EARLY LEFT VENTRICULAR DYSFUNCTION AND NON-DIPPING: WHEN EJECTION FRACTION IS NOT ENOUGH. A META-ANALYSIS OF SPECKLE TRACKING ECHOCARDIOGRAPHY STUDIES.

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ABSTRACT

Background and Aim There is evidence that a reduced nocturnal fall in blood pressure (BP) entails an increased risk of hypertensive-mediated organ damage (HMOD) and cardiovascular events. Most studies focusing on left ventricular (LV) systolic function, assessed by conventional LV ejection fraction (LVEF) in non-dippers compared to dippers failed to detect significant differences. To provide a new piece of information on LV systolic dysfunction in the non-dipping setting, we performed a meta-analysis of speckle tracking echocardiography (STE) studies investigating LV global longitudinal strain (GLS), a more sensitive index of LV systolic function.

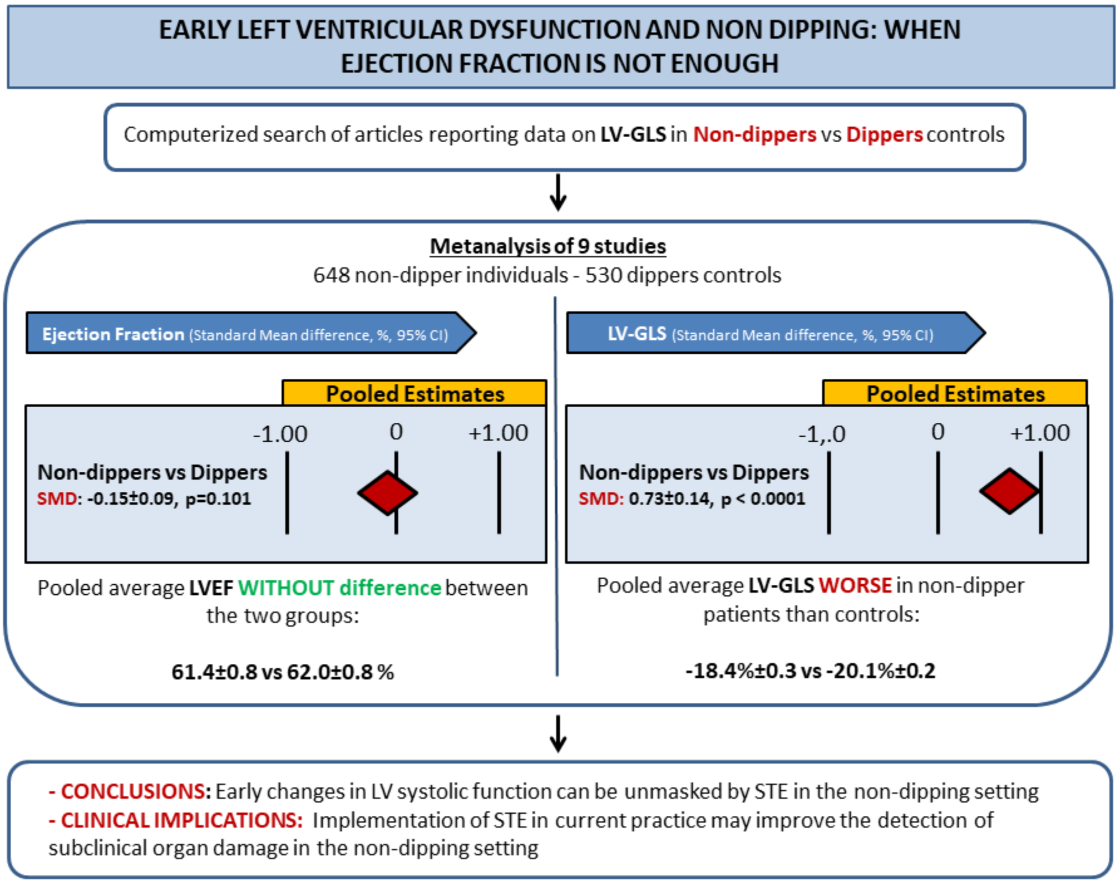
Methods A computerized search was performed using Pub-Med, OVID, EMBASE and Cochrane library databases from inception until July, 31 st2022. Full articles reporting data on LV GLS and LVEF in non-dippers and dippers were considered suitable.

