Neurohumoral Behavior in Cardiac Pacemaker Patients Controlled by the Autonomic Nervous System with Closed Loop Stimulation

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Summary

*The current goal for sensor-driven pacing is to find a physiological system to correct chronotropic incompetence. The objectives of this study were to evaluate changes in the heart rate effected by sympathetic sensor-driven pacing and to compare these with normal sinus function. Fifteen patients with AV block and a pacemaker controlled by Closed Loop Stimulation were studied. Six were female, 9 male, with ages ranging from 37 to 80 years. They were divided into Group I (8 patients with chronotropic incompetence) and Group II (7 patients with normal sinus function). All patients performed the Valsalva maneuver and tilt table test under catecholamine and renine dosages. For the 1st stage, the programmed pacing mode was: DDD, LR = 60 ppm, URL = 0.85 * (220 - age); the 2nd stage was in DDDR for Group I and VVIR for Group II. Tilt table test: In group I, heart rate variations occurred only in DDDR (after inclining). In Group II, heart rate changes were similar for both modes. For Group I, cathecholamine dosages were higher in DDD ($p < 0.05$) than in DDDR. The phase II and IV (Valsalva maneuver) did not change in Group I, DDD, but had near physiological behavior with sensor activated. The sympathetic SDP provided neurohumoral adjustment for patients with AV block and chronotropic incompetence.*

Key words

Heart rate response, artificial cardiac stimulation, chronotropic incompetence, Closed Loop Stimulation, circulating catecholamines

Introduction

Under normal circumstances, physiologic chronotropy is influenced by the sympathetic and parasympathetic nervous system, permitting cardiovascular adaptation to various situations such as rest, postural changes, physical effort, defecation, and others. Reflex bradycardia and tachycardia, which are essential in these circumstances and mainly triggered by arterial baroreceptors and the cardiopulmonary reflex, are dependent on pressure changes within the cardiac chambers and the great vessels (aorta and pulmonary artery).

The autonomic nervous system is crucial for the regulation of heart rate, contractility, and vascular resistance control, as well as cardiac output, blood flow distribution, and blood pressure regulation.

Under physiologic conditions, the most important factor regulating myocardial contractility is the norepinephrine concentration in cardiac sympathetic nerve endings. The most rapid modifications in cardiac contractility have been observed to occur after changes in the intensity of adrenergic nerve impulses [1].

When stimulated, the adrenal medulla releases epinephrine, which is carried to the heart where it stimulates beta-adrenergic receptors, increasing cardiac contractility. This mechanism is not as fast as norepinephrine release from cardiac nerve endings, but it can be vital to preserve cardiac output in some particular conditions.

If we consider stroke volume to be constant and cardiac output to be linearly correlated with heart rate, the ability to modify the heart rate will be an important mechanism in the control of cardiac output [2].

Therefore, the importance of the heart rate in maintaining cardiac output in patients with chronotropic incompetence is reflected in their inability to increase cardiac output, even when myocardial contractility is entirely normal. In those patients, a rate-adaptive pace-

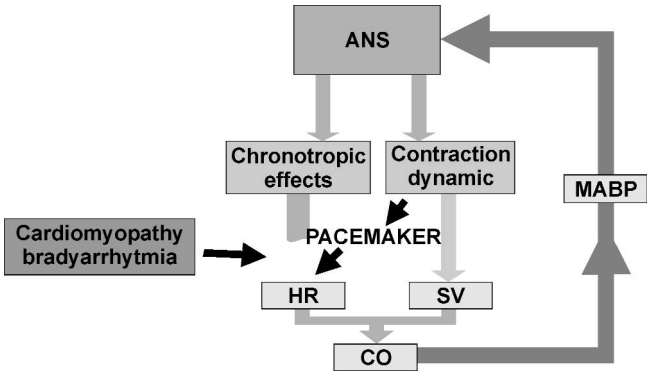

Figure 1. Closed loop system.

maker can guarantee that an adequate heart rate is maintained [3,4].

Among the many rate-adaptive artificial heart stimulation systems currently in use, we will evaluate the performance of a physiologic sensor model, called a sympathetic biosensor, that is able to capture the intracavitary myocardial signals, and which uses myocardial contractility as an indicator of the sympathetic tone [5].

