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The association of night-time systolic blood pressure with ultrasound markers of subclinical cardiac and vascular disease

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Introduction **The aim of this study was to examine the association of night-time systolic blood pressure (BP) with subclinical cardiac dysfunction measured by global longitudinal strain (GLS) and subclinical vascular damage measured by carotid intima–media thickness (CIMT) and carotid plaques.**

Methods **GLS was measured by speckle-tracking analysis of echocardiogram images. CIMT was measured at the distal 1 cm of the common carotid artery. The presence of carotid plaques was recorded. Philips QLAB cardiac and vascular ultrasound quantification software was used for analysis. The association of night-time systolic BP with GLS, CIMT and carotid plaques was assessed using linear and logistic regression.**

Results **Fifty (response rate 63%) individuals took part in this study. In univariable models, night-time systolic BP was significantly associated with GLS [β coefficient 0.85 for every 10 mmHg increase, 95% confidence interval (CI): 0.3–1.4] and carotid plaques (odds ratio 1.9 for every 10 mmHg increase, 95% CI: 1.1–3.2). Univariable analysis of daytime systolic BP did not show any statistically significant associations. In age-adjusted and sex-adjusted models, the association for night-time systolic BP and GLS remained significant (β coefficient 0.68 for every 10 mmHg increase, 95% CI: 0.1–1.3). The association for carotid plaques was no longer statistically significant. In multivariable models, findings were diminished.**

Discussion **Our results suggest a trend towards an association between night-time systolic BP and subclinical cardiac and vascular disease. When assessing ambulatory blood pressure monitoring results, the absolute night-time systolic BP seems to be a better prognostic parameter than daytime systolic BP, but ultimately a large randomised controlled trial involving chronotherapy is necessary to fully address this.** ***Blood Press Monit*** **22:18–26** **Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: ambulatory blood pressure monitoring, carotid intima–media thickness, global longitudinal strain, hypertension, ultrasonography

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Introduction

Cardiovascular disease remains the leading cause of mortality worldwide [1] and hypertension is the risk factor with the greatest population-attributable risk [2,3]. Prevalence rates of hypertension are high, whereas control rates are low [4]. Ambulatory blood pressure monitoring (ABPM) measures blood pressure (BP) over 24–48 h and has been shown to be superior to office BP for the prediction of clinical events [5,6]. Night-time systolic BP is a stronger predictor of events than daytime systolic BP [7].

Although it is unclear whether night-time BP should be a specific therapeutic target, chronotherapy has shown some promising results. In one study, patients were randomized to either take all of their antihypertensive medications in the morning or to take at least one of them at night. The decrease in nocturnal BP was associated with a reduced risk of total cardiovascular events. Similarly, patients with chronic kidney disease who took at least one antihypertensive at night had a lower hazard ratio of total cardiovascular events than those taking all of their medications in the morning [8,9].

The association of night-time BP with subclinical target organ damage has been investigated [10,11]. This would seem intuitive, given the greater association of night-time

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BP with clinical events, the continuum of cardiovascular disease [12] and subclinical disease being a prognostic marker for future cardiovascular events [13]. Many studies have focused on dipping status rather than the absolute BP level [14–16]. We have previously shown that absolute night-time systolic BP is better associated than dipping status with subclinical cardiac and vascular damage documented by electrocardiogram left ventricular hypertrophy (LVH) voltage criteria and microalbuminura in the Mitchelstown Cohort Study [17].

Echocardiography can measure the subclinical cardiac consequences of hypertension such as increased left atrial (LA) size and LVH. Speckle-tracking echocardiography has enabled the quantification of strain, which is a dimensionless measure of myocardial deformation. Global longitudinal strain (GLS) is a measure of the myocardial systolic deformation over the longitudinal axis [18]. There is emerging evidence for the prognostic importance of this measure [19,20]. It offers incremental prognostic information in the assessment of left ventricular (LV) function, particularly when the ejection fraction is near normal [21]. Few studies have examined the association of night-time BP and GLS measured by speckle-tracking analysis [22,23].

Carotid intima–media thickness (CIMT) measured by ultrasound is a marker of subclinical vascular damage and is recognized to be associated with cardiovascular risk factors and with the incidence of myocardial infarction and stroke [24,25]. There is evidence for the validity of CIMT as a suitable surrogate measure of atherosclerotic disease [26,27]. The addition of carotid plaques to risk prediction models including CIMT improves performance [28,29].

The present study aims to build on previous work by examining the association of night-time systolic BP with ultrasound markers of subclinical cardiovascular disease including abnormal GLS, CIMT and carotid plaques in a sample from the Mitchelstown Cohort Study.