Results A total of 648 non-dipper and 530 dipper individuals were included in 9 studies. LV GLS was worse in non-dipper than in their dipper counterparts (-18.4±0.30 vs -20.1±0.23%), SMD: 0.73±0.14, CI: 0.46/1.00, p < 0.0001) whereas this was not the case for LVEF (61.4±0.8 and 62.0±0.8%, respectively), SMD: -0.15±0.09, CI: -0.32/0.03, p=1.01). A meta-regression analysis between night-time systolic BP and myocardial GLS showed a significant, relationship between these variables (coefficient 0.085, p < 0.0001).

Conclusions Our findings suggest that early changes in LV systolic function not detectable by conventional echocardiography in the non-dipping setting can be unmasked by STE; implementation of STE in current practice may improve the detection of HMOD of adverse prognostic significance in individuals with altered circadian BP rhythm.

Key words: non-dipping, subclinical left ventricular systolic function, left ventricular ejection fraction, left ventricular global longitudinal strain.

Graphical abstract



INTRODUCTION

Since over 40 years, ambulatory blood pressure monitoring (ABPM) has progressively revealed the diagnostic and prognostic limits of office BP measurement in the assessment of hypertensive patients (1,2). This is because the discrepancy between office and out-office BP values has opened new horizons in the setting of cardiovascular medicine allowing to identify two discordant BP phenotypes characterized respectively by: I) high office BP not confirmed by the ABPM (i.e. white coat hypertension); II) normal office BP associated with high ambulatory BP (i.e. masked hypertension) (3-6). Furthermore, BP measurement carried out in the medical environment does not allow to assess BP changes that occur during the 24-hour circadian cycle (7). A large amount of evidence based on ABPM studies in different populations has consistently shown that BP at night usually falls by 10 and 20% compared to daytime values (8,9). Over the last 3 decades, individuals with nocturnal BP fall in the aforementioned range have been defined as dippers as opposed to those with reduced BP fall (i.e. non dippers) and with paradoxical night-time BP increase (i.e. reverse dippers) (10).

A blunted decrease in night-time BP has been found to be associated with several unhealthy conditions such as obesity, obstructive sleep apnea, diabetes mellitus, metabolic syndrome, chronic kidney disease, resistant hypertension as well as to an increased risk of hypertension-mediated organ damage (HMOD) and cardiovascular events (11-13).

Although it may be intuitive to assume that a reduced fall in BP during night-time may have unfavourable effects on cardiovascular structure as a direct consequence of a persistent hemodynamic stress over the course of 24 hours available evidence on this topic based on the dichotomous classification of dipping/non-dipping remains inconclusive, so far (14,15). Of note, most investigations on the association between the non-dipping pattern and HMOD have addressed the harmful effect of the disrupted BP circadian rhythm on cardiac structure and function. Left ventricular hypertrophy (LVH), due to its frequency and its established prognostic implications, was the most studied phenotype, with mixed results among the various studies (16).

Whether non-dipping may be a risk factor for early LV systolic dysfunction remains undefined as available information on this important aspect is based almost exclusively on the assessment of LV ejection fraction (LVEF), a time-honoured index but not sensitive enough to identify subtle changes in systolic function (17,18).

Starting of this premise, we performed a meta-analysis of speckle tracking echocardiographic (STE) studies that, in addition to conventional LVEF, provided data on LV deformation in individuals with normal and reduced nocturnal BP drop with the aim to shed light on the relationship between altered BP circadian rhythm and changes in LV mechanics as assessed by global longitudinal strain (GLS), a more sensitive and reproducible index of early systolic dysfunction compared to LVEF (19).

METHODS

We reported the systematic review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (20). Pertinent literature was systematically scrutinized to identify all papers targeting the association between non-dipper pattern and LV systolic dysfunction through the comparison of LVEF and GLS in individuals with normal and reduced nocturnal BP fall.

The PubMed, OVID-MEDLINE, and Cochrane library databases were systematically analysed to search English-language articles published from inception to July 31, 2022. Studies were identified by using Me-SH terms and crossing the following terms: “non-dipping”; “reverse-dipping”, "circadian BP rhythm" "ventricular mechanics", "systolic dysfunction", "global longitudinal strain", "echocardiography" and "STE echocardiography".

Two authors assessed all titles and abstracts retrieved with the search. When there was an agreement on a specific record, the full text of the study was analyzed by both reviewers in order to establish eligibility according to the inclusion criteria mentioned below. A third reviewer resolved disagreements on study judgments. Data extraction was performed by two reviewer and independently checked by another reviewer.

