

Camafort, M., Jhund, P. S. , Formiga, F., Castro- Salomó, A., Arévalo-Lorido, J. C., Sobrino-Martínez, J., Manzano, L., Diez-Manglano, J., Aramburu, O. and Pérez-Barquero, M. M. (2021) Utilidad pronóstica de las cifras ambulatorias de presión arterial en pacientes de edad avanzada con insuficiencia cardíaca. Resultados del estudio DICUMAP = Prognostic value of ambulatory blood pressure values in elderly patients with heart failure. Results of the DICUMAP study. *Revista Clínica Española*, 221(8), pp. 433-440. (doi: [10.1016/j.rce.2020.11.010](https://doi.org/10.1016/j.rce.2020.11.010))

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Deposited on 11 November 2020

PROGNOSTIC VALUE OF AMBULATORY BLOOD PRESSURE VALUES IN ELDERLY PATIENTS WITH HEART FAILURE. RESULTS OF THE DICUMAP STUDY

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Introduction:

Ambulatory blood pressure monitoring (ABPM) has demonstrated value in the prognostic assessment of hypertensive patients with or without cardiovascular disease different from heart failure (HF). The objective of this study was to evaluate whether ABPM can identify subjects with HF with a worse prognosis.

Methods and Results:

We carried out a prospective multicentre study that included clinically stable outpatients with HF. All patients underwent ABPM. A total of 154 patients from 17 centres were included, with a mean age of 76.8 years (± 8.3) and 55.2% were female: 23.7% had HF with a reduced ejection fraction (HFrEF), 68.2% were in NYHA functional class II, and 19.5% in NYHA functional class III. At one year of follow up, there were 13 (8.4%) deaths, of which 10 were attributed to HF. Twenty-nine patients required hospitalization, which was due to HF in 19. The presence of a non-dipper BP pattern was associated with an increased risk for readmission or death at one year of follow-up (25% vs 5%; $p = 0.024$). By Cox regression analysis, more advanced NYHA functional class and a higher proportional nocturnal reduction in diastolic BP were independently associated with death or readmission at one year; hazard ratios 3.51 (95%CI 1.70-7.26; $p 0.001$) for class III NYHA vs II, and 0.961 95%CI 0.926- 0.997; $p 0.032$ per 1% reduction of diastolic BP reduction, respectively.

Conclusion:

In older patients with chronic HF, a non-dipper BP pattern measured by ABPM was associated with a higher risk of hospitalizations and death due to HF.

Introduction:

Heart failure (HF) is one of the main health problems in our setting (1-2) and one of the main reasons for hospital admission in the developed world (3).

The role of hypertension in the development and prognosis of HF is well known (4). Epidemiological studies show that 75% of patients with HF have a history of hypertension and, in subjects with blood pressure (BP) > 160/90 mmHg, the probability of HF is double that of those with BP < 140/90 mmHg (1). Hypertension modulates the natural history of HF and is a relevant prognostic factor (5,6). There are known to be compensatory neuro-hormonal changes in HF that alter BP levels and patterns and heart rate patterns (7). These changes can cause poor hypertension control, which can precipitate the decompensation of HF (8). Lower clinical BP levels have been associated with a worse prognosis of HF (9,10), although most available data are based on office BP levels. However, home BP measurement using ambulatory blood pressure monitoring (ABPM) or self-measured BP (SMBP) improves the accuracy and reproducibility of these measures (11), meaning that ABPM may better assess the cardiovascular prognosis than office BP measurement in hypertensive patients without cardiovascular disease (12).

Despite this, currently there are few studies of the prognostic value of ABPM in HF, with a limited number of patients, and often with a partial focus on this problem. Therefore, the available studies provide partial and incomplete answers (13-15).

The objective of this study was to evaluate whether BP values measured by ABPM can identify individuals with stable HF who will have a worse clinical evolution.

