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Changes in the arrhythmic profile of patients treated for heart failure are associated with modifications in their myocardial perfusion conditions

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Abstract

Background: *Heart failure (HF) patients can benefit from a proper RS. We had observed that they show an increase in the number of arrhythmias during the first year of pharmacological treatment.*

Methods: *We carried out a prospective observational study in which patients in an HF Clinic were included when they had follow-up Holter monitoring. Patients also had a baseline myocardial perfusion scan (Tc99 sestaMIBI/dypiridamole) and a control scan.*

Results: *We included 90 patients with follow-up Holter and 35 with scintigraphy, for analysis. Fifty-six (62.2%) were men and the average age was 60.8 ± 14.6 years. Follow-up periods were divided by six-month intervals up to 18 months or more, an increase in premature ventricular contractions (PVCs) occurred in the six-month to one-year period (1915.4 ± ± 4686.9* vs. *2959 ± 6248.1, p = 0.09). In the one-year to 18-month control, PVCs went from 781.6 ± 1082.4 to 146.9 ± 184.1, p = 0.05. The increase in PVCs correlated with a reduction in scintigraphy-detected ischemic territories, 5.64 ± 5.9* vs. *3.18 ± 3 (p = 0.1) and a gain in those showing a reverse redistribution pattern (0.18 ± 0.6* vs. *2.09 ± 4.01, p = 0.1). Necrotic territories and time domain heart rate variability did not show significant changes.*

Conclusions: *PVCs increase during the first year of HF treatment, and then they tend to diminish and stabilize. These changes seem to correlate with changes in the perfusion state of the patient. While ischemic territories decrease, reverse redistribution increases, showing that endothelial dysfunction could have a relevant role in arrhythmia generation, possibly because of membrane instability of recovered hibernating myocardium.* (Cardiol J 2008; 15: 261–267)

Key words: heart failure, arrhythmias, Holter, scintigraphy, risk stratification

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Introduction

Ischemic heart disease and its complications are the main cause of heart failure (HF) in western societies. Ventricular arrhythmias are frequent in these patients. It is also well known that patients in better functional classes (classes I and II of the New York Heart Association, NYHA) tend to die suddenly, while people in worse NYHA classes (III–IV) tend to do so because of pump failure [1–3]. Such differentiated behaviour implies different risk profiles according to the stage of HF that the patient is in. This concept is similar to the one of time-dependence risk described for ventricular arrhythmias in patients with ischemic heart disease [4]. Another observation is that lower functional classes tend to be associated with better left ventricle ejection fractions (LVEF) but this is not a golden rule. These differentiated behaviours could be partially explained by the arousal of several neurohumoral compensatory mechanisms (renin-angiotensin-aldosterone system activation, liberation of cytokines and inflammatory mediators, among others) that are finally associated with an increase in plasmatic catecholamines. It is also known that modifications in the neurohumoral profile induce changes in the activity of the autonomic nervous system that can in turn be evaluated by several non-invasive tools. The bottom line is that more sympathetic activity is related to higher lethal ventricular arrhythmia risk, especially in the context of a damaged myocardium that cannot sustain cardiac output in the presence of high ventricular rates with short diastolic intervals [1, 5–8].

Several tools have been described to evaluate the sympathetic-parasympathetic equilibrium in patients with HF. Signal-averaged ECG, QT dispersion, heart rate variability and T wave alternans among others have been used, but possibly the most simple to clinically acquire and interpret is heart rate variability in the time-domain. This parameter is reduced among patients with increased sympathetic activity, such as those with HF. All those measurements, along with LVEF, NYHA functional class and the arrhythmic profile, allow the establishment of a risk profile in HF patients and the definition of low or high risk for sudden cardiac death [4]. Nevertheless, it is not well defined how medical treatment modifies the risk profile. It is assumed that pharmacological measures directed towards a better neurohumoral condition in these patients should have a positive influence on their arrhythmic profile [9–14]. Traditionally, the number and characteristics of the ventricular arrhythmias has been associated with increased arrhythmic risk; nevertheless, risk stratification continues to be controversial [15–18].

In a preliminary work, we reported that patients receiving pharmacological treatment for HF showed an increase in the number of ventricular arrhythmias in a medium-term follow-up (one year) [19]. A possible explanation for such apparently paradoxical behaviour could be the recovery of hibernating or ischemic myocardium.