Main inclusion criteria were: I) English articles published in peer-reviewed journals; II) comparative studies providing data on LVEF and LV mechanics (i.e. GLS) by 2D or 3D STE echocardiography in non-dippers and dippers; III) minimum set of clinical/demographic data (i.e. sex, age, body mass index; office and/or ambulatory BP). Specific exclusion criteria were: I) studies with less than 10 non-dipper patients; II) studies conducted in children and adolescents (age <18 years); III) reviews, editorials, and case reports.

The Newcastle-Ottawa Scale (NOS) was used to measure study quality. (http://www, ohri ca/programs/clinical_epidemiologyoxford htm).

Echocardiographic Methods

The analysis of cardiac structure and function as well as the assessment of LV myocardial deformation had been performed in all studies according to recommendations of contemporary guidelines. In particular, GLS was measured off-line from 2D-3D echocardiographic images in all studies using a commercial dedicated software; R-R gating was used for LV strain assessment. In all studies, LV endocardium was manually traced and corrected, if necessary, and average longitudinal strain curve was automatically provided by the software.

Statistical analysis

A pooled analysis of cardiac parameters was performed using fixed or random effects meta-analysis by Comprehensive Meta-Analysis Version 2, Biostat, Englewood, NJ. Standard means difference (SMD) with 95% confidence interval (CI) was used to calculate the statistical difference of continuous echocardiographic variables between non-dipper and dipper groups. Demographic and clinical data provided by selected studies were expressed as absolute numbers, percentage, mean ±SD, mean ±SE or mean with CI. Heterogeneity was estimated using the I-squared test; random effect models were applied when heterogeneity across studies was high (I^2>75). Publication bias was assessed by using the funnel plot method (Trim and fill test). Observed and adjusted values, their lower and upper limits have been calculated. Statistical significance was set at P<0.05.

RESULTS

After removing duplicates, the initial literature search identified 1206 papers**.** After the initial screening of titles and abstracts, 1135 studies were excluded as they were not related to the topic. Therefore, 71 studies were reviewed; of these, 40 did not report any data on myocardial mechanics, 11 did not provide separate data for dippers and non-dippers and 11 were reviews, commentary, and editorial articles. Thus, a total of 9 comparative studies reporting data on GLS and LVEF in non-dippers versus dippers and containing echocardiographic data of interest, were included in the final review (21-29) (Figure 1).

Table 1 summarizes methodological details regarding both office BP and ABPM measurements. Although all selected studies defined the non-dipping pattern as a reduction in average BP at night of at least 10% compared with average day-time value, five of them considered only systolic BP fall, three mean arterial pressure, and one both systolic/diastolic BP fall. Differences of BP measurement intervals and, consequently of the total number of recordings, during day and night periods were also present among the studies.

<u>Characteristics of the studies</u>

On the whole,648 non-dipping individuals and 530 dipper controls were included in 9 studies (sample size ranging from 70 to 290 participants), performed in four countries (Turkey= 3; China=3; Serbia=2; Oman=1).

Table 2 reports the key features of each study including type of design, number of participants, setting, anti-hypertensive treatment, comorbidities, NOS and main findings. Seven out of nine studies enrolled untreated and treated hypertensive patients without cardiovascular disease and preserved LVEF, whereas the remaining two studies examined normotensive individuals. Comorbidities and risk factors such as type 2 diabetes, dyslipidemia and/or smoking were reported by five of the selected studies. According to the NOS the quality of studies, ranged from 7 to 9 (i.e. score that identifies studies of fair or good quality). Therefore, no study was excluded based on its limited quality.

Table 3 shows demographic and clinical characteristics of non-dippers and dippers such as sample size, mean age, prevalence of men, body mass index (BMI), day-time and night-time systolic/diastolic BP. The mean age range in non-dippers was 27-59 years, the corresponding value in dippers was 27-57 years; 59% of non-dipper and 55% of dipper participants were men; BMI values ranged from 22.1±2.3 to 33.8±3.6 kg/m^2 in non-dippers and from 21.5±2.0 to 33.2±5.1 kg/m^2 in dippers.

In all studies, as expected, mean night-time systolic/diastolic BPs were significantly higher in non-dippers than in dippers. The opposite trend was observed for mean day-time systolic BP in 6 out of nine studies.