Methods:

Consecutive patients with HF and a previous admission were included in the Heart Failure: Usefulness of ABPM (DICUMAP) registry. This is a registry promoted by the Heart Failure Working Group of the Spanish Society of Internal Medicine. The inclusion criteria were: subjects > 40 years of age with HF and a previous admission, clinically stable (≥ 15 days after hospital discharge with no clinical deterioration, reappearance of symptoms or worsening of existing symptoms) capable of attending outpatient clinics. Exclusion criteria were significant valve disease as a primary cause of HF, contraindication to ABPM (arm circumference > 42 centimetres, working at night, atrial fibrillation with rapid ventricular response, frequent ventricular extrasystoles and other tachyarrhythmia).

Data collected from all patients included demographic, clinical, exploratory, and analytical variables, chest x-ray, electrocardiogram (ECG), ABPM, and echocardiogram (an echocardiogram performed up to 6 months previously, in the case of known HF, or up to 3 months after inclusion was considered valid), and treatment variables. A baseline visit was made with follow-up visits at 90 days and one year, and data was collected on deaths, hospitalizations and their causes.

The mean of two BP measurements was used to measure office BP, with the patient sitting after 5 minutes of rest. The two measurements were made with an interval of 2 minutes. If there was a large difference between the two measurements, a third measurement was made and the discordant measurement was discarded, according to the recommendations of the European Society of Hypertension (16).

ABPM was carried out on a day representative of the subject's life. Patients were instructed to avoid hard physical exercise and unusual stress and take their

usual medication at the usual time. Oscillometric monitoring devices (SPACELABS 90207 or 90217) were used, placing the sleeve on the non-dominant arm. ABPM lasted for a minimum of 24 hours, with a frequency between readings of 20 minutes. ABPM containing $\geq 70\%$ of valid readings and no more than one hour of inactivity were considered valid. Periods of activity (diurnal) and rest (nighttime) were defined a posteriori, as reflected by the patient's diary. A reduction of 10-20% in mean systolic BP (SBP) and/or diastolic BP (DBP) was defined as a normal reduction in nighttime BP compared with daytime BP (dipper pattern). A non-dipper pattern was defined as a $<10\%$ decrease in nighttime BP with respect to the mean daytime SBP and/or DBP. A riser pattern was defined as any increase in nighttime BP with respect to the mean SBP and/or DBP value (17).

The study was approved by the Ethics and Clinical Research Committee of the Sant Joan University Hospital of Reus, and written informed consent was obtained from all patients before inclusion in the registry.

Statistical analysis

Quantitative variables were expressed as mean \pm standard deviation (SD) and qualitative variables as frequencies and percentages. Comparisons were made using the Student's t test for quantitative variables and the Chi-square test or, when dichotomous variables did not allow its use, Fisher's exact test for qualitative ones.

Descriptive statistics were used to analyse the data, including: mean, median, mode, standard deviation, range, confidence intervals, minimum and maximum.

Kaplan Meier survival curves were constructed for ABPM values according to the circadian pattern (grouped as dipper and non-dipper) by SBP and DBP quartile for office BP, 24h-ABPM values, and BP during activity and rest, to assess

differences in terms of the main objective and their statistical significance, using the log rank test. A p value of <0.05 was considered significant.

To assess whether ABPM values which presented a survival curve with greater morbidity and mortality had prognostic significance, a bivariate analysis of individual categorical variables was made using a Chi-square test, and calculating the strength of the relationship of each variable with the main objective using the odds ratio and 95% confidence intervals (CI). Variables with a p value of < 0.05 were selected. An analysis of the relationship of continuous variables with the main objective was made using ANOVA, comparing the means and 95% CI. Variables with a p value < 0.05 were selected.

The selected variables were entered into a Cox proportional hazards regression model to identify variables with prognostic significance for the time to readmission or death. The analysis was made using SPSS 17.0 for Windows. All comparisons were bilateral and statistical significance was established as $p < 0.05$.

Results:

A total of 154 patients from 17 centres were included. Baseline patient data are shown in table 1. The mean age was 76.8 years (± 8.3), 55.2% were female, 58.8% were autonomous and 80.4% had no cognitive impairment.