Objective

The aims of this study were:

- to compare this pacemaker's biosensor heart-rate response with sinus node performance in patients with normal chronotropic response, and
- to evaluate the heart rate changes due to sensor response to modifications in myocardial contractility in patients with chronotropic incompetence.

These systems will be evaluated using tests that produce changes in heart dynamics, thus inducing reflex responses by the parasympathetic and sympathetic nervous system. In order to do that, catecholamine and plasma renin activity measurements will be conducted before and after tilt table testing. A Valsalva maneuver will also be performed for all patients [6].

Methodes

The artificial heart stimulation system implanted was the INOS^2 CLS (Biotronik, Germany), a biosensor governed by the ventricular contractions that provide the heart rate autoregulation [5] (Figure 1).

Patients

Fifteen patients with an advanced/complete atrioventricular block, with ages ranging from 37 to 80 years (mean 54.7 years) were prospectively studied. They underwent a pacemaker implantation or pacemaker replacement [7] between 09/97 to 03/99. These patients were divided into 2 groups. Group I consisted of 8 patients with a third degree atrioventricular block plus sick sinus syndrome. Group II consisted of 7 patients with normal sinus function and a third degree atrioventricular block. Patients' NYHA functional classes for heart failure and heart disease are described on Table 1.

Group	Nº	Name	Cardiomyopathy	NYHA class
I	1	A.S.	hypertensive	I
	2	F.G.P.	ischemic	I
	3	L.M.A.	Chagas'	I
	4	M.A.D.C.	idiopathic	I
	5	T.M.S.	Chagas'	I
	6	V.R.	Chagas'	I
	7	I.C.S.	Chagas'	I
	8	M.R.	idiopathic	I
II	9	Z.C.	ischemic	I / II
	10	O.M.S.	Chagas'	I
	11	O.R.S.	Chagas'	I
	12	A.R.	hypertensive	I
	13	A.P.A.	Chagas'	I
	14	S.J.P.	valvular	I / II
	15	A.G.	hypertensive	I

Table 1. Studied patients, cardiomyopathy and NYHA class.

Clinical follow-up for Group I patients ranged from 14 to 31 months (mean 22.3), while Group II patients were followed for 2 months.

All the patients had normal left-ventricular function as observed by echocardiography (left-ventricular ejection fraction (LVEF) > 0.60), except for 2 patients from Group II: one patient had ischaemic cardiomyopathy (LVEF = 0.52) and another had aortic valve disease (LVEF = 0.43).

Study Design

The first stage of the study consisted of performing examinations thirty days after implanting the pacemaker and programming it to a DDD mode, with a basic rate of 60 ppm and an upper tracking rate of 0.85 * (220 - age). All patients underwent tilt table testing (TTT) with plasma epinephrine (EP), norepineph-

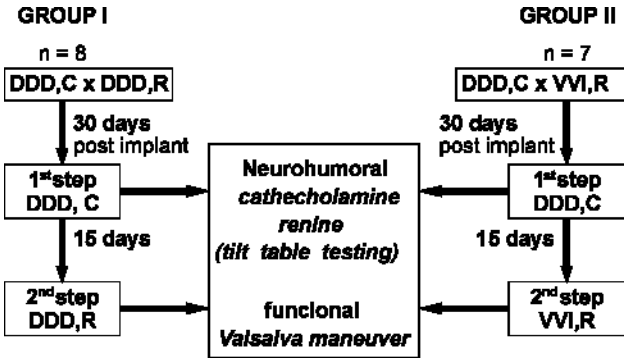

Figure 2. Study designer.

rine (NE), and plasma renin activity (PRA) measurements undertaken during baseline (after one hour of bed rest) and after a 60º inclination (Figure 2). After the end of the TTT, a Valsalva maneuver was performed.

Immediately after this, Group I patients had their pacemaker programmed to DDDR whereas Group II patients were reprogrammed to VVIR. Other than reprogramming the mode, the rest was unchanged.

In a 15-day follow-up after sensor activation, the examinations were repeated with the new pacing mode used in the second stage of the study.