Echocardiographic findings

Table 4 shows structural and functional echocardiographic variables in non-dipper individuals as compared to their dipper counterparts. As for LV structure, all selected studies providing this kind of information, with the exception of Efe's report (27), showed that non-dipping was associated with a significantly greater LVM indexed to body surface area (BSA). Data on relative wall thickness (RWT), a prognostically validated marker of LV geometry, reported by six studies showed mixed findings (a significantly increased RWT in non-dippers was reported by four studies, whereas no difference was found in the remaining two studies).

As for LV systolic function, assessed by conventional echocardiography, all studies but one failed to find any statistical difference in LVEF between non-dipper and dipper individuals. The ratio of early (E) peak of mitral inflow velocity to early (e') peak mitral annular velocity (E/e') (a diastolic function index as well as the early to late mitral flow velocity ratio reported in almost all studies), was found to be greater (worse) in non-dippers in four out of eight reports.

Finally, as for LV mechanics, eight of the nine studies showed a less negative (impaired) GLS in non-dipper patients than in their dipper counterparts.

Meta-analysis findings

Pooled average LVEF was not different between non-dippers and dippers: 61.4±0.8 and 62.0±0.8%. As shown by the forest plot in Figure 2, the meta-analysis of 9 studies did not reveal a significant difference in LVEF between groups (SMD: -0.15±0.09, CI: -0.32/0.03, p=1.01). On the contrary, GLS was less negative in non-dippers (-18.4±0.30%) than in their dipper counterparts (-20.1±0.23%). Figure 3 shows the results of the meta-analysis where SMD suggested a worse LV systolic function in the pooled non-dipper group (SMD 0.73±0.14, CI: 0.46/1.00, $p < 0.0001$).

The early to late mitral flow velocity ratio (E/A ratio) was lower in non-dippers than in dippers (0.99±0.05 vs 1.08±0.06) with a statistically significant SMD (-0.29 ± 0.06, CI: -0.41/-0.16, $p < 0.0001$). The average value of E/e' ratio was higher in non-dippers (8.3±0.36) than in dippers (7.4±0.26). The meta-analysis of eight studies providing data regarding this index showed a SMD of 0.38±0.06, CI:0.25/049, $p< 0.0001$ (Figure 4).

Pooled LVM index (LVMI) was higher in non-dippers (102.9±3.1 g/m^2) than in dippers (93.4±3.1 g/m^2). Figure 5 illustrates the findings of the meta-analysis of 8 studies where SMD suggested an increased LVMI in the pooled non-dipper group (0.41±0.06, CI: 0.29/0.57, $p < 0.0001$).

Publication bias

The presence of single study effect was excluded at sensitivity analysis; furthermore, a relevant publication bias was not present. In fact, a statistically significant difference in pooled LV GLS between non-dippers and dippers was still present after correction for publication bias (Supplementary Figure 1).

Correlation analyses

A meta-regression analysis assessing the relationship between night-time systolic BP and myocardial GLS in the whole pooled population (non-dippers and dippers) showed a significant, relationship (coefficient 0.085, $p < 0.0001$) between these variables (i.e. the higher the systolic BP, the less negative the GLS) (Figure 6).

Sensitivity analyses

A sensitivity analysis restricted to 7 studies performed in hypertensive patients confirmed that GLS (SMD:0.0.84±0.15, CI: 0.53/1.14, p<0.0001) (Supplementary Figure 2) but not LVEF (SMD: -0.11±0.11, CI: -0.32/0.01, p=0.21) was impaired in non-dippers compared to their dipper counterparts.

Additional analyses

In addition to GLS, global circumferential strain (GCS) and global radial strain (GRS) were calculated, respectively, in five and four out the nine studies included in the meta-analysis. Both parameters were lower in non-dippers than in dippers (GCS -20.9±1.5 vs -22.6±0.9% and GRS 35.45 ± 3.1 vs 39.9 ± 2.6 %, respectively). Supplementary Figure 3 reports the findings of the meta-analysis regarding the GCS where SMD suggested an impaired myocardial circumferential deformation in non-dippers (0.40 ± 0.08, CI : 0.24/0.56, p < 0.0001).