Previous Hypertension was recorded in 148 patients (94%), dyslipidaemia in 81 (52.6%) type 2 diabetes mellitus in 65 (42.2%), previous ischemic heart disease in 16.2%, and a history of atrial fibrillation in 51.3%, while 44.2% did present chronic kidney disease. A total of 76.3% of patients had HF with preserved ejection fraction

(HFpEF). The New York Heart Association (NYHA) functional classification was: 68.2% class II, 19.5% class III, and the remaining patients class I.

The BP and heart rate values obtained during ABPM are shown in table 2. With respect to circadian patterns of BP, 74.0% had a nighttime non-dipper BP pattern (34.2% had a rising pattern and 39.6% a non-dipper pattern), while the remaining patients had a dipper pattern (4.5% had an extreme-dipper pattern).

At one year of follow up, there were 13 deaths, of which 10 were attributed to HF: 29 patients were re-admitted, which was due to HF in 19. With respect to the main objective, the first admission due to HF or death during the follow up accounted for 26 events, representing 16.9% of patients.

In the survival analysis, from all the analyzed hemodynamic markers of ABPM (night-time dipper pattern, concordance between office BP and ambulatory BP control, and nocturnal hypertension), only the night-time dipper pattern showed significant differences. For this analysis, only the dipper pattern and the non-dipper pattern were included: given the small number of patients with extreme-dipper and riser patterns, these were assimilated to the dipper pattern and non-dipper pattern, respectively. In patients with a dipper pattern (n 40, 26.0%), only 2 patients (5%) presented an event, whereas in patients with a non-dipper pattern (n 114, 74.0%) 24 (21%) presented events during the follow-up. (Figure 1)

From all parameters, we selected those parameters that were relevant and could be included in a logistic regression model. Presence of peripheral arterial disease, being in NYHA functional class III, presenting a non-reducing pattern of the PA, and some degree of cognitive impairment were significant to be selected for the logistic regression model. Likewise, with respect to non-categorical variables,

glucose, haemoglobin and creatinine levels, estimated renal glomerular filtration rate, left atrial diameter and the percentage of nocturnal decrease in DBP reached statistical significance. Of these variables we selected, to be entered into a logistic regression model, those variables with significance in terms of death or readmission, once adjusted (table 3). Only NYHA functional class III was a predictor of death and readmission, with a hazard ratio of 3.5 (95% CI 1.7-7.3, p 0.001). The reduction in the percentage of nighttime DBP compared with daytime was weakly protective against death and readmission with a hazard ratio of 0.961 (95% CI 0.926-0.997, p 0.032)

Discussion:

The main finding of this study is that patients with any non-physiological circadian pattern (non-dipper, extreme dipper and riser) were associated with a worse prognosis compared to patients with a physiological BP-lowering pattern. In this same sense, a greater nocturnal reduction in DBP was associated with fewer hospitalizations and death. Our findings suggest that this pattern was not clearly shown to be a risk factor for a poor prognosis, but was a risk marker. In addition, a greater decrease in nighttime DBP compared with daytime DBP, which could contribute to a dipper pattern, was associated with a slight decrease in hospitalizations and death from HF. This issue has only been partially studied previously.

Patients included had similar characteristics to those normally admitted for HF (18-19) and particularly those admitted to Spanish internal medicine services (20-26). These patients, unlike those usually included in clinical trials in HF, are

older, with a percentage of women similar to men, and with a higher prevalence of hypertension as a cause of HF, and a greater number of comorbidities.

Seventy-four per cent of our patients had hypertensive heart disease, with a lower percentage of patients with ischemic heart disease and a high percentage of atrial fibrillation. The low percentage of patients with ischemic heart disease may be explained by a possible selection bias towards patients with hypertension.

As in other studies, patients admitted for HF had significant comorbidity, with the percentages of type-2 diabetes, dyslipidemia, peripheral arterial disease, cerebral vascular disease and chronic kidney disease being similar to the patients included in the RICA registry (27) and the UMIPIC study (28).

We found a combined rate of readmission and death of 16.8%, which is higher than that observed in some clinical trials such as the I-Preserve study (18), but lower than in the TOPCAT trial in the sub-study of the Americas (29), and the Paragon HF trial (30) were patients characteristics were clearly different of those included in this registry, but our results are similar to those found in other studies with similar characteristics to our patients (18-24),.

