Circadian blood pressure rhythm and intimal-medial thickness changes in non-dipper normotensive patients

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ABSTRACT

We investigated 25 *non-dipper* normotensive *vs* 25 *dipper* normotensive patients. The aim of our study was to evaluate carotid intimal-medial thickness (IMT) in the two groups. At the admission patients underwent anamnesis and general examination, blood sampling for lipid profile measurement, glycemia, homocysteine, ambulatory blood pressure measurement to assess the circadian blood pressure profile, and Doppler ultrasound to measure carotid IMT. Our results showed that IMT is significantly higher in the *non-dipper* group (P<0.006) *vs dippers*. *Non-dipper* status has been recognized in several studies as a condition with increased risk for target organ damage in hypertensive and normotensive subjects. However, to our knowledge, a possible relationship between IMT and normotensive *non-dipper* patients has not yet been clearly investigated. Our study instead has clearly demonstrated a significant relationship between IMT and the *non-dipper status*.

Introduction

Blood pressure (BP) shows a typical circadian rhythm, with the highest level in the early morning and declining progressively during the night. Night reduction should be at least 10%. Patients who present lower difference are named non-dippers.[1]

Ambulatory blood pressure monitoring (ABPM) is a non-invasive approach, which allows a careful and deeper evaluation of the hypertensive patient and represents the only method to measure blood pressure night-time (including dipper and non-dipper status).[2]

Carotid intimal-medial thickness (IMT) measurement is nowadays considered a valuable, low-cost, non-invasive tool to assess atherosclerotic burden in general population. A large body of evidence supports the estimates of absolute cardiovascular risk obtained from measurements of IMT.[3]

Several studies have showed a close relationship between non-dipper status and cardiovascular organ damage in hypertension.[4-10] Moreover a correlation between a blunted sleep-time relative blood pressure decline and cardiovascular risk has been described also in normotensive.[11,12] However, to our knowledge, the association between IMT thickness and non-dipper status has not yet been clearly demonstrated in the non-dipper normotensives. In the present study we investigated the possible relationship between non-dipper normotensives and IMT.

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Materials and Methods

We have enrolled 25 normotensive subjects (aged 32-71 years; 9 M-16 F; mean 57.4) with a non-dipping pattern, evaluated them for IMT and compared to a control group of 25 normotensive subjects with normal dipping pattern (aged 27-74; 11 M-14 F; mean 50.3).

Anamnesis and general examination were performed in all subjects.

Patients presenting in their anamnesis diabetes mellitus, rheumatoid arthritis, renal failure and smoking habits were excluded from the study and Doppler ultrasound with the measurement of IMT and ABPM

were performed (Spacelabs 90207; Spacelabs Medical, Inc., Redmond, WA, USA). Blood pressure values during daytime (6:00-22:00) and night-time (22:00-6:00) were within the normal range. In normotensives non-dipper patients, circadian rhythm was not maintained and blood pressure reduction during night-time was less than 10%.[1] Blood sampling for lipid profile measurement, glycemia, homocysteine was done.

Lipids profile tests and serum glucose were automatically performed by Fusion 5.1 chemistry analyzer (Ortho-Clinical Diagnostics, Inc., Raritan, NJ, USA); blood sampling for homocysteine was stored at 4°C and then centrifuged at 4°C, dosage of homocysteine was then automatically performed by Immulite 2000 (Siemens S.p.A., Milano, Italy).

Ethical evaluation was carried out in support of clinical evaluation. Helsinki Declaration was followed and each patient signed the informed consent.

Statistical analysis

The results are expressed as mean and standard deviation (SD).

The normality of data distribution was checked with D'Agostino and Pearson normality test. Comparison between groups was made by unpaired t-test. For categorical variables Fisher test was used. Statistical significance was defined at $P<0.05$.

Statistical analysis was performed using R version 3.2.3 (2015-12-10) (*Wooden Christmas-Tree* Copyright©2015; The R Foundation for Statistical Computing).

Results

Our results show that non-dippers had a greater IMT compared to dippers (0.836 *vs* 0.608; P=0.006). There was not statistically significant difference concerning low-density lipoproteins (LDL), high-density lipoproteins (HDL), LDL/HDL ratio, triglycerides and homocysteine levels between the two groups. Either group was composed mainly by women. Non-dippers were older than dippers (57.4±12.3 SD *vs* 50.3±11.7 SD; P=0.06) and more often smokers (P=0.454) but these differences were not statistically significant (Figure 1 and Table 1). ABPM values in the non-dipper and dipper categories are summarized in Table 2.

Data have been adjusted for confounding variables such as age, smoke and lipid levels.

