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Full Title

Nocturnal dipping status and left ventricular hypertrophy: a cardiac magnetic resonance imaging study

Running heading

Nocturnal dipping and LVH

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Conflict of interest

None

Key words

Hypertrophy; ambulatory blood pressure; nocturnal dip; myocardial strain

Abstract

We investigate the impact of dipper status on cardiac structure with cardiovascular magnetic resonance (CMR). Ambulatory blood pressure monitoring and 1.5T CMR were performed in 99 tertiary hypertension clinic patients. Subgroup analysis by extreme dipper (n=9), dipper (n=39), non-dipper (n=35) and reverse dipper (n=16) status was performed, matched in age, gender and BMI. Left ventricular (LV) mass was significantly higher for extreme dippers than dippers after correction for covariates ($100\pm 6\text{g}/\text{m}^2$ vs $79\pm 3\text{g}/\text{m}^2$, $P=0.004$). Amongst extreme dipper and dippers (n=48), indexed LV mass correlated positively with the extent of nocturnal blood pressure dipping ($R=0.403$, $P=0.005$). On post-hoc ANCOVA, the percentage of nocturnal dip had significant effect on indexed LV mass ($P=0.008$), but overall SBP did not ($P=0.348$). In the tertiary setting, we found a larger nocturnal BP drop was associated with more LV hypertrophy. If confirmed in larger studies, this may have implications on nocturnal dosing of anti-hypertensive medications.

Text

Introduction

The global burden of systemic hypertension is immense, affecting an estimated 25% of the Worldwide adult population and the prevalence of the disease is estimated to reach 1.56 billion by 2025[1]. 24 hour ambulatory blood pressure monitoring (ABPM) is an important tool for risk stratification of individuals with arterial hypertension[2]. The pattern of nocturnal blood pressure (BP) relative to diurnal BP on ABPM can be categorized into i) dipper ($\geq 10\%$ reduction in average systolic blood pressure (SBP) at night) and ii) non-Dipper ($< 10\%$ reduction in SBP at night) groups. Within the dipper group, there is a subset of subjects with exaggerated nocturnal BP dip ($> 20\%$ reduction in SBP at night) termed extreme dippers. Likewise, there is a further subgroup within the non-dippers who demonstrate an increase in SBP overnight and these subjects are known as reverse dippers[3]. The nocturnal BP subtypes are associated with different levels of cardiovascular risk in hypertension, with non-dipper status conferring the worse prognosis[4][5]. However, there remains debate about the impact of dipper status on target organ damage. For example, there is increasing evidence that extreme dipper status may result in increased cerebrovascular morbidity; extreme dippers had increased prevalence of ischaemic stroke in one study[6] and increased risk of intracerebral haemorrhage in another[7]. Studies assessing differences in cardiovascular structure and function have not yielded consistent results[8]. To date, the effect of dipper status subtypes on cardiac target damage has not been comprehensively investigated with cardiovascular magnetic resonance imaging (CMR), which is the current non-invasive gold-standard

investigation to assess left ventricular (LV) volumes, mass and systolic function[9]. Consequently, we aimed to investigate the impact of nocturnal dipper status on cardiac structure and function using a comprehensive multi-parametric CMR protocol, assessing LV volumes and mass, burden of myocardial replacement fibrosis and myocardial deformational strain parameters. We hypothesized that non-dipper status would be associated with the most adverse cardiac remodeling/hypertrophy.

Materials and methods

Study population

This was a prospective observational study. Inclusion criteria were consecutive patients being treated for hypertension referred for CMR with contemporaneous ABPM from the Bristol Heart Institute tertiary hypertension clinic between February 2012 and April 2015. The local research ethics committee confirmed that the study conformed to the governance arrangements for research ethics committees.

Subjects provided written consent. Baseline demographic and clinical characteristics were recorded, including prevalence of obstructive sleep apnea and number of nocturnal anti-hypertensive medications. Patients with any concomitant myocardial pathology that may confound the cardiac remodeling/hypertrophy were excluded.