The pacemaker programming mode was maintained in DDDR for Group I patients during follow-up through 04/00. Group II had their pacemaker sensor deactivated while atrioventricular synchronization took place (DDD mode).

Tilt Table Testing

In present practice, tilt table testing is used to assess cardiovascular changes related to postural modifications, as well as to evaluate syncope of unknown etiology [8].

The degree of postural hypotension, the heart rate response, and the circulating catecholamine levels were evaluated after a bed-rest period which was followed by tilting to an upright position in order to evaluate sensor rate response in both groups. This was done in both the first and second stages of the study.

TTT was undertaken after the patient had rested on his or her back for 1 hour. After this, the patient was then tilted upright at 60º.

Blood Sample Collection

After the venous puncture, the patient was kept in bed in a calm setting with the lights turned low. Plasma EP and NE were taken in cooled flasks. PRA was also measured during baseline. New blood samples were taken 10 minutes after tilting upright in order to measure EP, NE and PRA.

Plasma Catecholamine Measurements

Epinephrine and norepinephrine were measured by high performance liquid chromatography [9].

Measure of Plasma Renin Activity

PRA was measured by radioimmunoassay for angio tensine I in the presence of angiotensinase inhibitors.

Valsalva Maneuver

The Valsalva maneuver is normally performed in daily activities such as lifting weights, coughing, defecation, vomiting, pushing heavy objects and the expulsive period during childbirth. It consists of a forced exhalation against a closed glottis, with a subsequent rise in intrathoracic pressure (ITP). The increase in ITP promotes sudden changes in preload and afterload. As the pressure increases, it is transferred to the heart chambers and great vessels, leading to an increased pressure in the right atrium and intra-thoracic veins with consequent decline in venous return. According to Frank-Starling's law, the VM produces a decrease in myocardial fiber distension and a drop in stroke volume [10].

The VM was accomplished with the patient in a supine position. After a regular inspiration, the patients blows into a manometer to maintain a level of pressure ranging from 20 to 40 mmHg for 10 to 30 seconds. This pressure is enough to cause a drop in pulse pressure and a reflex peripheral vasoconstriction. Healthy individuals can attain up 40 to 60 mmHg of intrathoracic pressure during the maneuver.

Phases of the Valsalva Maneuver

The normal response to the VM has been divided in 4 phases [11] (Table 2):

- PHASE I: With the initial expiration, the increase in intrathoracic and intraabdominal pressure is transmitted to the left ventricle (LV) and aorta, producing an increase in stroke volume (SV) and transport of blood into the peripheral arteries. The sum of these effects produces a rise in blood pressure (BP). Pulse pressure is unchanged, since there is a rise in both diastolic and systolic pressures. The transient increase in BP leads to reflex bradycardia.

Phase	Action	ABP	HR	Mechanism
I	beginning expiration	↑	↓	↑ ITP
II	15 seconds expiratory strain	↓	↑	↓ VR, SV, PP and CO
III	end expiratory strain	↓	↑	abrupt ↓ ITP, ↓ ABP and ↑ HR
IV	return inspiration	↑	↓	ABP overshoot, reflex bradycardia and LV fast stuffing

Table 2. Phases of Valsalva maneuver. ABP = arterial blood pressure, ITP = intrathoracic pressure, VR = venous return, HR = heart rate, SV = stroke volume, CO = cardiac out put, PP = pulse pressure, LV = left ventricle, ↑ = increasing, ↑ = decreasing.

- PHASE II: As the expiratory strain and the elevation of ITP persist, there is a consequent drop in venous return, stroke volume, and blood pressure. Reflex tachycardia and peripheral vasoconstriction occurs 6 to 7 seconds after the start of Phase II, and prevent an unwarranted drop in blood pressure.
- PHASE III: Expiration is ended, causing a sudden drop in ITP, with a consequent decrease in BP and a reflex increase in HR during the subsequent 10 beats.
- PHASE IV: The patient inhales again. There is an increase in venous return associated with the vasoconstriction occurring in Phase III, which causes a rise in BP (the so-called overshoot phase) and reflex bradycardia 3 to 8 seconds after the end of the expiratory strain. This phase is used as qualitative indicator of the intensity of vasoconstriction attained by the maneuver. The increase in pulse pressure corresponds to a normal response [12].