DISCUSSION

The association between abnormal diurnal BP patterns and adverse cardiovascular outcomes significantly increased general interest for ABPM in the everyday clinical work-up of hypertensive patients (30,31).Although the substrate of adverse outcomes is represented by HMOD associated to non-dipping pattern, subtle changes in LV function, not detectable with conventional echocardiography, could also contribute to worse outcome in this setting. LV mechanics, and particularly GLS, are predictors of CV outcome in general, as well as in hypertensive population (32,33). This is the reason why GLS might be partly responsible for unfavourable CV outcome in patients with altered circadian BP rhythm.

Our meta-analysis revealed several important findings that deserve further discussion: (i) LV structure is significantly changed among non-dippers in terms of increased LVMI; (ii) LV diastolic function is worse in non-dippers than in dippers; (iii) longitudinal LV mechanics, measured by GLS, was impaired in non-dippers compared with dippers. This finding is of relevance as no difference in LVEF was present between these groups. (iv) the progressive increase of night-time SBP values were related with GLS worsening in the pooled population ; (v) GCS was also more deteriorated in non-dippers than in dippers in the subgroup of patients with available data regarding multidirectional strain.

The majority of studies investigating LV remodelling in patients with different circadian BP patterns reported a significant deterioration in LV structure and diastolic function in non-dippers in comparison with dippers (21,22,26,28,29). This may be related to the association between nocturnal hypertension in non-dippers and LV remodelling induced by overactivated sympathetic nervous system, renin-angiotensin-aldosterone system, sleep apnoea syndrome. In addition, mechanical effects of increased arterial stiffness and peripheral resistances as a result of the elevated nocturnal BP in non-dippers may contribute to LV structural and functional changes documented in these patients. Our meta-analysis showed that pooled non-dipper and dipper groups had similar average day-time systolic BP, thus, the higher mean nocturnal systolic BP load associated to non-dipping can be considered the major determinant of the differences in subclinical cardiac damage found between the two groups.

Mechanical LV changes recently implemented in clinical studies may reveal subclinical and subtle impairments in LV function previously undetectable with conventional echocardiographic assessment. Although differences were noticed for longitudinal, circumferential and radial strains (25,26,28), major attention has been paid to GLS, which represents not only a robust echocardiographic parameter that reveals subtle impairment of LV function, but also a paramount predictor of adverse outcomes, including mortality. GLS turned out to be a more sensitive and reproducible parameter than conventional LVEF in general (34) and hypertensive population (19).

Our meta-analysis showed that GLS was significantly more deteriorated in non-dippers than in dippers with a significant correlation between GLS impairment and night-time SBP increments. Considering the fact that LVEF was similar between the observed groups, our findings indicate that GLS represents a better parameter of subclinical cardiac damage in hypertensive patients with different circadian BP patterns than LVEF. The impairment of GLS may be a predictor of HFpEF, which is frequently seen in hypertensive heart disease. This implies that a timely recognition of this unfavourable development of heart failure would significantly reduce the burden for the whole healthcare system. Moreover, GLS may improve the assessment of LV function during antihypertensive treatment, as recently demonstrated in our meta-analysis (35). A follow-up study investigating the prognostic value of GLS in hypertensive patients with different circadian patterns has not been conducted yet, assume that these results will not vary from those obtained in the whole hypertensive population (33).

The importance of GCS and GRS in hypertensive patients has not been extensively investigated, so far. Some studies reported an impairment of these parameters in hypertensive patients as a whole and in patients with non-dipping BP pattern, although the clinical relevance of these findings has not been evaluated. Cardiac magnetic resonance-derived GCS showed an incremental independent prognostic value in addition to clinical variables, LVEF, and late gadolinium enhancement in a large population of patients referred to this examination for multiple reasons (36). It is reasonable to hypothesize that similar results may be obtained also in hypertensive population.

Two main clinical implications of our meta-analysis may be taken into account: (i) GLS may represent a screening test for subclinical cardiac impairment in hypertensive patients at high risk for development of heart failure due to unfavorable circadian BP pattern, high levels of BP or other associated CV risk factors; and (ii) GLS may represent a useful tool for monitoring the efficacy of antihypertensive therapy and BP control throughout 24 hours.