Exclusion criteria (Figure 1) consisted of: any evidence of moderate-severe valvular heart disease, acquired or inherited cardiomyopathy and suspected athlete's heart, on the basis of clinical and International imaging consensus guidelines[10], and severely decreased estimated glomerular filtration rate (eGFR) $<30\text{ml}/\text{min}/1.73\text{m}^2$. A history of myocardial ischaemia or infarction was not considered an exclusion criterion because both symptomatic and silent myocardial ischaemic are common in

hypertensive patients with left ventricular hypertrophy, even in the absence of epicardial coronary artery disease and LVH itself is a recognized causes of myocardial ischaemia[11][12][13][14].

Ambulatory blood pressure monitoring

Non-invasive 24-hour ABPM (Spacelabs, OSI Systems Company, USA) was performed during a weekday on the non-dominant arm with an automatic device[15]. The device obtained BP readings by the oscillometric method every 30 minutes for 24 hours. The subjects were instructed to conduct their usual daily activities but remain still at the time of BP measurement. The International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO) criteria were used (10 daytime measurements, 5 nighttime measurements) to determine satisfactory ABPM[16]. Nocturnal BP was defined as the mean BP readings from the time the patient went to bed until the time they got out of bed, with the remainder of the readings constituting the day time values. The ABPM data were analyzed with automated software to obtain mean overall/day-time/night-time systolic BP (SBP), diastolic BP (DBP) and mean arterial pressure (MAP). Dipper status was defined[3] as either:

- 1) Dipper ($\geq 10\%$ and $\leq 20\%$ reduction in average systolic blood pressure (SBP) at night),
- 2) Extreme dipper ($> 20\%$ reduction in SBP at night),
- 3) Non-dipper (0-10% reduction in SBP at night) or
- 4) Reverse dipper ($< 0\%$ reduction in SBP at night, i.e. nocturnal increase in SBP).

CMR cine protocol and analysis

CMR was performed at 1.5T (Avanto, Siemens, Erlangen, Germany). Short-axis steady-state free precession (SSFP) cines with whole left ventricular (LV) coverage (8mm slice thickness, no slice gap, temporal resolution 38.1ms, echo time 1.07ms, in-plane pixel size 1.5 x 0.8mm) were used for the estimation LV mass (LVM) and volumes and indexed to body surface area as previously described[17]. In accordance with the Society of CMR guidelines[18], a validated[19] threshold-detection software package (CMR42, Circle Cardiovascular Imaging Inc., Calgary, Canada) was used measure LVM, including papillary musculature and trabeculae in LVM estimation (Figure 1). LVH was defined as indexed LVM >95th percentile of established CMR reference ranges (men: 89-93g/m² and women: 77-78g/m² depending on age)[17]. LV mass to volume ratio (M/V), akin to relative wall thickness on echocardiography, was calculated and an increased M/V defined as >95th gender-specific percentile (men: >1.12g/ml and women: >1.14g/ml) from healthy volunteers, as described previously[20]. LV dilatation was defined as indexed EDV >95th percentile of the age and gender specific reference ranges. Left ventricular ejection fraction (LVEF) was reduced if <5th percentile of the same reference range. The CMR analysis was performed by an experienced CMR reader blinded to the ABPM data and CMR strain data.

Defining patterns of left ventricular remodeling and hypertrophy

Four patterns (Figure 2) of LV (left ventricular) remodeling / hypertrophy were defined as previously[21]: i) *Normal* = normal indexed LVM, normal indexed end-

diastolic volume (EDV) and normal mass to volume ratio (M/V), ii) *LV remodeling* = normal indexed LVM but increased M/V, iii) *Concentric hypertrophy* = increased indexed LVM, increased M/V, iv) *Eccentric hypertrophy* = increased LVM, increased indexed EDV, normal M/V and normal or reduced LVEF.

CMR late gadolinium protocol and analysis

Replacement myocardial fibrosis was assessed by late gadolinium enhancement (LGE) (Figure 1). An inversion-recovery fast gradient recall echo sequence performed 10-15minutes following injection of 0.1mmol/kg intravenous gadobutrol (Gadovist, Bayer Pharma AG, Germany) as previously described[22]. The inversion time was personalized to achieve optimal myocardial nulling in each subject. LGE was visually assessed as a consensus between 2 expert CMR readers, blinded to the remodeling/hypertrophy, CMR strain and ABPM data.

