Blood Pressure Circadian Rhythm and Variability in Subjects with Severe Heart Failure

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To explore whether a condition of severe heart failure results in alteration of the 24-h-blood pressure (BP) profile and BP circadian rhythm, 19 patients with severe heart failure (NYHA class III–IV, 17M, 2F, mean age 57 ± 8 years) were considered and compared to a control group of age- and sex-matched normal subjects. All subjects were submitted to non-invasive 24-h ambulatory blood pressure monitoring using a SpaceLabs 90207 unit (recording interval 15 min). Both systolic and diastolic BP profiles were evaluated using the two-step method of analysis reported by Staessen: the existence of a BP circadian rhythm was first tested using Siegel's runs test, then a Fourier multiple harmonic analysis allowed us to obtain the BP profile parameters Acrophases (Acro, hh:mm) and Amplitudes (Ampl, mmHg). The same methods were used for pulse rate. Our results showed the presence of a BP circadian rhythm in severe heart failure subjects, as well as in control subjects. Furthermore, no significant difference was found between the two groups when considering the BP profile parameters Acro and Ampl. In conclusion, in contrast with previous reports, our results show that both BP circadian rhythm and BP profile parameters are preserved in patients with severe heart failure. *Key words: ambulatory blood pressure monitoring, blood pressure circadian rhythm, blood pressure variability, heart failure.*

INTRODUCTION

Few studies have been conducted to examine the 24-h blood pressure (BP) profile in subjects with heart failure (HF) [1–4].

Discordant results have been reported when considering BP circadian rhythm in patients with HF: blunted profiles, preserved profiles, as well as a reduction in the amplitude of the BP circadian rhythm have been described [1–4]. In fact, BP rhythm could be modified by neuroendocrine activation subsequent to reduced cardiac function (including sympathetic nervous system, renin-angiotensin system and atrial natriuretic peptide, etc.) [1, 5].

The aim of this study was to verify whether a condition of severe HF affects the BP circadian rhythm and 24-h BP profile parameters.

MATERIALS AND METHODS

After having provided informed consent, two groups of subjects were considered for the study. Nineteen patients with HF (NYHA functional class III–IV; mean ejection fraction $19.6 \pm 6.4\%$; 17M, 2F; mean age 57 ± 8 years, 10 post-ischemic and 9 primary dilated cardiomyopathies) were enrolled and compared to a control group of age- and sex-matched subjects. These control subjects, having no history of heart or systemic disease, presented normal physical examination, electrocardiogram, echocardiogram and BP measurements.

All subjects enrolled in the study were non-smokers, in order to avoid possible influences on BP variability and BP profile.

The patients with HF, having been previously referred to our Institution for heart transplantation evaluation, showed the demographic and clinical characteristics reported in Table I. All patients were in washout for vasodilator therapy (i.e. ACE inhibitors: one week of withdrawal). The administration of digoxin and loop-diuretics was not discontinued for ethical reasons. For the same reasons, no longer period of withdrawal of ACE inhibitors was allowed. At the moment of the study, HF patients were in stable clinical condition, without fluid overload, in sinus rhythm and were not hospitalized. Diabetes was considered an exclusion criterion.

The left ventricular ejection fraction was determined by means of two-dimensional echocardiography (biplane area-length method, Vingmed CFM800), since haemodynamic assessment was not available for each patient.