Limitations

Several limitations of this meta-analysis should be mentioned. This type of analysis does not allow to adjust for cumulative BP values, BP variability, comorbidities, LVMI, E/e' and other clinical parameters that may influence the final results. Different definitions of non-dipping pattern based on night-time declines of systolic, systolic-diastolic, or mean BP were adopted by the authors. These methodological differences may have affected our results in some way. Classification of the night pattern based on a single ABPM is deemed insufficiently accurate, as its reproducibility over time is limited. The same issue can be raised for echocardiographic assessment of GLS as well as GCS that are affected by a challenging reproducibility and inter-vendor variability. It should be noted, however, that studies showed that GLS has better reproducibility than conventional echocardiographic parameters irrespective of vendor and level of echocardiographic training (37). Due to the cross-sectional design of the selected studies, a cause-effect relationship between the non-dipping and impaired GLS remains unproven.

Conclusion

Our meta-analysis including a large number of hypertensive patients clearly documented a significant negative impact of non-dipping status on GLS and GCS. This finding underlines the importance of novel imaging techniques, in addition to conventional echocardiographic parameters such as LVEF and E/e', in order to recognize subclinical cardiac damage and predict cardiac complications such as HFpEF. This meta-analysis also emphasizes the importance of ABPM for determination of circadian BP pattern and identify non-dipper subjects , who are under higher risk of adverse outcome. Finally, this study underlines the importance of GLS evaluation during routine echocardiographic studies in hypertensive patients at baseline and during follow-up as this parameter and the associated circadian BP pattern may identify patients at higher risk of adverse events.

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Figure Legend

Figure 1. Schematic flow-chart for the selection of studies.

Figure 2. Forest plot for standard means difference (SMD) of left ventricular ejection fraction (LVEF) in non-dippers and dippers (random model). Relative weight of each study is reported on the right side. CI= confidence intervals.

Figure 3. Forest plot for standard means difference (SMD) of left ventricular global longitudinal strain (LV GLS) in non-dippers and dippers (random model). Relative weight of each study is reported on the right side. CI= confidence intervals.

Figure 4. Forest plot for standard means difference (SMD) of the ratio of early (E) peak of mitral inflow velocity to mitral annular velocity (E/e' ratio) in non-dippers and dippers (fixed model). Relative weight of each study is reported on the right side.CI, confidence intervals.

Figure 5. Forest plot for standard means difference (SMD) of left ventricular mass index (LVMI) in non-dippers and dippers (fixed model). Relative weight of each study is reported on the right side.CI, confidence intervals.

Figure 6. Meta-regression analysis in non-dippers and dippers: bubble plot representing the correlation between average night-time systolic blood pressure (BP) and LV GLS.

Table 1. Summary of blood pressure measurement methods in 9 studies targeting left ventricular strain in non-dipper individuals.

Author (reference) **Publication year**	**Office BP: position and time of rest**	**Office BP: type of device**	**ABPM: type of device and time interval of recording**	**ABPM: recording quality criteria**	**ABPM: diagnostic criteria for ND**
Tadic[21], 2013	Sitting position 5 min rest.	Mercury sphygmomano-meter.	Schiller BR-102plus system. 15 min day-time 20 min night-time.	At least 70% of valid measurements.	Reduction of 10%, at least, in average SBP at night compared with average daytime SBP.
Kalaycıoğlu[22], 2014	Sitting position 5 min rest.	Mercury sphygmomano-meter.	Agilis-CD-ABPM 15 min day-time. 30 min night-time	At least 85% of valid measurements.	Reduction of 10%, at least, in average MAP at night compared with average daytime MAP.
Göksülük[23], 2017	Sitting position 10 min rest.	Aneroid sphygmomanometer,	Spacelabs Healthcare 90207 30 min day-time 45 min night-time.	At least 70% of valid measurements.	Reduction of 10%, at least, in average SBP at night compared with average daytime SBP.
Chen[24], 2018	n.a.	n.a.	Meditech ABPM-05 30 min over a 24-h period	n. a.	Reduction of 10%, at least, in average MAP at night compared with average daytime MAP.
Tadic[25], 2020	Sitting position 5 min rest	n.a.	Schiller BR-102 20 min day-time 30 min night-time	n.a.	Reduction of 10%, at least, in average SBP at night compared with average daytime SBP.
Chen[26], 2021	n.a.	n.a.	Spacelabs 90207 30 min day-time 60 min night-time	At least 80% of valid measurements.	Reduction of 10%, at least, in average SBP at night compared with average daytime SBP.
Efe[27], 2021	n.a.	n.a.	DiaSys Diagnostic Systems GmbH 15 min day-time. 30 min night-time	At least 70% of valid measurements.	Reduction of 10%, at least, in average SBP and DBP at night compared with average daytime values.
Sayed[28], 2022	n.a.	n.a.	GE Tonoport Healthcare 30 min day-time 60 min night-time	At least 80% of valid measurements.	Reduction of 10%, at least, in average MAP at night compared with average daytime MAP
Sun[29], 2022	n.a.	n.a.	Spacelabs 90207 30 min day-time 60 min night-time	n.a.	Reduction of 10%, at least, in average SBP at compared with average daytime SBP.