Discussion and Conclusions

The present study shows a significant relationship between IMT measured by Doppler ultrasound of the neck vessels and non-dipping pattern in normotensive subjects assessed with ABPM. The latter is by now recognized as the most reliable method for hypertension diagnosis and therapy monitoring. ABPM is also the only technique able to highlight nightly dipper and non-dipper status.[2]

Non-dipper status has been associated in several studies with an increased organ damage and cardiovascular risk in hypertensive patients. ABPM can be regarded as very useful for this purpose, since it identifies non-dipper hypertensive patients at higher cardiovascular risk.[4-10] Recently, Hermida *et al*. showed a significant correlation between non-dipper status and target organ damage also in normotensives.[11]

IMT on the other side has been shown to be a reliable marker of early atherosclerosis and cardiovascular risk.[3] It can be easily and quickly measured by Doppler ultrasound of neck vessels. Recently, an important population-based study has demonstrated that IMT is positively associated with non-dipping pattern in hypertensive.[13] However, to our knowledge, non-dipper status and target organ damage has been rarely investigated in normotensives.[11,12] In our study IMT turned out to be significantly increased in non-dipper normotensives *vs* dippers. In our opinion, this is a significant finding, since till now non-dipper pattern has been evaluated and shown as a cardiovascular risk factor mainly in hypertension[4,6,8,10] and, to our knowledge, IMT has been correlated with non-dipping pattern only in hypertensive. Soylu *et al*. showed in their study a relationship between non-dipping pattern and morning blood pressure increase in normotensives and left ventricular mass index together with urinary albumin excretion; IMT was not investigated.[12] Recently, Manios *et al*. studied the impact of masking effect on subclinical carotid atherosclerosis in normotensives, untreated masked hypertensive and hypertensive patients. They found a significant correlation with IMT only in hypertensive.[14]

Our results confirm that non-dipper pattern is an

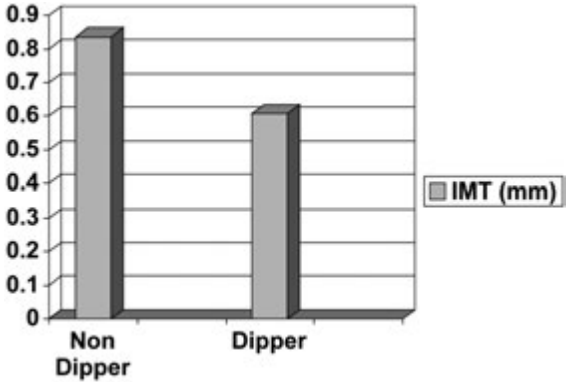

Figure 1. Intimal-medial thickness (IMT) in dipper and non-dipper patients.

Table 1. Clinical and biochemical features and intimal-medial thickness values of dipper and non-dipper patients.

Patients parameters	Non-dippers (n=25)	Dippers (n=25)	P-value
Age (years)	57.4±12.3	50.3±11.7	0.11
Women (no./%) Men (no./%)	16/64% 9/36%	14/56% 11/44%	0.773
BMI (kg/m^2)	26.7±5.06	27.7±4.03	0.242
Smoking habit (packs/year)	6.60	4.52	0.237
LDL (mg/dL)	130±34.6	130±40.3	0.528
HDL (mg/dL)	58.4±18.4	55.8±18.4	0.412
LDL/HDL ratio	2.41±0.848	2.47±0.879	0.874
Triglycerides (mg/dL)	107±51.8	103±53.0	0.672
Glycemia (mg/dL)	89.7±9.95	88.4±8.53	0.495
Homocysteine (µmol/L)	12.0±3.75	12.5±5.53	0.214
IMT	0.836±0.239	0.608±0.233	0.008

BMI, body mass index; LDL, low-density lipoproteins; HDL, high-density lipoproteins; IMT, intimal-medial thickness.

Table 2. Ambulatory blood pressure monitoring values in dipper and non-dipper patients.

	Non-dippers	Dippers
PAS day time (mmHg)	120.44 (108-132)	121.72 (111-137)
PAS night-time (mmHg)	112.96 (103-124)	108.12 (88-117)
PAD day time (mmHg)	73.64 (63-84)	74.68 (56-86)
PAD night-time (mmHg)	68.56 (53-80)	60.28 (51-70)

PAS, arterial systolic pressure; PAD, arterial diastolic pressure.

important cardiovascular risk factor also in normotensive patients. Moreover, no significant differences were found between the two groups concerning lipids, serum glucose and homocysteine, which are well-known risk factors for atherosclerosis; so that it is plausible to argue that IMT augmentation is due mainly to the non-dipper status. The statistical sample studied is small and further larger studies are needed to confirm these results.

In conclusion ABPM is a practical and economical technique and its use should be increased in daily clinic.[2] Even if it is premature to propose its application in normotensives, our data emphasize the importance of non-dipping status as a cardiovascular risk factor also in this category of patients and the fact that it seems reasonable to attempt to restore normal diurnal rhythm of the BP even in normotensive subjects. Evaluation of IMT might be a useful, cheap and fast tool to assess early atherosclerosis and cardiovascular risk in this category of patients.

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