Methods

In 2010, the Mitchelstown Cohort Study recruited 2047 participants from a single large primary care centre, the Livinghealth Clinic in Mitchelstown, a town in the south of Ireland [30]. Of these, 1207 (response rate 59%) also underwent 24-h ABPM. These individuals provide the sample for the present study. On the basis of the initial ABPM results, the sample was divided into four groups: normotension, isolated nocturnal hypertension, isolated daytime hypertension and day–night hypertension. Twenty participants were selected randomly from each group and invited to attend for echocardiogram and carotid ultrasound in 2014. This study therefore includes analysis of baseline ABPM data and follow-up imaging data.

Height and weight measurements

A trained researcher carried out the physical measures. Height and weight were measured without footwear using a Seca (Hamburg, Germany) measuring and weighing station. BMI and body surface area (BSA) were calculated.

Study blood pressure

At the baseline visit after the participant had been in a relaxed seated position for at least 5 min, three BP readings were taken on the right arm, 1 min apart, using an OMRON M7 digital automatic BP monitor (OMRON Healthcare Europe B.V., Hoofddorp, the Netherlands). The average of the second and third BP reading was defined as the study BP.

Ambulatory blood pressure monitoring

ABPM measurements were performed at baseline using the MEDITECH (Budapest, Hungary) ABPM-05 and data were stored using the dabl ABPM system (dabl Ltd, Dublin, Ireland). The monitors were programmed to record the BP every 30 min throughout the 24-h period. Participants kept a diary of the times they went to bed and got up. Diary times were used to calculate the mean daytime and night-time BP. The mean 24-h BP was calculated as the mean of all the readings throughout the 24-h period.

Echocardiography

A Philips iE33 ultrasound machine (Philips Healthcare, Guildford, UK) and a S5-1 phased array transducer were used for image acquisition. All scans were carried out by the same operator (I.B.). I.B. is accredited in transthoracic echocardiography by the British Society of Echocardiography. A standard echocardiogram protocol was used. Parasternal long and short axis, apical four-chamber, two-chamber and three-chamber views were obtained. Optimization of frame rate was carried out by reducing the sector depth and width.

LV wall thickness and diameters were measured from the parasternal long axis view. LV mass was calculated using the Devereux formula [31]. LV mass was indexed for BSA. LVH was defined as LV mass more than 115 g/m^2 in men and more than 95 g/m^2 in women [32]. LV volumes and ejection fraction were calculated from the apical four-chamber view using the single-plane method of discs [33]. LV volumes were indexed for BSA. LA volume was calculated from the apical four-chamber view using the single-plane method of discs. LA volume was indexed for BSA [32].

Diastolic function parameters were measured in the apical four-chamber view. Mitral inflow early (E) and late (A) velocities and E wave deceleration time were obtained by pulse-wave Doppler with the sample volume at the mitral valve tips. Peak diastolic mitral annular (e') velocity was measured from the septal and lateral mitral annulus and averaged. The E/e' ratio was then calculated. Diastolic dysfunction was defined as $E/A \leq 0.7$ or

deceleration time >260 ms; or $E/A>0.7$ and ≤ 1.5 and e' velocity <7 cm/s; or $E/A>1.5$ and e' velocity <7 cm/s or deceleration time <140 ms [34].

The acquired images were saved using digital media and speckle-tracking GLS analysis was carried out offline by a single reader (A.M.O.F.) from apical four-chamber, two-chamber and three-chamber views using Philips QLAB cardiac and vascular ultrasound quantification software (version 9.0; Philips). The region of interest was identified by the selection of three points, one on either side of the mitral valve annulus and one at the apex for each view. Adequate tracking was confirmed visually and, if deemed inadequate, the region of interest was edited. If inadequate tracking persisted, problematic segments were excluded. If more than two segments in a single view had to be excluded, the entire study was excluded from speckle-tracking analysis [32]. GLS average was obtained from 17 ventricular segments represented on a bulls-eye plot from these views. Normal cut-off was taken as -19.7% [35].

Carotid ultrasound

A Philips Cx50 portable ultrasound machine and an L12-3 linear array transducer were used for image acquisition. All scans were carried out by the same operator (A.M.O.F.). A.M.O.F. received formal training in CIMT image acquisition. Patients were examined in the supine position with their head tilted to the opposite side. A Meijer arc was used to ensure optimal positioning. A thorough transverse and longitudinal scan of the extracranial carotid arteries was carried out to evaluate for the presence of atherosclerotic plaques. Ultrasound images of the distal portion of the far wall of both common carotid arteries were obtained for assessment of CIMT. Far-wall still frames were taken from anterior, lateral and posterior angles. Three still frame images were taken from each angle [36].