All subjects were submitted to non-invasive ambulatory blood pressure monitoring, using a SpaceLabs 90207 unit (recording intervals: 15 min) and followed standardized resting–activity periods during BP monitoring, in

Table I. *Characteristics of the patients with heart failure enrolled in the study*

No.	Sex	Age (years)	Myocardial disease	Follow-up (1 year)	NYHA class	LVEF (%)	SBP	DBP	HR	LVIDD (mm)	Height (cm)	Weight (kg)	BSA (m^2)
1	M	64	IHD	alive	III	13	95	60	72	77	162	76	1.81
2	M	59	IHD	THX	IV	22	116	64	77	77	168	68	1.77
3	M	64	Primary	dead	IV	21	105	60	96	72	160	65	1.68
4	M	59	IHD	dead	IV	22	110	70	107	76	177	71	1.87
5	M	65	IHD	dead	III	31	140	80	103	72	183	88	2.10
6	M	57	IHD	alive	III	22	144	90	94	68	168	74	1.84
7	M	62	Primary	THX	III	14	90	60	80	72	166	75	1.83
8	M	48	IHD	dead	III	31	98	68	82	82	168	74	1.84
9	M	63	Primary	alive	IV	14	110	80	82	81	174	63	1.76
10	M	48	IHD	THX	IV	24	116	84	75	72	167	66	1.74
11	M	68	IHD	dead	III	22	100	72	66	77	166	76	1.84
12	F	54	Primary	alive	III	12	134	84	104	60	152	53	1.48
13	F	70	Primary	dead	III	30	156	82	70	69	158	73	1.75
14	M	36	Primary	THX	III	20	116	70	91	75	185	90	2.14
15	M	44	Primary	THX	IV	11	134	94	97	81	167	68	1.76
16	M	52	IHD	alive	III	16	124	84	78	73	164	67	1.73
17	M	62	IHD	dead	IV	20	128	80	94	70	172	85	1.98
18	M	51	Primary	THX	IV	16	110	80	74	72	165	74	1.81
19	M	57	Primary	dead	IV	12	122	82	86	75	170	74	1.85

LVEF = Left Ventricular Ejection Fraction; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Heart Rate; LVIDD = Left Ventricle Internal Diastolic Dimension; BSA = Body Surface Area; IHD = Ischemic Heart Disease; THX = Heart Transplantation.

extra-hospital environments: 06.00–23.00 h = daily activity period comprising breakfast (≈06.00–07.00 h), lunch (≈12.00–13.00 h) and dinner (≈19.00–20.00 h); 23.00–06.00 h = bed rest.

The recordings were verified by an expert operator and eventual artefacts were excluded (systolic BP >240 mmHg or 50 mmHg; diastolic BP >140 mmHg or <40 mmHg; pulse rate 150 bpm or <40 bpm).

Both systolic and diastolic BP profiles were evaluated using a two-step method of analysis reported by Staessen and co-workers [6]: the existence of a circadian rhythm is first tested using the Siegel's runs test [6], then a Fourier multiple harmonic analysis allows us to obtain the BP profile parameters Acrophases (Acro) and Amplitudes (Ampl). The same methods were applied to pulse rate.

From Siegel's runs test, the statistical z-value was obtained and subjected to a one-sided significance test for systolic and diastolic BP, as well as for pulse rate, for all subjects studied. A *p*-value <0.05 was considered significant.

Fourier analysis, limited to the first five harmonics, was performed on systolic and diastolic BP equalized data (as well as on pulse rate) for each subject. Acro (time corresponding to the absolute maximum of the curve) and Ampl (half the difference between the maximum and minimum values) were then estimated. Mean values and standard deviations were calculated for all examined samples, using a circular method for Acro and a linear one for Ampl. The Watson-Williams test and Aspen-Welch

test were respectively used for Acro and Ampl comparison.

Diurnal, nocturnal and whole day (24-h) mean BP values and mean pulse rate values were obtained. When comparing diurnal vs nocturnal mean values, the diurnal period was from 10.00 to 20.00 h and the nocturnal period from 24.00 to 06.00 h. Previous studies have demonstrated that these time intervals exclude the transition periods between sleep and waking, in which BP often undergoes sudden and marked variations [7]. Furthermore, comparisons were made between diurnal, nocturnal and 24-h mean values of the two samples studied, using the Student's *t*-test or the Aspen-Welch test.

RESULTS

The results of our profile analysis are reported in Table II, while the BP profiles for the two groups are showed in Figs. 1 and 2.