CMR strain imaging

Strain imaging was performed off-line using 4-chamber, 2-chamber and short-axis stack SSFP cine images with voxel-tracking software (Tissue Tracking, CVM42, Circle Cardiovascular Imaging Inc., Calgary, Canada) as previously described[23] (Figure 1). The software defines the position of each myocardial voxel at end-diastole and tracks their location of the cardiac cycle in 2D. It is based on a previously described algorithm[24][25]. Briefly, endocardial and epicardial end-diastolic borders were defined excluding papillary muscles and trabeculae. The end-diastolic mitral valve annular plane was defined. Global longitudinal strain was the averaged strain from 4-chamber and 2-chamber analysis. Circumferential strain was calculated as a mean

value of mid myocardial segments from the short-axis cine 2D strain model, in order to minimize partial-volume averaging and through-plane motion at the base and apex. All strain analysis was performed by an experienced CMR reader blinded to the ABPM data and other CMR data.

Statistical analysis

Statistical analysis was performed using SPSS Version 21 (Armonk, NY, USA: IBM Corp). Normally distributed continuous variables were expressed as mean \pm standard deviation and compared using one-way analysis of variance with Bonferroni post-hoc correction. Categorical variables were expressed as percentages and analysed using the Fisher's exact test. Multiple linear regression was used to control for covariates of age, gender, body mass index, diabetes, day-time SBP, day-time DBP and day-time MAP with Bonferroni correction for multiple post-hoc comparisons. To determine the relative impact of day-time blood pressure levels and degree of nocturnal dip on indexed LV mass amongst dippers, linear regression analysis controlling for day-time systolic blood pressure was performed. Statistical significance was set at two-sided $P < 0.05$.

Results

Study population

One hundred and eleven hypertensive subjects were screened, 12 subjects were excluded due to concomitant cardiac pathology or inadequate CMR study (Figure 1), resulting in a final sample size of 99. The demographics and baseline clinical

characteristics are displayed in Table 1. Dipper, extreme dipper, non-dipper and reverse dipper subgroups were matched in terms of age, gender and BMI.

Blood pressure in dipper subgroups

When all subjects with nocturnal dip $<10\%$ (non-dippers and reverse dippers, $n = 51$) were compared with all subjects with nocturnal dip $\geq 10\%$ (dippers and extreme dippers, $n = 48$), the combined non-dipper and reverse dipper cohort had significantly higher mean overall ABPM SBP (157 ± 23 mmHg vs 147 ± 19 mmHg, $P = 0.008$) and nocturnal ABPM SBP (155 ± 23 mmHg vs 130 ± 15 mmHg, $P < 0.0001$) compared to the combined dipper and extreme dipper cohort. However, when the individual dipper subgroups were compared, it was only the dipper subgroup (with nocturnal dip $\geq 10\%$ and $<20\%$) that exhibited significantly lower overall ABPM SBP compared to the non-dipper subgroup (with nocturnal dip $0-10\%$) (145 ± 18 mmHg vs 161 ± 23 mmHg, $P = 0.009$) (Table 1). The extreme dipper subgroup showed no significant difference in overall and day-time ABPM SBP compared with non-dipper and reverse dipper subgroups respectively.

Cardiac structure and function in dipper subgroups

When all subjects with nocturnal dip $<10\%$ (non-dippers and reverse dippers, $n = 51$) were compared with all subjects with nocturnal dip $\geq 10\%$ (dippers and extreme dippers, $n = 48$), there was no significant difference in indexed LV mass (nocturnal dip $\geq 10\%$: 83 ± 20 g/m² vs nocturnal dip $<10\%$: 89 ± 25 g/m², $p = 0.208$) (Figure 3).