The acquired images were saved using digital media and measurement was carried out offline by a single reader (A.M.O.F.) using Philips QLAB cardiac and vascular ultrasound quantification software (version 9.0; Philips). Measurements were made on the three still frame images from each angle over a length of 1 cm at the distal common carotid artery (CCA). The reference point for the commencement of the measurement was where the CCA began to dilate before the bifurcation. A mean measurement from each angle was obtained. The mean of these means was obtained to yield the measurement for each side. The mean of the left and right was then taken as the CIMT. Normal cut-off was taken as the 75th percentile [37]. The presence of plaques in the extracranial carotid arteries was recorded as a binary variable. A plaque was defined according to the Mannheim Consensus as a focal protrusion into the blood vessel of at least 50% of the thickness of the adjacent IMT or focal IMT more than 1.5 mm [38].

Reproducibility

Intraobserver and interobserver reproducibility was assessed before carrying out the study. Ten patients undergoing routinely indicated echocardiography were asked to consent to have their images analysed by speckle-tracking analysis. All echocardiograms were carried out by the same operator (I.B.). Speckle-tracking analysis was carried out offline by A.M.O.F. and repeated for intraobserver reproducibility. An independent observer (E.H.) also analysed the images for interobserver reproducibility. Ten healthy volunteers underwent a carotid ultrasound twice within the same week carried out by the same investigator (A.M.O.F.), who also analysed the images for intraobserver reproducibility. An independent observer (E.H.) analysed the second set of images for interobserver reproducibility.

The intraobserver intraclass coefficient (ICC) for GLS was 0.93 [95% confidence interval (CI): 0.70–0.98]. The interobserver ICC was 0.86 (95% CI: 0.51–0.96). The intraobserver ICC for CIMT was 0.91 (95% CI: 0.69–0.98). The interobserver ICC was 0.97 (95% CI: 0.88–0.99).

Statistical analysis

Statistical analysis was carried out using Stata 12 (StataCorp LP, College Station, Texas, USA). Continuous variables are described by mean $\pm$ SD. Categorical variables are described using proportions. Univariable linear and logistic regression analysis was used to compare echocardiographic and carotid ultrasound findings between groups.

The association of baseline night-time, daytime and study systolic BP with GLS and CIMT was assessed using univariable and multivariable linear regression. The association of baseline night-time, daytime and study systolic BP with carotid plaques was assessed using logistic regression. Regression models were initially adjusted for sex and age. Multivariable regression analysis was also carried out with adjustments applied for sex, age, BMI, smoking status, diabetes mellitus and total cholesterol. Interaction terms including antihypertensive medications with night-time, daytime and study systolic BPs, respectively, were also included in the models.

Ethical considerations

The study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals and was carried out in accordance with the Declaration of Helsinki. All participants provided informed consent.

Results

Fifty (overall response rate 63%) individuals took part in this study. The mean period of follow-up was 3.9 years. The mean age of the participants was 60 years and 26 (52%) were men. Baseline characteristics are presented in Table 1, together with the baseline characteristics of the full cohort and those who underwent ABPM.

Table 1 Baseline characteristics

	Total cohort ($n=2047$)	Sample with satisfactory ABPM ($n=1072$)	Sample ($n=50$)
Age	59±6	60±6	60±5
Male	1008 (49)	567 (47)	26 (52)
Education category			
Primary	537 (28)	335 (30)	7 (15.5)
Secondary	936 (49)	547 (48)	22 (49)
Tertiary	435 (23)	253 (22)	16 (35.5)
IPAQ category			
Low	932 (49)	571 (50)	31 (62)
Moderate	566 (30)	318 (28)	19 (38)
High	420 (22)	248 (22)	0 (0)
Smoking status			
Nonsmoker	1002 (51)	615 (53)	27 (54)
Former smoker	671 (34)	378 (32)	18 (36)
Current smoker	292 (15)	175 (15)	5 (10)
Medical history			
Hypertension	567 (29)	407 (34)	19 (40)
Myocardial infarction	49 (2)	33 (3)	2 (4)
Stroke	22 (1)	13 (1)	0 (0)
Heart failure	8 (0.4)	6 (0.5)	1 (2)
Diabetes	174 (9)	114 (10)	5 (10)
Medication			
Antihypertensive	584 (29)	405 (35)	21 (42)
Cholesterol lowering	711 (36)	457 (39)	21 (42)
BMI (kg/m^2)	29±5	30±5	29±5
Waist circumference	97±13	97±14	100±13
LDL (mmol/l)	3.2±0.9	3.2±0.9	3.2±0.8
Creatinine (μmol/l)	71±16	72±16	74±17
ACR (mg/mmol)	0.7±2.1	0.8±2.1	0.6±0.7
eGFR (mls/min)	90±13	89±13	87±13
Cystatin C	0.83±0.18	0.83±0.18	0.87±0.14
Study systolic	130±17	134±18	134±16
Study diastolic	80±10	83±10	82±10
Daytime systolic	–	131±14	132±12
Daytime diastolic	–	77±9	78±9
Night-time systolic	–	112±14	117±14
Night-time diastolic	–	63±8	66±9
Twenty-four hour systolic	–	124±13	126±11
Twenty-four hour diastolic	–	72±8	74±8

