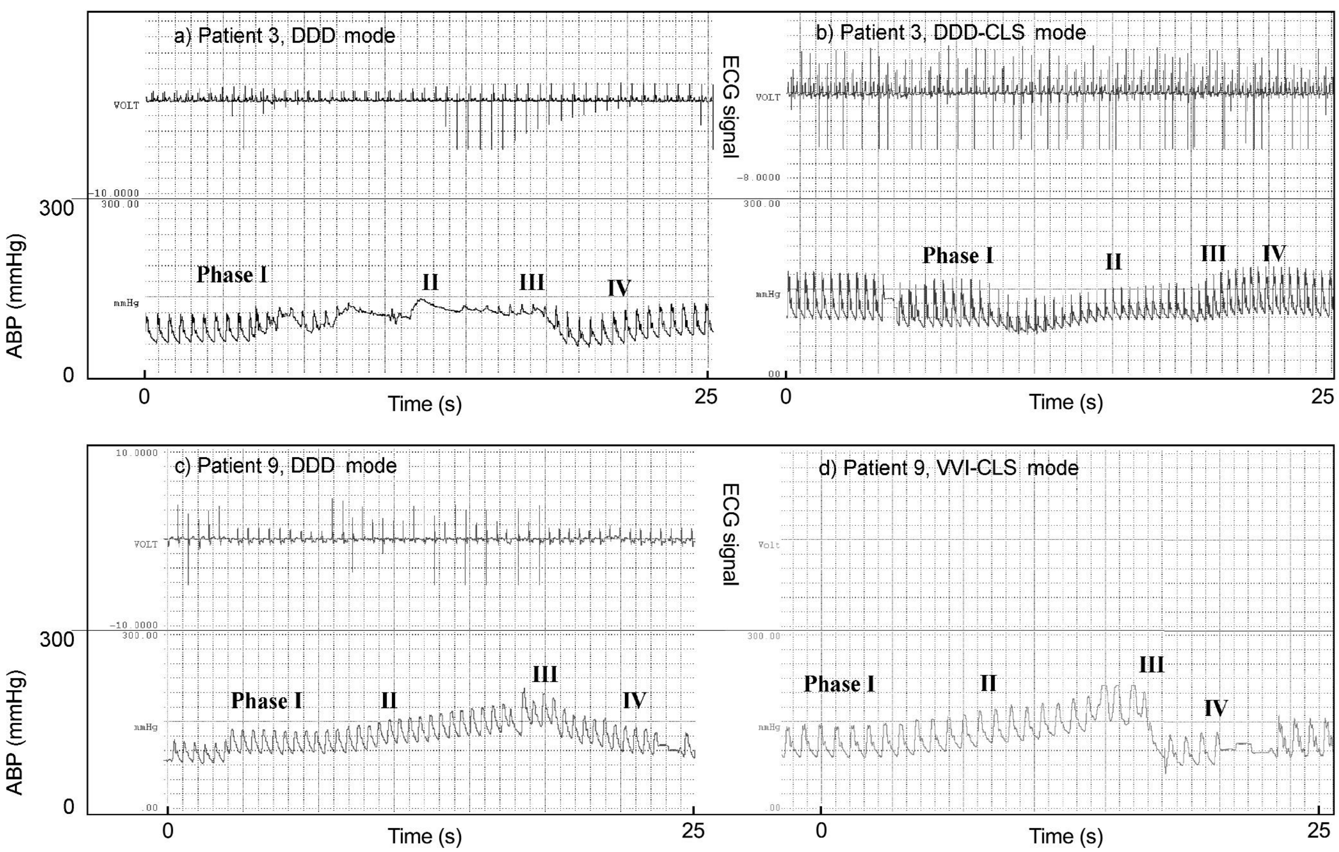

Figure 1. Phases of Valsalva maneuver. Patient 3 from group I with AV block and chronotropic incompetence with inactive sensor/DDD mode (panel a) and active sensor/DDD-CLS mode (panel b). Patient 9 from group II with AV block and normal sinus function with inactive sensor/DDD mode (panel c) and active sensor/VVI-CLS mode (panel d).

and VVI-CLS modes, and no change occurred during coughing. During activities such as handgrip or defecation, higher BP increases were measured in VVI-CLS than in the DDD mode (Figure 3).

Discussion

The fact that chronotropic competence was restored by PM-sensor activation (VVI-CLS or DDD-CLS modes) was the main observation of this study; function was restored even during tilt table testing and the Valsalva maneuver. The paradoxical HR response observed during phase IV of the Valsalva maneuver may have been caused by an increase in myocardial contractility detected by the sensor, a consequence of an increase in venous return and peripheral resistance. This paradoxical HR behavior during phase IV of the Valsalva maneuver was not symptomatic. The presence of SND during DDD pacing was apparent in abnormal Valsalva maneuver phases II and IV. Plasma catecholamine levels were increased under resting conditions and indicated sympathetic hyperactivity. However, during DDD-CLS pacing, plasma catecholamine levels decreased significantly in addition to the Valsalva maneuver normalization. Patients with NSF had comparable changes in phases II and IV of the Valsalva maneuver and catecholamine levels during DDD and VVI-CLS pacing. Pharmacological tests during sensor activation showed an increase in HR in both groups, probably due to a transitory increase in myocardial contractility.