Contrary to the hypothesis, it was the extreme dippers whom demonstrated the highest prevalence of concentric LVH (67%) and had the highest indexed LV mass

(103 ± 29 g/m²) (Table 2), despite the non-dippers and reverse dippers having similar overall and day-time ABPM SBP and significantly higher night-time ABPM DBP (Table 1). Within the subgroup of patients with preserved nocturnal dip $\geq 10\%$, the extreme dipper cohort had significantly higher indexed LV mass than the dipper cohort (103 ± 29 g/m² vs dippers: 78 ± 15 g/m², $P = 0.021$) (Table 2). However, there were no significant differences in systolic function in terms of LVEF, longitudinal strain and circumferential strain between the cohorts (Table 2 and Figure 3). The prevalence of myocardial replacement fibrosis was not significantly different between the subgroups (Table 2).

Dipper versus extreme dipper

To determine whether the increased indexed LV mass observed amongst the extreme dipper cohort compared to the dipper cohort was simply due to the association with higher day-time SBP, To determine whether the increased indexed LV mass observed amongst the extreme dipper cohort compared to the dipper cohort was simply due to the association with higher day-time SBP, a one-way analysis of covariance (ANCOVA) was performed to assess for persistent differences in indexed LV mass between extreme dipper and dippers, controlling for covariates of age, gender, BMI, diabetes, day-time SBP, day-time DBP and day-time MAP (Table 3). Extreme dippers still demonstrated a significantly higher indexed LV mass compared to dippers (100 ± 6 g/m² vs 79 ± 3 g/m², $P = 0.004$) even after correcting for these covariates (Figure 3).

Amongst dippers (n = 48), indexed LV mass correlated positively with percentage of nocturnal dip (R = 0.403, P = 0.005). Linear regression analysis was performed to assess the relationship between percentage nocturnal dip amongst dippers and indexed LV mass, controlling for day-time systolic blood pressure. A significant relationship persisted between indexed LV mass and percentage nocturnal dip ($\beta = 0.371$, 95th confidence intervals: 0.479 – 3.477, p = 0.011) but not between indexed LV mass and day-time systolic blood pressure ($\beta = 0.131$, 95th confidence intervals: -0.164 – 0.450, p = 0.352). Essentially, the exaggerated swing in SBP between day-time and night-time is more likely to be the reason for more advanced LV hypertrophic responses in extreme dippers compared to dippers, than higher day-time SBP.

Significant positive correlations were demonstrated between percentage nocturnal dip and: 1) peak circumferential strain (r = 0.412, p = 0.004) and 2) peak longitudinal strain (r = 0.345, p = 0.016) but not with peak radial strain (r = -0.161, p = 0.276).

Essentially, the greater the nocturnal dip, the worse the circumferential and longitudinal deformation, as these are negative indices by convention. Linear regression analysis was also performed to assess the relationship between LV strain indices and indexed LV mass, controlling for day-time systolic blood pressure. A significant relationship persisted between 1) peak circumferential strain ($\beta = 0.393$, 95th confidence intervals: 0.099 – 0.599, p = 0.007) and 2) peak longitudinal strain ($\beta = 0.321$, 95th confidence intervals: 0.025 – 0.489, p = 0.031) with percentage nocturnal dip, but not with day-time systolic blood pressure in either of the statistical models respectively ($\beta = 0.078$, 95th confidence intervals: -0.037 – 0.065, p

= 0.581), ($\beta = 0.097$, 95th confidence intervals: -0.32 – 0.063, $p = 0.504$). After correcting for day-time systolic blood pressure, there was no significant relationship between peak radial strain and percentage nocturnal dip ($\beta = -0.215$, 95th confidence intervals: -3.821 – 0.626, $p = 0.155$). Essentially, the exaggerated swing in SBP between day-time and night-time is more likely to be the reason for circumferential and longitudinal strain impairment in extreme dippers compared to dippers, rather than higher overall SBP.

Discussion

Summary of results

We investigated the impact of dipper status on cardiac structure and function using CMR. We show that in the tertiary setting, extreme dippers exhibit the highest indexed LV mass, after correction for covariates of age, gender, BMI, diabetes, day-time SBP/DBP/MAP, and that larger nocturnal drops in BP are associated with more advanced myocardial hypertrophy, independent of day-time SBP.