Note some missing data.
Values are given as mean±SD or *n* (%).
ABPM, ambulatory blood pressure monitoring; ACR, albumin : creatinine ratio; eGFR, estimated glomerular filtration rate; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein.

The echocardiogram and carotid ultrasound findings by BP strata are presented in Table 2. Speckle-tracking echocardiography analysis was not possible in one study because of poor image quality. In univariable models, night-time systolic BP was significantly associated with GLS (β coefficient 0.85 for every 10 mmHg increase, 95% CI: 0.3–1.4) and carotid plaques (odds ratio 1.9 for every 10 mmHg increase, 95% CI: 1.1–3.2). Univariable analysis of daytime systolic BP did not show any statistically significant associations (Table 3). In age-adjusted and sex-adjusted models, the association for night-time systolic BP and GLS remained significant (β coefficient 0.68 for every 10 mmHg increase, 95% CI: 0.11–1.25). The association for carotid plaques was no longer statistically significant (Table 4). In multivariable models, findings were attenuated (Table 5). Interaction terms including antihypertensive medications with night-time, daytime and study systolic BPs, respectively, were included in the models, but were not statistically significant (data not shown).

Discussion

We have shown an association of night-time systolic BP with two measures of subclinical cardiovascular disease, GLS and carotid plaques, in a community-based middle-aged population. These associations were attenuated in multivariable models. No such associations were found for daytime or study systolic BPs and subclinical cardiovascular disease.

Cumulative BP exposure over a 25-year period is associated with subclinical systolic and diastolic dysfunction assessed by speckle-tracking echocardiography in middle age [39]. Uncontrolled 24-h BP has also been shown to be associated with abnormal GLS, whereas uncontrolled office BP was not, in treated hypertensive patients [40]. Few studies have specifically addressed the association of night-time BP and GLS. Kalaycioglu *et al.* [22] found a significant reduction in GLS in nondippers compared with dippers in a sample of 86 treated hypertensive diabetic patients with a mean age of 57.8 years. They also reported night-time systolic BP to be associated independently with GLS and GLS rate in linear regression models adjusted for age, sex and LV mass index [22]. In untreated hypertensive patients, Tadic *et al.* [23] found reduced two-dimensional and three-dimensional LV GLS and reduced atrial longitudinal strain in nondippers compared with dippers. Acar *et al.* [41] also examined LA strain in dippers and nondippers and found reduced atrial function in nondippers. Others have examined right heart mechanics and found reduced function in nondippers [42]. Our results suggest an association between increased night-time systolic BP and subclinical LV systolic dysfunction. We also found night-time systolic BP to have a stronger association than daytime systolic BP and study BP with other echocardiographic markers of subclinical cardiac damage such as LA volume and LV mass (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/BPMJ/A27*).

CIMT does improve cardiovascular risk prediction models, but the overall impact is small [43]. There are concerns regarding measurement methods [44]. Moreover, increasing IMT is recognized as a normal ageing phenomenon that further complicates interpretation of CIMT measurements [45–47]. The use of CIMT is therefore not without controversy and therefore European and American guidelines no longer recommend routine measurement of CIMT in clinical practice for the assessment of cardiovascular risk [48,49]. The addition of plaques has been shown to improve the predictive performance of CIMT [28,50]. Findings on the association of night-time BP and CIMT are conflicting. Cuspidi *et al.* [10] reported no difference in CIMT or plaques between those with nocturnal normotension and nocturnal hypertension. However, Wang *et al.* [51] reported an association between