Methods

We carried out a prospective observational study in 90 consecutive patients with HF that had baseline Holter monitoring and at least another control study in a two-year lapse. All of them were stable patients (NYHA I–III) that assisted to the outpatient Heart Failure Clinic (HFC) of the institute. The group included 56 men (62.2%) and 34 women. The mean age of the study population was 60.8 ± 14.6 (range 20 to 83) years at baseline and 62.7 ± 14.8 (range 22–83) years at follow-up. All of them were started on a standardized pharmacological treatment (diuretics, angiotensin converting enzyme inhibitors — ACEI, angiotensin receptor blockers — ARB, aldosterone blockers, digitalis and beta-adrenoceptor blockers) aimed at heart failure. Chronic stable ischemic heart disease was found in 53 (58.9%) of them. None had unstable angina or acute coronary events in the three months prior to inclusion. Fifty-one ischemic patients (56.7%) had had a revascularization procedure (angioplasty or thrombolysis) related to an acute myocardial infarction at least three months prior to inclusion in the HFC.

Routine Holter controls are made at different intervals to evaluate clinical changes in the arrhythmic profile. Such intervals are dictated by the time it takes for the patient to reach an individualized maximal dosage of all the medications used (optimal pharmacological treatment), but it also depends on stabilization of their clinical condition and on their adherence to follow-up visits. Every patient that showed a high ventricular arrhythmia risk at baseline (complex arrhythmias), as well as those who required specific antiarrhythmic treatment, were not included in the study.

From the Holter monitoring we recorded maximal (HRmax), minimal (HRmin) and average heart rate (HRa), as well as a heart rate dispersion value (HRdisp) obtained from the difference between maximal and minimal heart rates. We also registered heart rate variability parameters in time domains, such as the standard deviation of each

normal to normal beat (SDNN), average of the standard deviation of each normal to normal beat in five-minute intervals (ASDNN5) and the standard deviation of the average of each normal to normal beat interval in five minutes (SDANN5). We also registered the number of supraventricular premature beats (SVPC) and ventricular premature complexes in the 24-hour Holter recording, considering the total number of SVPCs and premature ventricular contractions (PVCs) in 24 hours and the hourly average.

We compared the baseline measurements with those of the follow-up, and the intervals were divided in controls: less than 6 months from baseline, 6 months to one year, one year to 18 months and more than 18 months. Every patient was his/her own control.

On the other hand, myocardial perfusion scans with Tc-99m (sestaMIBI) with rest/stress (dypiridamole) protocol using conventional technique were performed at baseline and during follow-up in 35 subjects.

The study was approved by the local bioethical committe and all patients gave their informed consent.

Statistical analysis

Continuous variables are expressed as mean ± ± standard deviation and the categorical variables as percentages. To compare between measurements in the same subject we used Student's T test for related samples. To compare means we used independent samples for Student's T test and variance analysis (ANOVA). A p value < 0.05 was considered significant. We used the SPSS Inc. 10.0 statistical package to calculate statistics.

Results

Among the included patients, 57 (65.5%) were in NYHA functional class I, 17 (19.5%) in functional class II and 11 (12.6%) in class III. The mean LVEF was 39.1 ± 15.2%. Forty-seven (54%) patients had systolic dysfunction, 17 (19.5%) had diastolic dysfunction and 18 (20.7%) had mixed dysfunction. Only three cases (3.4%) had right heart failure. The remaining patient characteristics are shown in Table 1, along with the drugs they received during HFC follow-up.

The mean interval between baseline and first follow-up Holter was 20.7 ± 17.3 months, and the interval between the baseline and a second follow-up study was 44.3 ± 22.8 months. Table 2 summarizes the main values for heart rate and heart rate variability, specifically SDNN since ASDNN5 and SDANN5 did not show significant differences and were eliminated from further analysis.

The mean PVCs number in the baseline Holter was 1197.8 ± 3026.8 (range 0 to 21078) and 1241.09 ± 3640.15 (range 0 to 27971, p = NS) in the first follow-up Holter. The mean minute count was 0.8 ± 2.1 PVCs at baseline and 0.86 ± 2.5 at follow-up (p = NS). Supraventricular premature beats were 278.7 ± 680.9 daily at baseline and

Table 1. Patient's characteristics.