Conclusion

The sympathetically driven PM sensor was associated with a physiological HR behavior and appropriate HR increase in response to a decrease in systemic vascular resistance during atrioventricular pacing in patients with CI, and a normal functional and neurohumoral response in patients with NSF, including during solely ventricular pacing. This second conclusion will require further evaluation in a larger patient population.

Acknowledgement

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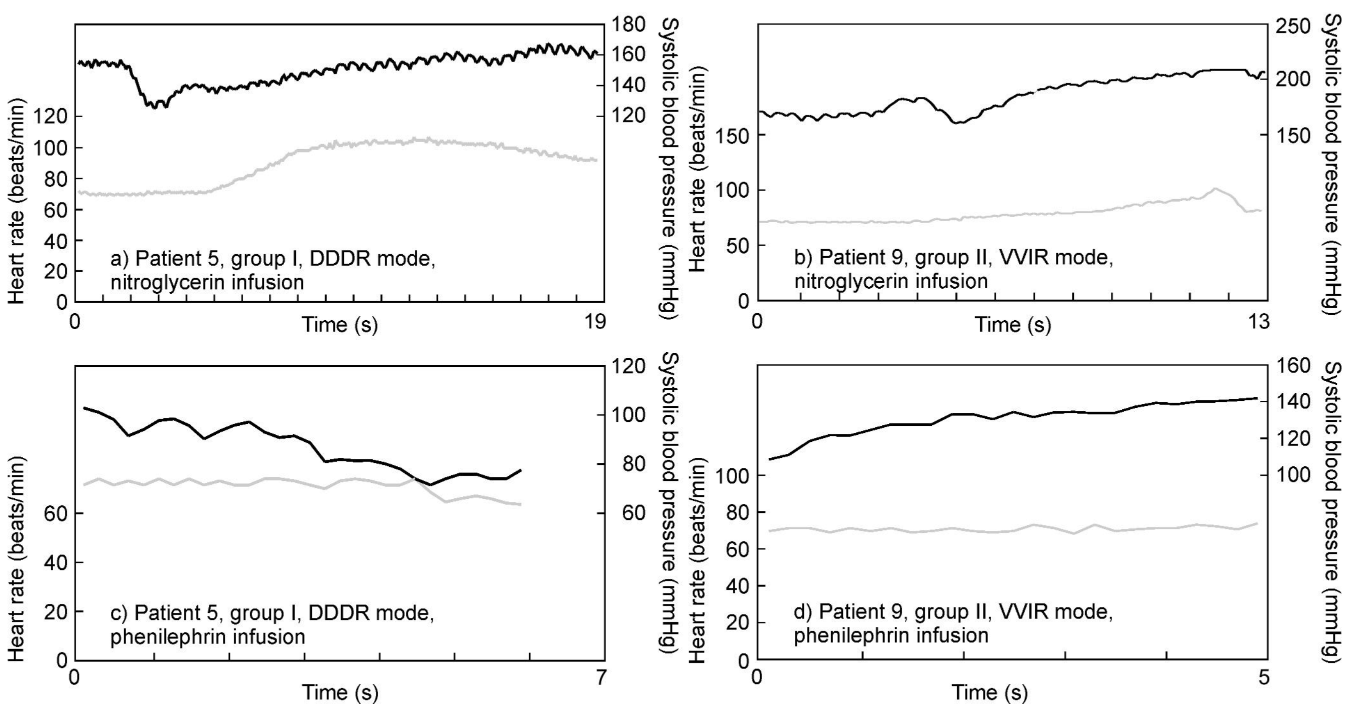

Figure 2. Pharmacological tests in patient 5 from group I with atrioventricular block and chronotropic incompetence in the DDD-CLS mode showing nitroglycerin infusion (panel a) and phenilephrine infusion (panel b) and in patient 9 with AV block and normal sinus function in VVI-CLS mode showing nitroglycerin infusion (panel c) and phenilephrine infusion (panel d).