Table 2 Echocardiogram and carotid ultrasound characteristics

	Total sample ($n=50$)	Normotension ($n=11$)	Isolated nocturnal hypertension ($n=14$)	Isolated daytime hypertension ($n=14$)	Sustained day–night hypertension ($n=11$)
Echocardiogram					
LA volume index (ml/m^2)	32.0 ± 9.4	27.7 ± 7.3	32.6 ± 9.7	31.3 ± 7.7	36.2 ± 12.0*
LV mass index (g/m^2)	99.3 ± 24.2	85.5 ± 19.7	101.5 ± 24.7	97.8 ± 17.5	112.4 ± 29.9*
Left ventricular hypertrophy	16 (32)	2 (18)	5 (36)	4 (29)	5 (45)
LV end diastolic volume (ml/m^2)	48.3 ± 8.4	45.8 ± 7.6	48.6 ± 10.3	48.2 ± 7.0	50.5 ± 8.7
LV end systolic volume (ml/m^2)	17.2 ± 5.2	17.7 ± 6.8	17.5 ± 7.0	16.3 ± 2.9	17.6 ± 3.6
LV ejection fraction (%)	65.1 ± 6.2	64.5 ± 7.2	64.9 ± 7.5	66.0 ± 5.0	65.0 ± 5.3
Global longitudinal strain (%)	−21.2 ± 3.0	−22.6 ± 2.9	−21.0 ± 2.9	−21.9 ± 2.8	−19.2 ± 2.6*
Abnormal GLS	16 (33)	1 (10)	5 (36)	3 (21)	7 (64)
E/*A*	0.98 ± 0.3	1.04 ± 0.2	0.95 ± 0.4	0.89 ± 0.2	1.05 ± 0.3
E wave deceleration time (ms)	253.9 ± 74.2	224 ± 54	282 ± 90.1	255.4 ± 60.0	246 ± 80.3
E′ (cm/s)	7.7 ± 1.8	8.2 ± 1.0	7.3 ± 2.0	7.8 ± 2.2	7.9 ± 1.6
E/*e*′	9.5 ± 1.9	9.4 ± 0.9	9.9 ± 1.9	8.6 ± 2.1	10.2 ± 2.3
Diastolic dysfunction	30 (60)	4 (36)	10 (71)	10 (71)	6 (55)
Carotid ultrasound					
Common carotid IMT (mm)	0.72 ± 0.13	0.64 ± 0.10	0.76 ± 0.14*	0.71 ± 0.14	0.76 ± 0.12*
Common carotid IMT > 75th percentile	12 (24)	1 (9)	4 (29)	3 (21)	4 (36)
Plaques	33 (66)	5 (45)	12 (86)*	8 (57)	8 (73)

GLS analysis not possible in one study because of poor image quality.
Values are given as mean ± SD or *n* (%).
GLS, global longitudinal strain; IMT, intima–media thickness; LA, left atrium; LV, left ventricle.
P values represent comparison with the normotensive group.
*$P < 0.05$.

Table 3 Univariable linear and logistic regression results

	GLS [β coefficients (95% CI)]	*P*-value	CIMT [β coefficient (95% CI)]	*P*-value	Plaques [OR (95% CI)]	*P*-value
Sex (male vs. female)	2.70 (1.15–4.24)	0.001	0.09 (0.02–0.16)	0.02	6.5 (1.7–24.7)	0.006
Age	0.05 (−0.11–0.21)	0.5	0.009 (0.002–0.015)	0.009	1.2 (1.0–1.3)	0.03
Antihypertensives (yes vs. no)	−0.91 (−2.65–0.84)	0.3	−0.03 (−0.11–0.05)	0.4	0.3 (0.1–1.1)	0.06
BMI	0.20 (0.03–0.37)	0.02	−0.004 (−001–0.004)	0.3	1.1 (0.96–1.2)	0.2
Smoking status (current vs. non/ex)	−0.18 (−3.05–2.69)	0.9	0.18 (0.06–0.29)	0.004	2.2 (0.2–21.4)	0.5
Diabetes mellitus (yes vs. no)	3.16 (0.43–5.88)	0.02	0.02 (−0.11–0.15)	0.7	2.1 (0.2–20.9)	0.5
Total cholesterol	0.05 (−0.89–0.99)	0.9	−0.02 (−0.06–0.03)	0.4	0.67 (0.34–1.3)	0.2
Night-time SBP	0.85 (0.3–1.4)	0.003	0.02 (−0.002–0.05)	0.08	1.9 (1.1–3.2)	0.03
Daytime SBP	0.47 (−0.24–1.17)	0.2	0.02 (−0.01–0.05)	0.3	1.2 (0.7–2.0)	0.4
Study SBP	0.53 (0.01–1.06)	0.05	0.01 (−0.01–0.03)	0.4	1.16 (0.8–1.7)	0.4

β Coefficients and odds ratios for night-time SBP, daytime SBP and study SBP represent per 10 mmHg increase.
CI, confidence interval; CIMT, carotid intima–media thickness; GLS, global longitudinal strain; OR, odds ratio; SBP, systolic blood pressure.

nocturnal hypertension and CIMT in patients with chronic kidney disease. Cuspidi *et al.* [52] have recently reported the results of a meta-analysis that examined the association of nondipping with carotid atherosclerosis and found higher CIMT and greater prevalence of plaques in nondippers. Although we found no association between night-time systolic BP and CIMT, we did find an association with carotid plaques in univariable analysis. We measured CIMT at the distal 1 cm of the common carotid artery as the guidelines recommend, while we assessed all of the extracranial carotid vessels for plaques [36]. This may have contributed towards the differential findings for CIMT and plaques as they likely reflect different stages of atherosclerosis and plaques are more likely to develop in areas of turbulent flow such as the bifurcation [53]. In addition, we may not have had sufficient power to detect an association between night-time BP and CIMT.