The percentage changes in systolic blood pressure, diastolic blood pressure, and heart rate in phases II and IV compared to baseline were used to assess the performance of the sensor. The Valsalva index, which consists of the ratio of the highest and the lowest HR, was also analyzed.

Results

Tilt Table Testing

The following results were observed with the pacemaker sensors on and off:

- Group I: After activating the pacemaker sensor (DDDR mode) and the consequent chronotropic competence, a more physiologic response to the stimulation was observed for the HR and BP (Figure 3 - patient 2).
- Group II: In the test results, a good correlation was observed between the sensor-activated pacemaker (VVIR mode) and the physiologic response of patients with normal sinus function (DDD mode). This can be observed for patient number 2 (Figure 4).

Plasma Catecholamine Measurements

Baseline plasma epinephrine and norepinephrine levels in patients with chronotropic incompetence and an implanted pacemaker programmed to DDD mode were significantly higher ($p < 0.05$) than those for patients programmed to DDDR mode. Furthermore, patients with chronotropic incompetence who were programmed to DDDR mode tended to have a smaller increase in norepinephrine level after upright tilting. As for those patients with intact sinus function and a pacemaker programmed to VVIR, baseline norepinephrine levels were similar to patients with chronotropic incompetence and the pacemaker programmed to a DDDR mode (Table 3).

Plasma Renin Activity Measurements

Baseline PRA measurements were normal for both groups (DDD mode). After tilting upright, there was a tendency toward an increase in the average PRA measurement for patients programmed to DDD as well as those programmed to DDDR (Group I) and VVIR (Group II). A milder increase in PRA could be observed for the group of patients with chronotropic incompetence who were programmed to DDD mode (Table 3).

Valsalva Maneuver

Group I

When evaluating the response observed in patients with chronotropic incompetence, we observed that if Closed Loop Stimulation was disabled (DDD mode),

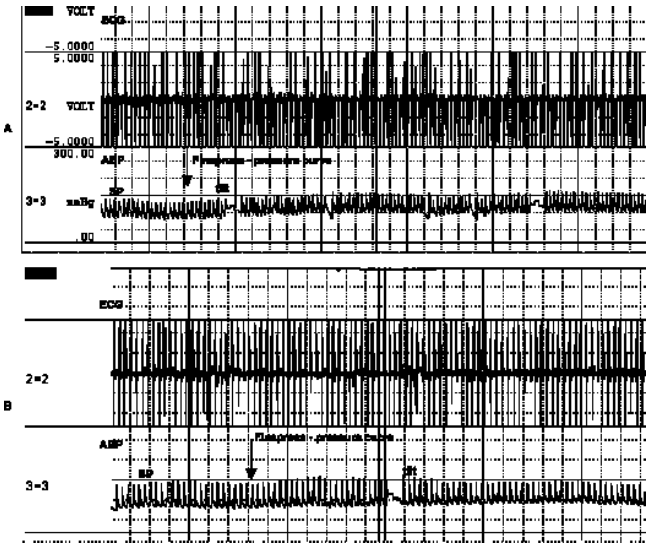

Figure 3. Tilt table testing (Patient 6 - Group I). A: inactive sensor (DDD, C mode). In this situation, the heart rate did not increase after inclination at 60°. B: active sensor (DDD,R mode). We observed an increase in heart rate after inclination at 60° and also arterial blood pressure increased.