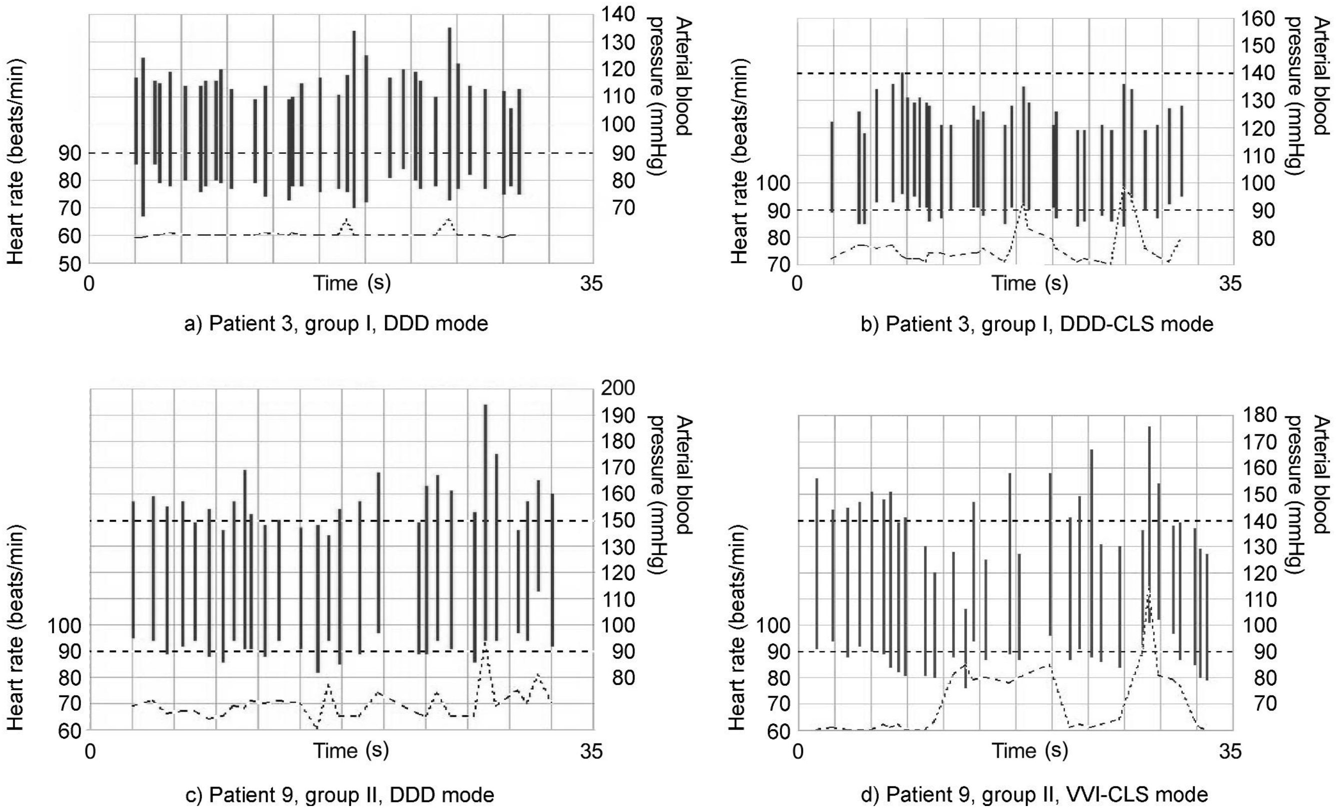

Figure 3. Physiological tests in patient 3 from group I with AV block and chronotropic incompetence with an inactive sensor/DDD mode (panel a) and active sensor/DDD-CLS mode (panel b) and in patient 9 from group II with AV block and normal sinus function with an inactive sensor/DDD mode (panel c) and active sensor/DDD-CLS mode (panel d).

References

[1] Mitchell IH, Wallace AG, Skinner NS Jr. Intrinsic effects of heart rate on left ventricular performance (abstract). Am J Physiol. 1963; 205: 242.

[2] Martinelli Filho M, Nishioka SAD, Lopez H, et al. Neurohumoral behavior in recepients of cardiac pacemakers controlled by a closed-loop autonomic nervous system-driven sensor. PACE. 2000; 23: 1778-1782.

[3] Christ T, Brattstrom A, Kblin H, et al. Effect of circulating catecholamines on the pacing rate of the closed loop stimulation pacemaker. Prog Biomed Res. 1998; 3: 143-146.

[4] Goldstein DS, Feuerstein G, lzzo JL Jr, et al. Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine in man. Life Sci. 1981; 28: 467-475.

[5] Porth CIM, Bamrah VS, Tristani FE, et al. The Valsalva maneuver: Mechanisms and clinical implications. Heart Long. 1984; 13: 507-518.

[6] Parlow J, Viale JP, Aniiat G, et al. Spontaneous cardiac baroreflex in humans. Comparison with drug-induced responses. Hypertension. 1980; 46: 213-218.

[7] Berne RM. Control of the heart. In: Berne RM, Levy MN (editors). Cardiovascular Physiology. Fourth edition. St. Louis: Mosby. 1981: 145-181.

[8] Hachul D. Hipotensão arterial e síncope: Conceito, fisiopatologia e diagnóstico diferencial. In: Timerman A, Machado Cesar LA (editors). Manual de Cardiologia SOCESP, Silo Paulo, Brazil: Ed Atheneu. 2000: 65-68.

[9] Pope SE, Stinson EB, Daughters GT II, et al. Exercise response of the denervated heart in long-term cardiac transplant recipients. Am J Cardiol. 1980; 46: 213-218.

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