The evidence for the prognostic importance of night-time BP is compelling [7]. However, the potential underlying mechanisms are unclear and include altered sympathetic nervous system activity, disturbed baroreflex sensitivity, increased sodium sensitivity and obstructive sleep apnoea [7]. It may be that night-time BP is subject to less variability and more accurately represents true BP [54]. Reverse causality is also possible and elevated night-time BP may merely be a marker of more severe end organ damage. Cuspidi and colleagues have recently carried out a systematic review and meta-analysis on the association of nocturnal hypertension with subclinical cardiac and carotid disease documented by ultrasound and found increased LV mass index and CIMT in those with nocturnal hypertension compared with those with nocturnal normotension [55]. They acknowledge the cross-sectional nature of existing data

Table 4 Sex-adjusted and age-adjusted linear and logistic regression results

	GLS model 1 [β coefficient (95% CI)]	*P*-value	GLS model 2 [β coefficient (95% CI)]	*P*-value	GLS model 3 [β coefficient (95% CI)]	*P*-value
Sex (male vs. female)	2.21 (0.64–3.77)	0.007	2.61 (0.89–4.33)	0.004	2.44 (0.64–4.23)	0.009
Age	−0.0.5 (−0.20–0.10)	0.5	0.01 (−0.14–0.16)	0.9	0.002 (−0.15–0.15)	1.0
Night-time SBP	0.68 (0.11–1.25)	0.02	–	–	–	–
Daytime SBP	–	–	0.08 (−0.61–0.78)	0.8	–	–
Study SBP	–	–			0.17 (−0.40–0.74)	0.6
	CIMT model 1 [β coefficient (95% CI)]	*P*-value	CIMT model 2 [β coefficient (95% CI)]	*P*-value	CIMT model 3 [β coefficient (95% CI)]	*P*-value
Sex (male vs. female)	0.07 (−0.01–0.14)	0.07	0.07 (−0.01–0.14)	0.09	0.08 (−0.0003–0.16)	0.05
Age	0.01 (0.0001–0.01)	0.05	0.01 (0.001–0.01)	0.02	0.01 (0.001–0.01)	0.02
Night-time SBP	0.01 (−0.02–0.03)	0.6	–	–	–	–
Daytime SBP	–	–	0.01 (−0.02–0.04)	0.6	–	–
Study SBP	–	–	–	–	−0.005 (−0.03–0.02)	0.7
	Plaques model 1 [OR (95% CI)]	*P*-value	Plaques model 2 [OR (95% CI)]	*P*-value	Plaques model 3 [OR (95% CI)]	*P*-value
Sex (male vs. female)	4.8 (1.16–19.86)	0.03	6.11 (1.39–26.75)	0.02	8.4 (1.64–43.01)	0.01
Age	1.11 (0.97–1.28)	0.1	1.14 (0.99–1.31)	0.06	1.15 (1.00–1.32)	0.05
Night-time SBP	1.47 (0.80–2.69)	0.2	–	–	–	–
Daytime SBP	–	–	0.95 (0.55–1.65)	0.9	–	–
Study SBP	–	–	–	–	0.80 (0.49–1.30)	0.4

β Coefficients and odds ratios for night-time SBP, daytime SBP and study SBP represent per 10 mmHg increase.
Model 1: night-time SBP adjusted for sex and age.
Model 2: daytime SBP adjusted for sex and age.
Model 3: study SBP adjusted for sex and age.
CI, confidence interval; CIMT, carotid intima–media thickness; GLS, global longitudinal strain; OR, odds ratio; SBP, systolic blood pressure.

and that the causal relationship between nocturnal hypertension and subclinical cardiovascular disease remains unproven. Our study provides some prospective data on subclinical target organ damage and our results suggest that elevated night-time BP may contribute more than daytime or office BP towards cardiac and vascular end organ damage. However, large prospective randomized trials with interventions aimed at normalizing night-time BP are required to resolve the questions that remain on the importance of night-time BP as a therapeutic target. The methods of a large prospective open-label blinded randomized-controlled trial have recently been published, which may help to answer this question. The treatment in morning versus evening trial aims to randomize 10 269 hypertensive patients to either morning or evening dosing of antihypertensive medications. The primary end-point is vascular death or hospitalization for the composite of nonfatal myocardial infarction or nonfatal stroke [56].