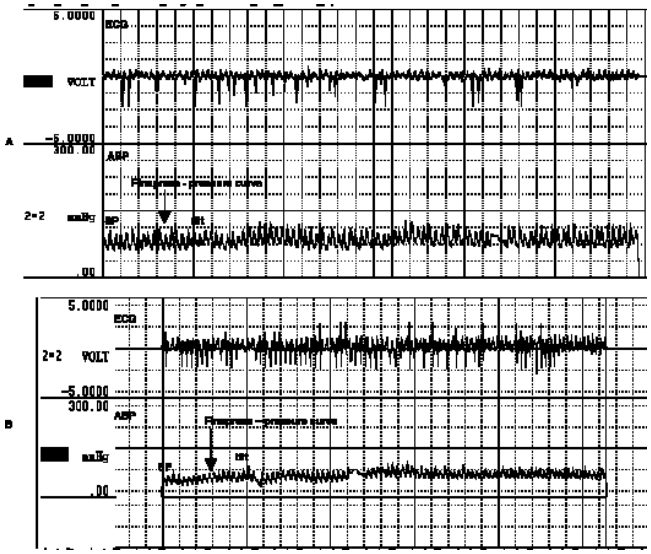

Figure 4. Tilt table testing (Patient 13 - Group II). A: inactive sensor (DDD, C mode). B: active sensor (VVI, R mode). In both conditions A (DDD,C mode) and B (VVI,R mode), there was an increase in heart rate and arterial blood pressure after inclination at 60°.

phases II and IV of the Valsalva maneuver could not be well defined. However, after activation of Closed Loop Stimulation (DDDR mode), it was possible not only to define all Valsalva maneuver phases but also to maintain a physiological response in phases I, II and III. In one patient a slight paradoxical HR response could be noted at the start of phase IV (Figure 5).

Group II

This group of patients presented an almost physiological response to the Valsalva maneuver during each of its phases when programmed to the VVIR mode compared to the DDD mode. Although the curve behavior was similar under both conditions, there was a slight paradoxical HR response during phase IV of the Valsalva Maneuver. It is interesting to note that, in this group, the 2 patients who had left-ventricular dysfunction showed an abnormal response to the Valsalva maneuver (a "square wave" response), which remained unchanged in both situations (patients 9 and 14, Figure 6).

Valsalva Index

For Group I, the mean value was near 1.0 in the DDD mode, indicating a flat heart rate trend without any response to the Valsalva maneuver. In the DDDR mode, the Valsalva index increased to 1.4. For Group II, the mean value of the Valsalva index was 1.3 in DDD as well as in VVIR (Table 4).

Discussion

The present study was based on the principle that a clinical indication of a new stimulation system, a heart rate responsive pacing driven by the sympathetic tone, demands the maximum advantage of knowledge, along with the favorable general behavior shown by many authors [13]. More consistent information concerning the intrinsic mechanisms of the pacing system, mainly involving the neurohumoral changes, are still necessary to improve its application [14].

First of all, our initial expectation was justified by the general findings of this study: The VVIR pacing mode (Group II) provided similar behavior to the physiological stimulation (DDD mode with normal sinus function) during resting conditions, upright tilting, and the Valsalva maneuver. Two patients with chronotropic incompetence had a more physiologic response during TTT and the Valsalva maneuver when the pacemaker sensor was activated (DDDR mode).

The inclusion of Valsalva maneuver in our methodolo-

GROUP I

Patients	Inactive sensor						Active sensor					
	EP rest	EP tilt	NE rest	NE tilt	PRA rest	PRA tilt	EP rest	EP tilt	NE rest	NE tilt	PRA rest	PRA tilt
1	71	58	709	1000	0.2	0.3	14	19	227	538	0.2	0.2
2	25	30	233	559	0.6	0.9	indet.	25	267	424	1.0	1.5
3	45	106	1050	824	0.7	0.6	09	18	168	343	0.2	0.4
4	indet	13	183	407	0.2	0.7	16	16	262	421	0.6	0.6
5	25	223	429	283	0.2	0.2	26	111	250	411	0.5	0.7
6	36	40	227	288	0.5	0.6	16	64	142	385	1.9	4.5
7	indet	indet	269	276	0.5	0.4	indet	26	166	295	0.7	1.2
8	55	50	334	564	1.0	1.0	indet	44	294	362	0.8	0.5
Mean	43*	74*	429*	525*	0.5	0.6	16*	40*	222*	397*	0.7	1.2