Hypertensive LVH and dipper status

The extreme dipper subgroup had the highest indexed LV mass and the highest prevalence of concentric LVH. There is heterogeneity in the literature regarding LV mass and dipper status. Importantly, it is only relatively recently that dipping profiles have been subdivided into extreme dipper and reverse dipper subgroups. Ivanoic *et al.* did look at all 4 dipper subgroups and demonstrated the highest prevalence of LVH in reverse dippers[26]. However, 69% of this cohort were untreated and LV mass was indexed to height^{2.7}, which has been shown to

systematically misclassify subjects regarding LVH presence [27]. The effect of drug treatment on the relationship of dipper status and cardiac function may be an important variable. For example, Muxfeldt *et al.* showed no significant differences in LV mass indexed to BSA amongst dipper, non-dipper, reverse dipper and extreme dipper subgroups in the context of resistant hypertension using echocardiography[28]. The current study differs from the previous studies by at least one of the following variables: 1) imaging modality for measuring LV mass (CMR), 2) definition of LVH (CMR specific cut-offs for age and gender indexed to BSA), 3) treatment status of patients (on treatment) and 4) type of patient (recruited from tertiary setting). Consequently, the current findings apply to a specific, but important, cohort of hypertensive patients.

Mechanisms for LVH in extreme dippers

Why extreme dippers develop the most LVH is not clear. Extreme dippers had comparable overall SBP levels compared to non-dippers and reverse dippers, suggesting a complex relationship beyond absolute BP level.

An excessive early morning BP surge is associated with increased cardiovascular events[29]. The level of morning surge in BP has been demonstrated to be significantly associated with cardiovascular remodeling independent of 24 hour BP level, daytime BP variability and nocturnal BP decline in subjects >60 years old on antihypertensive medications[30]. Extreme dippers may be most prone to exhibit early morning surge in BP, which may account for the fact that extreme dipping has been associated with increased cardiovascular events[6][7]. A potential unifying

explanation for these observations is that early morning surge may be a result of increased morning sympathetic activity[29]. Elevated day-time sympathetic nerve activity may result in not only day-time BP increases but also directly stimulate the myocardium potentially directly inducing LVH itself[31].

Equally, the exaggerated fall in SBP at night may contribute to LVH in extreme dippers. Recently, we demonstrated that increased cerebrovascular resistance and reduced cerebral blood flow were present before the onset of increased muscle sympathetic nerve activity in the borderline hypertensive subjects, suggesting cerebral hypoperfusion may be a factor in triggering and exacerbating hypertension[32]. The exaggerated nocturnal drop in BP in extreme dippers could theoretically aggravate nocturnal cerebral perfusion and result in rebound increases in neurogenically-mediated sympathetic nerve activity. This relative nocturnal hypoperfusion may also help account for the increased cerebrovascular pathology identified in extreme dippers in some studies[6][7].

Extreme dipping may have direct cardiac effects. Theoretically, relative nocturnal hypotension may result in reduced myocardial perfusion pressure. If this were to fall below a critical threshold, it may trigger subclinical hypoperfusion/hypoxemia which itself will trigger low level myocardial inflammation and hypertrophy of the myocardium. Indeed, Kotsis *et al.*[33] previously demonstrated a significantly higher Gensini score (a computerized scoring system of coronary artery disease severity that depends on the degree of luminal narrowing, the geographic importance of each stenosis, the ejection fraction and possible collateral circulation of coronary

arteries) in extreme dippers. Excessive sympathetic activity to the heart, for example via the aforementioned selfish brain hypothesis, may cause coronary vasoconstriction and potentially compound cardiac hypoperfusion during dipping.

Clinical implications

The *post-hoc* analysis of the current study suggests that it is the actual exaggerated nocturnal dip response that is associated with advanced LVH and not simply a higher daytime SBP. If the findings are validated in larger scale studies, this may have implications for anti-hypertensive regimens. It is common practice to suggest patients take their anti-hypertensive medications at night if they are developing pre-syncope symptoms during the day. Whilst several antihypertensive medications have appropriate pharmacodynamics and pharmacokinetics to allow single dosing, if the medications are taken at night, they may actually contribute to a larger nocturnal dip that could have pathological implications to the brain and heart as discussed above. More insight into this may be gained when the Hellenic Anglo Research into Morning Or Night antihypertensive drug delivery (HARMONY) trial, a randomized cross-over trial of 100 participants comparing day-time and evening dosing of antihypertensive medications, reports its findings. Therefore, it is proposed that ABPM is performed, to define whether dipping occurs and to assess its extent, and the impact of long-acting and/or nocturnal anti-hypertensive regimens.