ABPM= ambulatory blood pressure ; BP=blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; ND=non dipping; SBP=systolic blood pressure

Table 2. Summary of 9 studies targeting the association between left ventricular strain, as assessed by speckle tracking echocardiography, and non-dipping.

Authors and year of publication	Type of study	Whole Sample size (n)	Setting	BP lowering drugs	Comorbidities/risk factors	NOS	Main Findings
Tadic [21], 2013	PNCS	147	Uncomplicated HTN	No	No	8	GLS was less negative (worse) in non dippers than in dippers.
Kalaycıoğlu [22], 2014	PNCS	86	Uncomplicated HTN	Yes	Type 2 diabetes	7	GLS was less negative (worse) in non dippers than in dippers.
Göksülük [23], 2017	PNCS	88	Uncomplicated HTN	Yes	No	7	GLS was less negative (worse) in non dippers than in dippers.
Chen [24], 2018)	PNCS	183	HTN	Yes	Type 2 diabetes; dyslipidemia	9	GLS was less negative (worse) in non dippers than in dippers.
Tadic [25], 2020	PNCS	142	Essential HTN	No	No	9	GLS was less negative (worse) in non dippers and reverse-dippers than in dippers
Chen [26], 2021	PNCS	72	Healthy normotensive indivduals	No	Prevalent smoking	7	Non-dippers had lower GLS than dippers after acute HA.
Efe [27], 2021	RNCS	70	Healthy normotensive indivduals	No	No	8	GLS did not differ between non-dippers and dippers.
Sayed [28], 2022	PNCS	100	Uncomplicated HTN	Yes	Type 2 diabetes; dyslipidemia, smoking	7	GLS was less negative (worse) in non dippers than in dippers.
Sun [29], 2022	PNCS	290	Uncomplicated HTN	Yes	Type 2 diabetes; smoking	7	GLS was less negative (worse) in non dippers than in dippers.

BP=blood pressure; GLS=global longitudinal strain; HA=high altitude; HTN=hypertension; NOS=Newcastle Ottawa Score ; PNCS=prospective non-randpmized case studies; RNCS = retrospective non-randpmized case studies

Table 3. Summary of clinical variables in 9 studies targeting left ventricular mechanics in non-dippers as compared to dippers.

	Sample size (N)		Age (years)		Men Prevalence (%)		BMI (kg/m2)		Day-time BP		Night-time BP	
Author (reference) **Publication year**	**ND**	**D**	**ND**	**D**	**ND**	**D**	**ND**	**D**	**ND**	**D**	**ND**	**D**
Tadic[21], 2013	61	86	48±9	49±10 ns	56	52 ns	26.6±3.1	26.2±2.8 ns	144±13/83±7	141±11/85±8 ns	132±12/81±9	123±10/75±8 **
Kalaycıoğlu[22], 2014	51	35	59±8	56±8 ns	49	34 ns	31.5±4.5	33.2±5.1 ns	141±16/79±10	143±14/81±10 ns	143±18/78±10	125±10/67±9 **
Göksülük[23], 2017	43	45	52±13	57±11 ns	65	58 ns	27.9±3.2	27.3±4.4 ns	144±10/85±10	148±11/87±8 ns	130±14/79±11	123±9/74±6 **
Chen[24], 2018)	117	66	47±13	45±11 ns	55	64 ns	26.4±4.2	25.6±3.9 ns	139±15/86±13	140±15/89±13 ns	133±15/83±12	122±12/77±11 **
Tadic[25], 2020	60	82	53±12	54±11 ns	58	55 ns	27.0±3.8	26.5±3.5 ns	138±17/83±11	140±15/83±10 ns	129±15/78±9	119±14/72±8 **
Chen[26], 2021	36	36	27±6	27±9 ns	58	67 ns	22.1±2.3	21.5±2.0 ns	120±11/72±8	124±7/7±35 ns	115±9/66±9	101±6/57±4 **
Efe[27], **2021**	30	40	53±11	49±14 ns	73	65 ns	n.a	n.a.	124±9/76±9	125±7/78±8 ns	119±9/70±9	108±6/68±7 ** (SBP)
Sayed[28], **2022**	71	29	51±11	51±9 ns	69	62 ns	33.8±6.3	32.5±7.5 ns	145±16/92±19	137±20/87±18 * (SBP)	138±17/84±13	119±13/71±9 **
Sun[29], 2022	179	111	52±13	49±12 ns	59	50 ns	27.1±3.6	27.0±3.7 ns	144±20/90±14	144±19/91±14 ns	139±20/85±15	122±17/76±13 **