*p < 0.05

GROUP II

Patients	Inactive sensor						Active sensor					
	EP rest	EP tilt	NE rest	NE tilt	PRA rest	PRA tilt	EP rest	EP tilt	NE rest	NE tilt	PRA rest	PRA tilt
9	58	85	303	474	1.3	1.5	45	75	174	284	1.6	1.6
10	18	69	225	439	1.7	1.7	30	68	264	690	0.6	0.9
11	48	67	425	687	2.1	3.1	58	49	281	508	3.2	3.5
12	indet	indet	501	738	2.2	2.3	indet	534	indet	758	1.6	1.9
13	30	49	157	296	0.7	1.4	16	32	109	258	0.3	0.8
14	36	45	190	327	1.2	1.4	33	70	345	515	1.5	1.5
15	indet	33	140	309	1.2	1.6	43	89	345	491	1.4	1.7
Mean	38	58	277	467	1.5	1.9	38	131	294	501	1.5	1.7

Table 3. Epinephrine (EP), norepinephrine (NE) and plasma renin activity (PRA) plasmatic values obtained in patients of Groups I and Groups II.

gy in order to try to reproduce daily activities allowed additional clinical outcomes to be obtained. The paradoxical HR response observed during phase IV of the Valsalva maneuver can be related to an increase in myocardial contractility recognized by the sensor. The increase in contractility is produced by a rise in venous return together with an increase in peripheral resistance [15]. In spite of the paradoxical rise in HR during phase IV of the Valsalva maneuver, patients remained asymptomatic during the entire examination. The Valsalva Index values observed in Group I (DDD mode) were a consequence of an unchanged heart rate during phases II and IV of Valsalva maneuver, but under DDDR-mode sensor activation there was a tendency to the index normalization. In Group II, we observed similar variations in phases II and IV for both conditions (DDD and VVIR modes), providing a near normal index value.

Concerning the catecholamine behavior, we observed interesting responses in both groups. In Group II (NSF), the NE and EP plasma levels, showed normal and similar values during resting and tilting conditions (DDD and VVIR modes). Group I patients had an abnormal plasma catecholamine level that increased during resting conditions (DDD mode), which indicates an important sympathetic influence. Under tilting, the plasma level rose less than expected. Yet, during activated sensor (DDDR mode), NE and EP resting levels normalized. This is similar to the observed NSF patient's behavior.

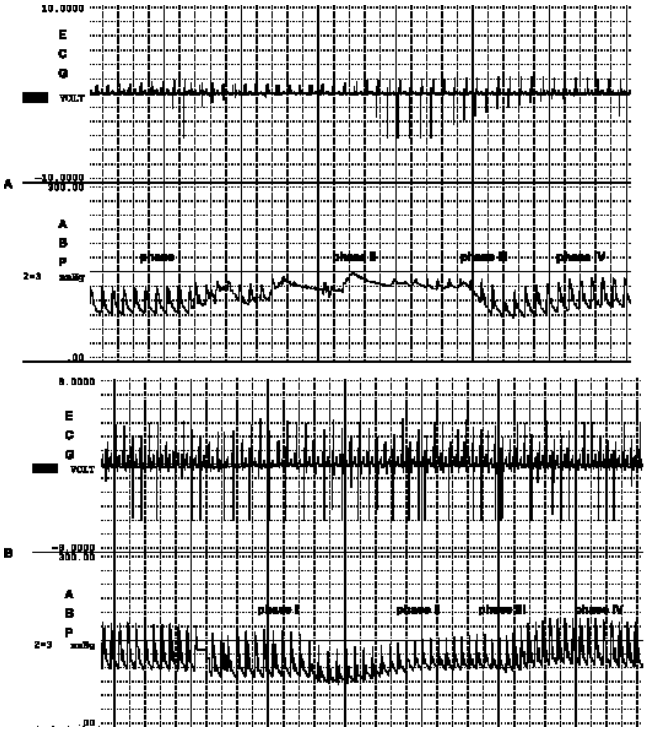

Figure 5. Phases of Valsalva maneuver (patient 3) with AV block and chronotropic incompetence (Group I). A: inactive sensor (DDD,C mode). B: active sensor (DDD,R mode).