No significant differences were found between the two groups when considering BP circadian rhythm. In fact, a preserved BP circadian rhythm was found in almost all HF patients, as well as in control subjects (although non-significant for statistics, both patients without BP significant rhythm in the HF group presented a condition of ischaemic heart disease, NYHA class IV, and were dead at one-year follow-up).

Furthermore, HF patients showed BP profile parameters (Acro and Ampl) similar to those of the control

Table II. *Blood pressure profile analysis*

	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)		Heart rate (bpm)	
	HF	N	HF	N	HF	N
Rhythm	89%	94%*	100%	100%*	94.7%	94.7%*
Acrophase (h:mm)	15:51 ± 4:22	17:15 ± 3:49*	16:33 ± 4:48	17:15 ± 4:14*	15:10 ± 4:25	13:50 ± 4:05*
Amplitude	24 ± 2.2	22 ± 1.8*	18 ± 1.6	18 ± 1.4*	7.5 ± 1.7	9.5 ± 2.3*

HF = subjects with heart failure; N = control subjects; * = non-significant difference vs HF patients.
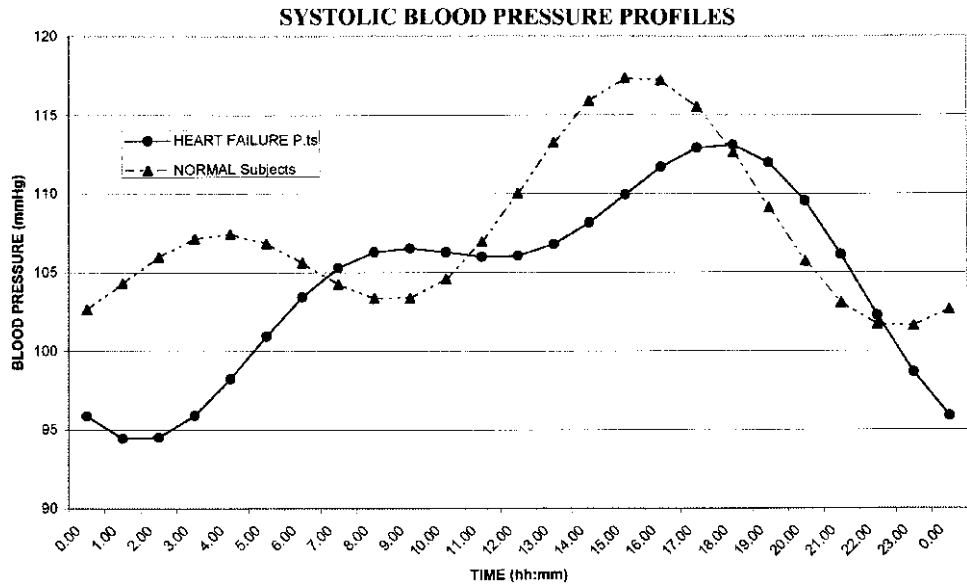
Fig. 1. Systolic blood pressure profiles.

subjects. Nevertheless, when considering the systolic BP profile of the HF group (Fig. 1), a shift of the nocturnal minimum of the curve can be easily appreciated with respect to controls (minimum of the curve: 23 h).