The importance of certain BP patterns measured by ABPM, with a lower nighttime decrease in BP figures, and even with high nighttime BP figures (known as nocturnal hypertension) is that all these situations have been associated with increased cardiovascular morbidity and mortality (25,26). However, this relationship has been described in hypertensive subjects, sometimes with pre-diabetes (27) or dyslipidemia (28), but there is little data on the prevalence of abnormal circadian patterns and their relationship with morbidity and mortality in patients with HF.

Our results show that 74% of patients had a non-dipper BP pattern, similar to the 78% found by Mallion et al (29).

Studies describe the non-dipper BP pattern and nighttime hypertension as a marker and, possibly, a prognostic predictor of CVD. However, careful analysis of these studies shows that this situation occurs in registers and series where CVD is systematically excluded, or does not affect > 15% of patients (34-38).

The importance of our study lies in the fact that there is little data on the prognostic role of the parameters obtained by ABPM in patients with established CVD, and even fewer data on patients with HF, and there are practically no studies in elderly patients with HF and comorbidities.

Only two studies have assessed the influence of ABPM data in the prognosis of HF. Our study included the largest number of real world patients. Our data indicate that a non-dipper nighttime pattern is a marker of poor prognosis in patients with HF.

Of the available data, the study by Canesin et al (39) shows a higher mortality rate in patients with SBP <105mmHg measured by ABPM than those with SBP \geq 105mmHg. However, this study was carried out in only 38 patients with NYHA functional class 4, limiting the utility of the results.

Shin et al (40) analysed ABPM values in 118 male patients with HFrEF and found that the non-dipper pattern was associated with an increased risk of death and readmissions due to HF after a 4-year follow-up. The dipper pattern was a risk factor, as was the heart rate, probably because the follow up was longer than in our study. However, in our study, the patient profile was more similar to that usually seen in real world situations, and therefore the results of the Shin study may be more applicable to younger patients with HFrEF.

Finally, Komori et al (41), analyzed a prospective, observational cohort study of five hundred and sixteen hospitalized HF patients who underwent ABPM. Finding that the riser BP pattern subgroup had a significantly higher incidence of the composite outcome (all-cause mortality and cardiovascular events such as coronary events, HF rehospitalization, and stroke) than the other subgroups of HFpEF patients (HR, 3.01; 95% CI: 1.54–6.08, $P < 0.01$), but not the HFrEF patients. The results are similar to those of our study but in this cohort, ABPM was realized at hospitalization, where changes in treatment are usually realized. In our study ABPM is performed when patients are on stable treatment. On the other hand Komori's study included Japanese population.

The strengths of the study are that it was a multi-centre study carried out in 17 Spanish centres covering the whole country and patients had a highly-prevalent disease such as HF and characteristics similar to those usually admitted to our centres.

The study had some limitations. First, the limited number of patients included. However, based on the sample calculation the number of patients recruited seems sufficient for an initial assessment of this issue. Secondly, the follow up was limited to one year. Thirdly, patients with non-advanced stages of HF were selected. This bias may be due to the characteristics of the study, which selected stable patients able to attend outpatient consultations and carry out ABPM. Fourthly, data on natriuretic peptides or troponins, were initially not included at the protocol and are therefore not available.

In conclusion, a non-dipper circadian BP pattern measured by 24-hour ABPM (with a reduction of $< 10\%$ during the resting period) was associated with a greater

number of hospitalizations and higher mortality in patients with HF. Neither nocturnal hypertension nor the SBP or DBP quartiles in each of the three periods measured were significantly associated with a worse prognosis in patients with HF. The non-dipper pattern was not a risk factor for a poor prognosis, but was a risk marker. If this is so, this situation would not be susceptible to therapeutic intervention. The explanation would probably be due to characteristics that are not entirely clear and which merit further study.