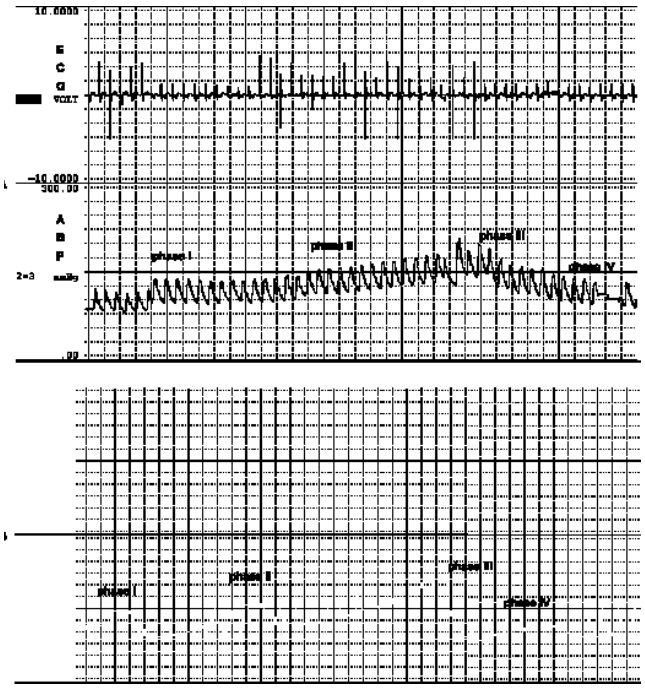

Figure 6a. Phases of Valsalva maneuver (patient 9) with AV block and NSF (Group II). A: inactive sensor (DDD,C mode). B: active sensor (VVI,R mode).

GROUP I		
Patients	**DDD, C index**	**DDD, R index**
1	1.1	1.1
2	1.0	1.4
3	1.0	1.3
4	1.1	1.3
5	1.1	1.1
6	1.0	2.1
7	1.1	1.4
8	1.1	1.6
Mean	1.1	1.4
GROUP II		
Patients	**DDD, C index**	**VVI, R index**
9	1.1	1.2
10	1.3	1.3
11	1.3	1.4
12	1.5	1.5
13	1.2	1.3
14	1.3	1.3
15	1.6	1.3
Mean	1.3	1.3

Table 4. Mean value of the Valsalva index in Group I and II.

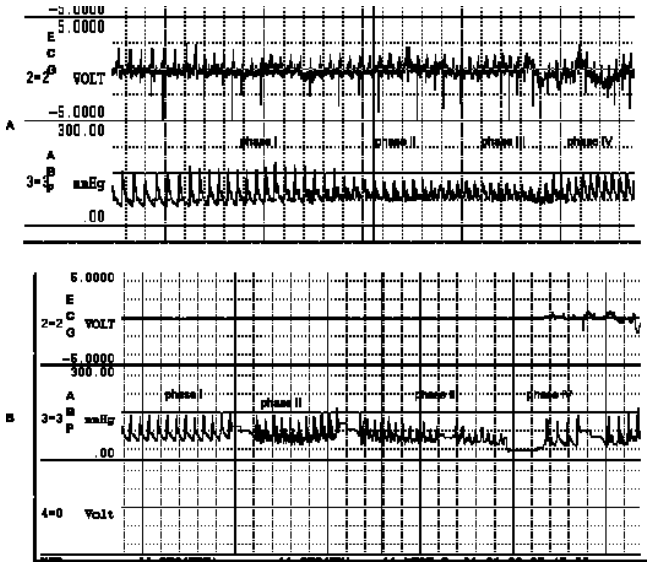

Figure 6b. Phases of Valsalva maneuver (patient 14) with AV block and NSF (Group II). A: inactive sensor (DDD,C mode). B: active sensor (VVI,R mode).

These findings clearly showed that patients with chronotropic incompetence were not able to increase the heart rate according to the humoral release when the sensor was deactivated (DDD mode). In addition, the significant decrease in plasma catecholamine levels during sensor activation (DDDR mode) reinforced our outcomes.

In conclusion, the present study, which was proposed in order to evaluate new findings concerning a sympathetically-mediated pacing system, seems to have been an important contribution to the knowledge of the intrinsic mechanism involved in its documented physiological performance.

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