Limitations

There are several limitations of this study. Firstly, the sample size is small. However, the increased precision, accuracy and reliability of CMR over 2-dimensional

echocardiography increases the statistical power, reducing the sample size required to detect a statistically significant change in LV mass of 10g with 90% power ($1 - \beta$ error) by 6-fold[34]. There is a relatively low prevalence of extreme and reverse dippers in our cohort but the proportions of these subgroups to the overall study size are comparable to previous echocardiographic studies[26][28]. However, one of the relative strengths of this study, in our opinion, is the real-world data captured by the study design, which was a prospectively maintained clinical database of consecutive hypertensive patients referred for CMR. The low prevalence of extreme dipper subgroups reflects our real world-practice. It represents a small but clinically important subgroup of patients with nocturnal dip >10%. We performed additional analyses looking at nocturnal blood pressure dip as a continuous variable, in addition to looking at pre-defined dipper subgroups. These findings provide further support to the notion that percentage of nocturnal dip is an important variable and mitigate against, although do not completely exclude, a type 1 error.

This study was conducted in a specialist hypertension clinic. We, therefore, can only conclude that the findings are applicable in this tertiary setting. Further study is required to determine whether the same findings occur in, for example, untreated, newly diagnosed patients with hypertension in the primary care / community setting.

Due to the prolonged subclinical course of the disease, it was not possible to accurately correct for the duration of subclinical and established hypertension. Finally, the dipper status of our subjects was only confirmed on a single ABPM

reading, rather than two contemporaneous ABPM investigations. In addition, routine clinical CMR is likely to be inferior to echocardiography at assessing diastolic dysfunction and this has been previously investigated[35].

Conclusion

In the tertiary hypertension setting, extreme dippers with nocturnal dip >20% exhibit the most advanced hypertrophic response which appears to be independent of daytime BP and related to the relative swings in sympathetic activity and BP from night to day. This was contrary to the original hypothesis that non-dipper status would be associated with the most adverse cardiac remodeling/hypertrophy. If confirmed in larger studies, this may have implication on the recommendation of nocturnal dosing of anti-hypertensive medications.

Acknowledgments

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Figure legends

Figure 1. A flow chart showing the study exclusions. (HOCM = hypertrophic obstructive cardiomyopathy, LVNC = LV non-compaction cardiomyopathy, DCM = dilated cardiomyopathy, mod AR = moderate aortic regurgitation, AVR = aortic valve replacement, * = artefact from implantable loop recorder). Representative examples of the multi-parametric CMR protocol: A) Steady-state free precession left ventricular short-axis mid-cavity cines images at end-diastole with bloodpool threshold detection software analysis to define endocardial contours (red line) and manual definition of epicardial contours (green line) to estimate LV mass, LV volumes and LV ejection fraction (every other image shown for illustrative purposes), B) Voxel tracking software analysis, which is applied in a post-processing step to steady-state free precession images to derive estimates of longitudinal strain, circumferential strain and radial strain and C) Inversion-recovery late gadolinium enhancement left ventricular short-axis mid-cavity image at end-diastole demonstrating a cases of subtle replacement fibrosis at the right ventricular insertion points (solid white arrows).

Figure 2. Different patterns of left ventricular remodeling and hypertrophy.

Figure 3. Summary of key findings, including deformational strain (circumferential strain, longitudinal strain and radial strain) versus time graphs for the different dipper subgroups. *¹one-way ANCOVA correction for covariates of age, gender, BMI, diabetes mellitus, day-time SBP, day-time DBP and day-time MAP. *² Linear regression analysis.

Tables

Table 1. Demographic and ambulatory blood pressure data for dipper subgroups

Table 2. Cardiovascular magnetic resonance for all subjects, dipper and non-dippers

Table 3. Subgroup analysis of subjects with dipper status with correction for
covariates