Baseline characteristics	
Age (mean ± SD)	60.8 ± 14.6
Male patients	56 (62.2%)
Previous MI	51 (56.7%)
Diabetes	42 (46.7%)
Hypertension	59 (65.5%)
Dyslipidemia	70 (77.8%)
Left ventricular ejection fraction	39.1 ± 15.2%
Medications used during HFC follow-up	
Beta-blockers	83 (92.2%)
ACE inhibitors/ARB's	89 (98.9%)
Thyazide diuretics	58 (64.4%)
Loop diuretics	15 (16.7%)
Digitalis	65 (72.2%)
Oral nitrates	38 (42.2%)
Amiodarone	6 (6.7%)
Anticoagulation	5 (5.6%)

MI — myocardial infarction; HFC — Heart Failure Clinic; ACE — angiotensin converting enzyme; ARB — angiotensin receptor blockers

Table 2. Heart rate and time-domain variability values.

Parameter	Mean ± SD	p	Range (min.–max.)
HRmax 1	109.1 ± 20.8		74–176
HRmax 2	104.9 ± 20.9	0.2	55–167
HRmin 1	49.9 ± 10.5		31–77
HRmin 2	49.8 ± 12.5	0.9	30–108
HRmean 1	70.3 ± 10.2		49–97
HRmean 2	68.6 ± 12.04	0.1	37–98
HRdisp 1	59.2 ± 23.02		22–134
HRdisp 2	57.2 ± 24.7	0.2	20–161
SDNN 1	160.2 ± 83.2		37.1–369.3
SDNN 2	154.2 ± 118.5	0.5	37.1–796.8
LP 1	1.4 ± 0.3		1.1–2
LP 2	1.7 ± 0.5	0.5	0.9–3.1

HR — heart rate; SDNN — standard deviation of each normal to normal beat; LP — longest pause

Table 3. Changes in the evaluated parameters by follow-up time segment (baseline, first control)

Parameter	Less than 6 months (n = 17)	P	Between 6 months and 1 year (n = 24)	P	Between a 1 year and 18 months (n = 10)	P	More than 18 months (n = 39)	P
HRmax 1	100.3 ± 17.4		106.1 ± 17.1		114.5 ± 19.2		113.4 ± 23.7	
HRmax 2	100.2 ± 17.7	0.9	104.9 ± 20.4	0.8	115.4 ± 26.9	0.8	106.8 ± 26.2	0.1
HRmin 1	51.3 ± 8.3		53.2 ± 11.4		47.7 ± 12.5		47.8 ± 10.02	
HRmin 2	52.5 ± 8.7	0.6	52.8 ± 13.5	0.8	46.7 ± 10.7	0.7	47.7 ± 13.4	0.9
HRmean 1	69.4 ± 10.6		70.9 ± 10.3		72.7 ± 12.2		78.5 ± 24.2	
HRmean 2	68.8 ± 11.2	0.8	70.04 ± 13.7	0.7	70.8 ± 10.4	0.6	66.4 ± 14.6	0.2
SDNN 1	154.4 ± 83.7		146.4 ± 88.73		213.2 ± 100.65		157.6 ± 72.37	
SDNN 2	154.5 ± 122.5	0.9	173.3 ± 171.9	0.3	146.7 ± 99.8	0.06	144.3 ± 77.4	0.2
RR 1	1.4 ± 0.3		1.5 ± 0.3		1.5 ± 0.3		1.5 ± 0.3	
RR 2	1.8 ± 0.5	0.07	1.3 ± 0.3	0.4	1.8 ± 0.4	0.8	1.7 ± 0.4	0.1
PVCs 1	1053.5 ± 2020.1		1915.4 ± 4686.9		781.6 ± 1082.4		950.1 ± 2416.6	
PVCs 2	746.7 ± 1924.3	0.6	2956.3 ± 6248.1	0.09	146.9 ± 184.1	0.05	666.9 ± 1719.2	0.2

HR — heart rate; SDNN — standard deviation of each normal to normal beat; PVCs — premature ventricular contractions; RR — the longests RR interval detected by 24 hr Holter measurement [s]

310.6 ± 686 at follow-up (p = NS). Table 3 shows the behaviour of premature beats separated by month intervals between baseline and first follow--up studies, as well as heart rate parameters and heart rate variability. Six patients (6.7%) showed ventricular triplets in the first follow-up control (3.2 ± ± 1.2 episodes) that prompted antiarrhythmic treatment. A third control study for them showed PVCs but no complex arrhythmias.