Limitations

This is a small study and the sample size may have provided insufficient power to detect true associations between night-time systolic BP and target organ damage in multivariable models and for CIMT in particular. The ultrasound machines used were in fulltime clinical use and could only be used for research scans at the end of the working day; therefore, collection of imaging data was limited by access. This resulted in a prolonged data collection period. Given these feasibility issues, a decision was taken after 50 participants had been recruited to proceed with data analysis. On the basis of our results, we had 86% power to detect a true association between night-time systolic BP and GLS. However, for CIMT, we had just 33% power and would have required a sample size of 162 to avoid a type II error [57].

Selection bias is another limitation as those who took part in this study were more likely to self-report a history of hypertension; therefore, the sample is not representative of the full Mitchelstown Cohort (40 vs. 29% previous doctor diagnosis of hypertension). Similarly, they were more likely to report being on antihypertensive medication at baseline (42 vs. 29%). Also those who took part in the study were better educated (35% had tertiary education compared with 23% of the full cohort) and less physically active (all of those taking part had low or moderate physical activity levels and nobody had high physical activity levels). In addition, the use of antihypertensive medications in the sample increased between 2010 and 2014 from 42% ($n=21$) to 61% ($n=30$), which may have impacted the results, although one would expect that increased use of antihypertensive medications would be more likely to influence results towards the null hypothesis. Although interaction terms did not suggest effect modification by antihypertensive therapy, we repeated the univariable regression analysis between night-time systolic BP and ultrasound markers of subclinical cardiovascular disease by treatment status. We found that the association between night-time systolic BP and subclinical cardiovascular disease was greater for untreated individuals (data not shown). This needs to

Table 5 Multivariable adjusted linear and logistic regression results

	GLS model 1 [β coefficient (95% CI)]	*P*-value	GLS model 2 [β coefficient (95% CI)]	*P*-value	GLS model 3 [β coefficient (95% CI)]	*P*-value
Sex (male vs. female)	1.79 (−0.03–3.6)	0.05	1.97 (0.03–3.9)	0.05	2.02 (0.03–4.01)	0.05
Age	0.002 (−0.17–0.17)	1.0	0.06 (−0.10–0.21)	0.5	0.06 (−0.10–0.22)	0.5
BMI	0.06 (−0.13–0.26)	0.5	0.11 (−0.08–0.30)	0.2	0.11 (−0.08–0.30)	0.2
Smoking (current vs. non/ex)	−0.01 (−2.82–2.80)	1.0	0.27 (−2.61–3.15)	0.9	0.28 (−2.60–3.16)	0.8
Diabetes mellitus (yes vs. no)	1.91 (−0.75–4.56)	0.2	2.16 (−0.57–4.89)	0.1	2.16 (−0.61–4.93)	0.1
Total cholesterol	0.28 (−0.62–1.17)	0.5	0.38 (−0.54–1.29)	0.4	0.38 (−0.54–1.31)	0.4
Night-time SBP	0.52 (−0.13–1.16)	0.1	–	–	–	–
Daytime SBP	–	–	0.04 (−0.66–0.75)	0.9	–	–
Study SBP	–	–	–	–	−0.01 (−0.61–0.58)	1.0
	CIMT model 1 [β coefficient (95% CI)]	*P*-value	CIMT model 2 [β coefficient (95% CI)]	*P*-value	CIMT model 3 [β coefficient (95% CI)]	*P*-value
Sex (male vs. female)	0.07 (−0.01–0.15)	0.07	0.07 (−0.01–0.15)	0.1	0.07 (−0.01–0.16)	0.08
Age	0.01 (−0.001–0.01)	0.08	0.01 (0.004–0.01)	0.04	0.01 (0.0003–0.1)	0.04
BMI	−0.003 (−0.01–0.004)	0.4	−0.003 (−0.01–0.004)	0.4	−0.0.003 (−0.01–0.004)	0.5
Smoking (current vs. non/ex)	0.15 (0.03–0.27)	0.02	0.16 (0.04–0.28)	0.01	0.16 (0.04–0.28)	0.01
Diabetes mellitus (yes vs. no)	0.02 (−0.10–0.13)	0.8	0.02 (−0.09–0.14)	0.7	0.02 (−0.10–0.14)	0.7
Total cholesterol	−0.01 (−0.05–0.03)	0.5	−0.01 (−0.05–0.03)	0.6	−0.01 (−0.05–0.03)	0.6
Night-time SBP	0.01 (−0.02–0.03)	0.5	–	–	–	–
Daytime SBP	–	–	0.01 (−0.02–0.04)	0.5	–	–
Study SBP	–	–	–	–	0.001 (−0.02–0.95)	0.2
	Plaques model 1 [OR (95% CI)]	*P*-value	Plaques model 2 [OR (95% CI)]	*P*-value	Plaques model 3 [OR (95% CI)]	*P*-value
Sex (male vs. female)	4.66 (0.78–27.80)	0.09	5.70 (0.84–38.50)	0.07	6.57 (0.93–46.49)	0.06
Age	1.17 (0.99–1.38)	0.07	1.19 (1.01–1.40)	0.03	1.21 (1.02–1.42)	0.03
BMI	1.10 (0.93–1.30)	0.3	1.13 (0.95–1.33)	0.2	1.13 (0.96–1.34)	0.1
Smoking (current vs. non/ex)	6.81 (0.30–157.32)	0.2	10.28 (0.38–280.48)	0.2	9.16 (0.39–217.16)	0.2
Diabetes mellitus (yes vs. no)	0.61 (0.04–10.57)	0.7	0.74 (0.04–12.38)	0.8	0.93 (0.05–16.23)	1.0
Total cholesterol	0.63 (0.25–1.56)	0.3	0.69 (0.29–1.64)	0.4	0.70 (0.29–1.70)	0.4
Night-time SBP	1.31 (0.65–2.66)	0.5	–	–	–	–
Daytime SBP	–	–	0.86 (0.46–1.62)	0.6	–	–
Study SBP	–	–	–	–	0.78 (0.45–1.37)	0.4