The pulse rate analysis also showed a preserved circadian rhythm and non-significant differences with respect to normal controls, in terms of Acro and Ampl parameters.
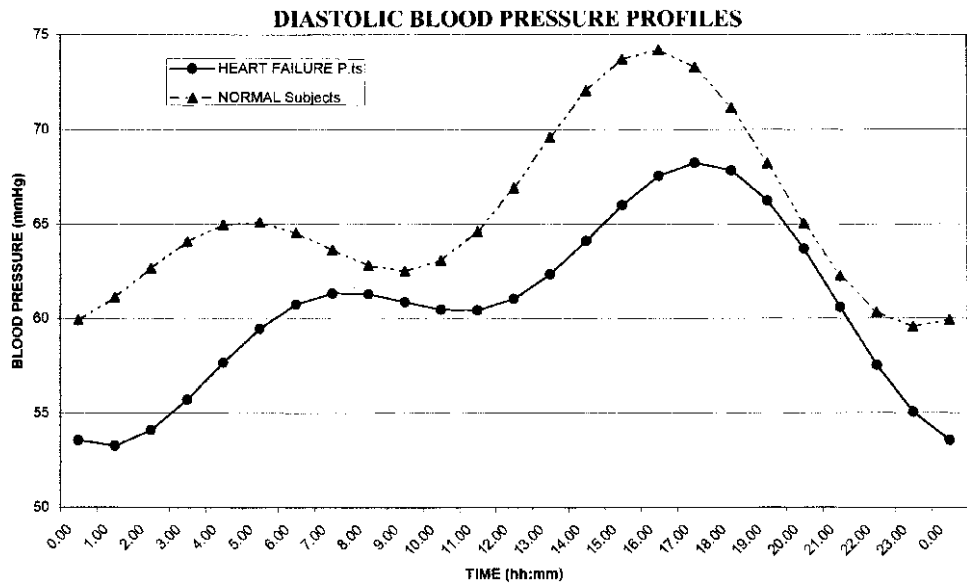

Fig. 2. Diastolic blood pressure profiles.

Table III. *24-h, diurnal and nocturnal mean values*

	Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)			Heart rate (bpm)		
	24-h	Diurnal	Nocturnal	24-h	Diurnal	Nocturnal	24-h	Diurnal	Nocturnal
Control subjects	109.3 ± 5.3	111.5 ± 5.8	102.0 ± 3.5	71.7 ± 2.4	77.1 ± 2.8	62.6 ± 1.8	71.1 ± 7.7	76.2 ± 8.5	64.2 ± 7.9
Heart failure patients	106.6 ± 6.3	109.2 ± 6.9	99.4 ± 4.8	68.9 ± 2.4	77.08 ± 3.8	66.3 ± 1.8	73.9 ± 12.7	81.2 ± 12.3	66.9 ± 14.3
Significance probability	$p < 0.05$	n.s.	n.s.	$p < 0.05$	n.s.	n.s.	n.s.	n.s.	n.s.

When considering the 24-h, diurnal and nocturnal means (Table III), although lower BP means and higher pulse rate means were found in the HF group, significant differences were only found in the 24-h systolic and diastolic means.

DISCUSSION

In contrast with previous reports [1–4], our results show that both BP circadian rhythm and BP profile parameters are preserved in patients with HF. In fact, such patients present a condition of neuroendocrine activation that could influence the normal BP circadian rhythm [1, 5]. According to some reports [4], patients with HF can be divided into two groups: those with and without BP circadian rhythm. Notwithstanding, our results show a significant BP rhythm in almost all patients. Furthermore, the phase of the rhythm was not shifted in our patients with HF (Acro comparison).

Patient selection (different HF functional class), fluid overload, pharmacological treatment (various pharmacological agents and dose), concomitant diseases (i.e. renal failure) and especially different methods for BP profile analysis may be major reasons for different results in the literature.

Methods for analysis other than Siegel's runs test could verify the existence of a BP circadian rhythm, but some methods are invalidated in the case of non-standard BP profiles (daytime peak and decrease during night-time). Furthermore, these methods do not allow effective study of BP profiles with variable recording intervals (different intervals between diurnal and nocturnal hours) or with a cycle shorter than 24h [6]. Conversely, Siegel's runs test is not affected by these occurrences, nor by the absolute BP values observed, thus partially justifying our results in contrast with previous reports [6].

Finally, when considering BP variability, as expressed by the amplitude of the BP profile, no significant differences were found between our patients and the control group.

In conclusion, our study sample presented a preserved endogenous BP circadian rhythm (and pulse rate), in spite of conditions of severe HF.

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