Seventeen patients had a second control. In 4 of them it was performed before 18 months and in the remaining 13 it was done after that period. Among these patients, the number of PVCs in 24 hours went from 4238 ± 4232.9 at baseline to 689 ± 1182.6 in the first control at 8 months (p = = 0.1) and to 1444.5 ± 2330.4 (p = 0.2) in a second control at 14 months. Heart rate variability did not show any significant changes. In the remaining 13 patients, the second control was performed a mean of 51.4 ± 18.2 months after the baseline study. The number of PVCs went from 2298.5 ± 5801.1 at baseline to 2799.3 ± 7672.1 in the first (p = 0.5) and diminished to 2590.5 ± 7273.8 in the second control (p=0.4). Heart rate variability (SDNN) went from 194.7 ± 86.5 ms to 137.4 ± 73.8 ms (p = 0.04) in the first control and to 116.1 ± 38.03 ms in the second control (p = 0.3 between controls and p = 0.01 between baseline and second control). Nonetheless, all of these values are within normal range.

In thirty-five patients we performed a control myocardial perfusion scintigraphy 2.4 ± 1.5 years after the baseline one. The mean number of affected territories went from 8.8 ± 5.09 to 8.6 ± 5.3 (p = NS). When the type of lesion was differentiated, it was found that the territories showing a reverse redistribution pattern went from 0.46 ± 2.2 to 1.49 ± 2.91 (p = 0.03), while the number of ischemic territories went from 4.97 ± 4.67 to 3.6 ± 4.1 (p = 0.06). The number of necrotic territories did not show significant changes: 3.5 ± 3.79 *vs*. 3.5 ±4.2 (p = NS). Table 4 shows a comparison of the perfusory changes and the number of PVCs, taking into account the different periods between studies.

Discussion

These findings show a tendency towards an increase in the number of PVCs during the first year of treatment in the HFC that later on tend to diminish and stabilize. Possibly this risk profile modification is influenced by the therapeutic intervention and even with the progression of the disease. Nowadays, HF treatment pretends to modify the neurohumoral profile of these patients through chan-

Table 4. Number of scintigraphy-detected affected territories and premature ventricular contractions (PVCs) according to time intervals between baseline Holter and controls.

	Baseline Holter *vs.* control less than 6 months	Baseline Holter *vs.* control 6 months 1 year	Baseline Holter *vs.* 1 year to 18 months	Baseline Holter *vs.* control more than 18 months
Sum of territories with reverse redistribution, baseline	0 ± 0	0.18 ± 0.6	0.5 ± 1.22	1.1 ± 1.8
Sum of territories with reverse redistribution, control	1.25 ± 2.38 (p = 0.1)	2.09 ± 4.01 (p = 0.1)	1.17 ± 1.8 (p = 0.3)	1.2 ± 2.7 (p = 0.9)
Sum of ischemic territories, baseline	3.25 ± 2.55	5.64 ± 5.94	7.17 ± 4.75	4.3 ± 4.3
Sum of ischemic territories, control	1.25 ± 1.8 (p = 0.04)	3.18 ± 3.09 (p = 0.1)	3.8 ± 6.27 (p = 0.05)	5.8 ± 6.2 (p = 0.2)
Sum of necrotic territories, baseline	5.1 ± 3.6	2.55 ± 3.45	4.5 ± 5.1	2.8 ± 3.5
Sum of necrotic territories, control	4.75 ± 3.41 (p = 0.7)	3.91 ± 4.99 (p = 0.4)	1.17 ± 1.6 (p = 0.08)	3.6 ± 5.1 (p = 0.5)
Sum of affected territories, baseline	8.4 ± 3.34	8.36 ± 6.12	12.2 ± 4.7	8.2 ± 4.8
Sum of affected territories, control	7.25 ± 3.73 (p = 0.7)	9.18 ± 4.6 (p = 0.06)	6.2 ± 6.1 (p = 0.02)	10.6 ± 6.35 (p = 0.2)
Number of PVCs, baseline	1053 ± 2020.2	1915.4 ± 4686.9	781.6 ± 1082.4	950.1 ± 2416.6
Number of PVCs, control	746.7 ± 1924.3 (p = 0.6)	2956.3 ± 4248.1 (p = 0.09)	146.9 ± 184.1 (p = 0.05)	666.9 ± 1719.2 (p = 0.2)