Conflicts of interest Statement: The authors declare they have no conflict of interest

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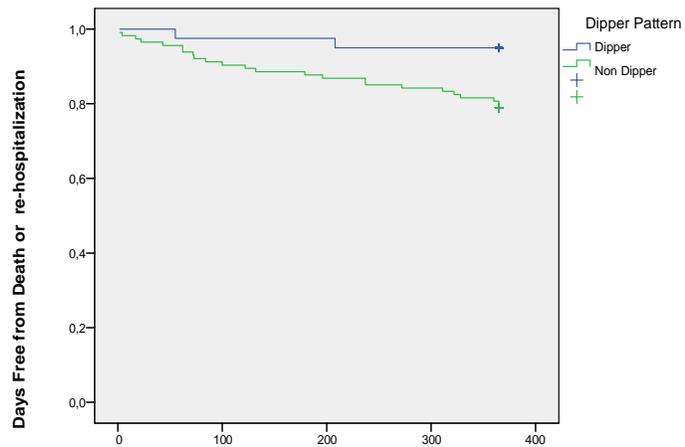


Figure 1: Survival curve (days free of death or readmission) according to dipper pattern of nighttime blood pressure. The log rank test showed that the difference observed by the Kaplan- Meier curve was statistically significant (χ^2 5.131, p 0.024).

Variable	Mean (\pm SD)/%
Age at first visit (years)	76.8 (\pm 8.3)
Women	55.2 %
Hypertension	94%
Ischemic Cardiomyopathy	17%
Mean Office SBP (mmHg)	137.4 (\pm 19.4)
Mean Office DBP (mmHg)	74.8 (\pm 11.4)
Office Heart rate (BPM)	73.1 (\pm 11.5)
Body mass index (Kg/m ²)	29.9 (\pm 4.8)
Abdominal perimeter (cm)	100 (\pm 11)
Glucose (mg/dL)	121.5 (\pm 35.7)
Diabetes (%)	42.2%
GFR (ml/min/1.73m ²)	58.3 (\pm 23.2)
CKD (GFR < 60 ml/min/1.73m ²)	45.85%
LVEF (%)	56.9 (\pm 13)
HFREF (%)	23.7%
HFPEF (%)	76.3%
Dependency	41.2%
Cognitive impairment	19.6%

Table 1: Baseline subject characteristics

Dependency was defined as Barthel index below 60 points, cognitive impairment was defined as equal or more than 5 points in Pfeiffer's short portable mental state questionnaire.

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BPM: Beats per minute GFR: Glomerular filtration rate; CKD: Chronic Kidney disease. LVEF: Left Ventricular Ejection Fraction, HFREF: Heart Failure with reduced ejection fraction, HFPEF Heart failure with preserved ejection fraction .

Variable	Mean \pm SD/%
SBP 24h (mean) mmHg	124.2 \pm 16.4
DBP 24h (mean) mmHg	66.1 \pm 9.7
24h HR (mean) BPM	70,8 \pm 12.1
SBP activity (mean) mmHg	126,4 \pm 16.7
DBP activity (mean) mmHg	68,7 \pm 10.7
Activity HR (mean) BPM	73,0 \pm 13.2
SBP rest (mean) mmHg	121,3 \pm 18.9
DBP rest (mean) mmHg	62,9 \pm 10.4
Heart rate rest (mean)	68,6 \pm 13.5
Reduction in SBP %	4,1 \pm 16.7
Reduction in DBP %	9,0 \pm 15.8
Dipper Pattern	21.43%
Super Dipper Pattern	4.55%
Non Dipper Pattern	39.61%
Riser Pattern	34.42%

Table 2: Baseline Blood Pressure and Heart Rate parameters.

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BPM: Beats per minute. HR: Heart Rate

Variables	Hazard Ratio	Significance	Lower 95% CI	Upper 95% CI
NYHA Stage	3,511	0 ,001	1,699	7,256
Left Atrial Diameter	1,032	0,058	0,999	1,066
% of DBP reduction	0,961	0,032	0,926	0 ,997

Table 3. Stepwise Cox regression for death/readmission of significant variables in bivariate analysis. NYHA: New York Heart Association, DBP: Diastolic Blood Pressure