β Coefficients and odds ratios for night-time SBP, daytime SBP and study SBP represent per 10 mmHg increase.
Model 1: night-time SBP adjusted for sex, age, BMI, smoking, diabetes mellitus and total cholesterol.
Model 2: daytime SBP adjusted for sex, age, BMI, smoking, diabetes mellitus and total cholesterol.
Model 3: study SBP adjusted for sex, age, BMI, smoking, diabetes mellitus and total cholesterol.
CI, confidence interval; CIMT, carotid intima–media thickness; GLS, global longitudinal strain; OR, odds ratio; SBP, systolic blood pressure.

be interpreted with caution, given the small numbers included in the analysis. However, future studies should ideally recruit those who are not on antihypertensive therapy. Although our study provides some prospective imaging data in a community-based sample, the lack of ultrasound data at baseline recruitment means that it is not possible to draw inference on the temporal relationship for the observed associations of night-time systolic BP with GLS and carotid plaques.

In addition, night-time BP profiles are not fully reproducible [58,59]. We could assess the reproducibility of BP profiles in 47 of those who took part in this study. There were no significant differences in the mean BP levels between 2010 and 2014. However, the reproducibility of dipping status was poor, with just 24% maintaining the same profile after 4 years. The reproducibility of BP profiles defined by the absolute BP level was better, but still just 40% (Supplementary Tables 2–4, Supplemental digital content 2, *http://links.lww.com/BPMJ/A28*). These findings highlight the limitations of applying thresholds and categories to continuously distributed risk factors but also the need to be cautious when interpreting results of studies examining nocturnal BP profiles on the basis of a single ABPM recording.

The strength of this study lies in the novel question addressed as limited studies have assessed the association of night-time BP and GLS [22,23]. In addition, these participants will continue to be followed up for the Mitchelstown Cohort Study; thus, further prospective data will be available over time.

Conclusion

This study suggests a trend towards an association between night-time systolic BP with markers of subclinical cardiac and vascular disease, although the sample size limits interpretation of the multivariable analysis. We did not find any significant association between these markers and daytime systolic BP. When assessing ABPM results, the absolute night-time BP seems to be a better prognostic parameter than daytime systolic BP. However,

whether normalizing night-time BP improves prognosis remains unanswered and only a large randomized-controlled trial involving chronotherapy can address this.

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Conflicts of interest

Dr Anne Marie O'Flynn is currently receiving funding from a Health Research Board Ireland research training fellowship for healthcare professionals (reference HPF/2012/14) and has also received the John Feely research bursary from the Irish Heart Foundation to support this work. She has also received payment unrelated to the submitted work through her institution for the development of the European Society of Cardiology e-learning platform. Dr Ronan Curtin has received funding and subsistence support for lectures and activities outside of the submitted work from A. Menarini, Daichi Sankyo, Astra Zeneca, Bayer, Bristol Myers Squibb, Pfizer and Servier pharmaceutical companies. Professor Patricia Kearney has received grants from the Health Research Board Ireland and the European Union FP7 for work outside of the submitted work. Drs Emily Ho and Eamon Dolan have no conflicts of interest.

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