ges in intracavitary pressures (pre-load), a reduction in the after-load (vasodilators, ACEI, ARB), a reduction in the effects of aldosterone (spironolactone), a reduction in fibrosis and atrial and ventricular remodelling (ACEI, ARB, spironolactone) and an optimization of myocardial perfusion in ischemic patients, reducing myocardial oxygen consumption (beta-adrenoceptor blockers, nitrates) [1]. Without regard to the etiology, virtually every subject with HF shows perfusion abnormalities suggestive of ischemia or other forms of endothelial dysfunction less well defined, such as reverse redistribution, that can in turn be early expressions of that problem, possibly related to increases in the wall-stress or higher myocardial oxygen consumption.

Pharmacological treatment of heart failure enhances myocardial perfusion, especially among those with an ischemic origin, through a reduction in the number of areas with hibernating or contused myocardium and the periods of contusion related to reperfusion damage. The present results confirm the previous findings of our group in which reverse redistribution was associated with a reduction in NYHA functional class and LVEF, giving clinical relevance to the perfusion abnormalities [20]. On the other hand, it suggests that the reduction in the ischemic territories takes place in accordance with an increase in those territories that show reverse redistribution, without changes in necrotic areas. Such changes could be involved in the genesis of electric instability and could also explain the temporary pattern of arrhythmia presence that could be related to a beneficial effect on functional myocyte recovery derived from early treatment.

Our findings are in apparent contradiction with those of the SAVE trial [21]; for example, were they found a consistent increase related to time progression of HF and apparently induced by left ventricular remodelling and without any favourable change induced by ACE inhibition or beta-blocking agents. The sample size did not allow the detection of any beneficial effect. Our sample is smaller but the patients received a combination of medications in an intensive treatment. In the long-term follow-up, arrhythmias stabilized but did not show a continuously decreasing pattern that could be in relative accordance with the above-mentioned results.

The initial reduction could be explained by treatment-induced acute changes in the neurohumoral variables, as well as by some antiarrhythmic effect from beta blockers and possibly ARB (since irbesartan is associated with a reduction in the

incidence of atrial fibrillation). Later on, hibernating myocardium recovery with somehow unstable membranes or local electrolytic changes and increased differences in refractory periods and local automatism could explain the later presence of more arrhythmias [22, 23]. In another previous work, it was also found that there was a relation between the increase of ventricular arrhythmias and a reduction in the number of ischemia-affected territories [19]. The present work suggests that reverse redistribution that could be related with endothelial dysfunction happens in a somehow "critical" period from an "arrhythmic standpoint" and so could support the thesis that arrhythmia risk increases with hibernating myocardium recovery to stabilize after that. The mild increase in the number of necrotic territories, although non-significant, could explain the reduced abnormal automatism, but also an increase in re-entry arrhythmias since those areas establish fixed slow-conduction / normal conduction zones [21].

Such findings are relevant in countries such as ours, since the use of implantable cardioverter--defibrillators (ICD) is limited because of socio-economic factors. The ICD has a clear positive influence on survival, but it apparently does not avoid progression towards pump-failure [24–29]. It has also been described somewhere else that ICD are especially useful during the first year after an ischemic event; the permanence of the device could be re-evaluated once this "critical period" has finished. On the other hand, pharmacological measures to control arrhythmias should be reinforced during that period, although the CAST results must be kept in mind when choosing antiarrhythmics [30, 31]. It is also important to emphasize that high-risk subjects (non-sustained ventricular tachycardias with low LVEF, people who have recovered from sudden death or subjects with other MADIT II criteria) must receive an ICD since survival benefits are widely demonstrated, but findings such as these could help re-define high-risk criteria on a dynamic temporary basis.

One limitation of the study is the HFC population itself, which consists mainly of people from low socio-economic strata who do not live in this city. Because of this, control appointments are irregular. The sample size is another limitation, but complete cases show useful information. The different timing between Holter and scintigraphy itself can be a confusing factor, even if the apparent relation between the arrhythmic profile and scintigraphic changes seems consistent.

Conclusions

In conclusion, the arrhythmic profile of patients with HF seems to have a dynamic, temporary profile that is associated with favourable changes in the myocardial perfusion pattern, even in the presence of an apparent stability of the main heart condition.

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