BMI=body massa index; BP=blood pressure; D=dippers; ND=non-dippers; NS=not significant; SBP= systolic blood pressure

Data are presented as absolute numbers, percentage, mean±SD. * <.0.05 ,** < 0.001.

Table 4. Summary of echocardiographic variables in 9 studies targeting left ventricular mechanics in non-dippers as compared to dippers.

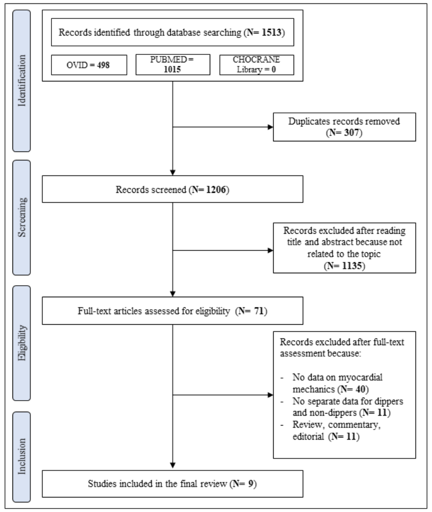
	LVMI		RWT		LVEF		GLS		E/e'	
Author (reference) **Publication year**	**ND**	**D**	**ND**	**D**	**ND**	**D**	**ND**	**D**	**ND**	**D**
Tadic [21], 2013	111±30 g/m²	101±28 ** g/m²	0.41±0.05	0.39±0.04 **	64±5 %	65±6 % ns	-17.3±1.8 %	-19.6±1.7% **	8.8±2.4	7.1±1.9 **
Kalaycıoğlu [22], 2014	117±29 g/m²	98±35 ** g/m²	0.46±0.08	0.43±0.07 ns	59±5 %	60±6 % ns	-17.8±1.5 %	-19.6±1.9% **	9.7±4.3	7.7±3.8 *
Göksülük [23], 2017	105±20 g/m²	97±19 * g/m²	0.45±0.06	0.42±0.05 **	63±3 %	62±3 % ns	-18.1±3.1 %	-20.5±2.4 **	n.a.	n.a.
Chen [24], 2018	101±29 g/m²	92±22 * g/m²	0.43±0.07	0.41±0.06 *	63±5 %	64±5 % ns	-18.2±3.0 %	-19.6±3.1%* *	8.6±2.3	7.6±2.0 **
Tadic [25], 2020	94±12 g/m²	85±10 ** g/m²	0.42±0.12	0.40±0.11 ns	64±4 %	63±5 % ns	-18.4±2.3 %	-20.1±2.7% **	9.4±2.6	8.4±2.3 ns
Chen [26], 2021	n.a.	n.a.	n.a.	n. a.	58±4 %	60±4 % ns	-19.7±2.3 %	-20.7 ±1.5% *	6.4±1.2	6.7±0.9 ns
Efe [27], 2021	97±22 g/m²	101±29 ns g/m²	n.a.	n. a.	60±3 %	60±4 % ns	-19.8±1.2 %	-19.9±1.5% ns	6.6±3.0	6.8±2.4 ns
Sayed [28], 2022	91±28 g/m²	76±20 ** g/m²	0.43±0.08	0.39±0.07 **	62±6 %	63±4 % **	-18.2±3.3 %	-22.4±3.3% **	8.5±2.0	6.8±1.5 **
Sun [29], 2022	108±29 g/m²	98±24 * g/m²	n.a.	n.a	59 % (58-61)	60% (59-65) ns	-18.0±3.5 %	-19.2±3.0%*	8.0 (6.2-10.6)	7.9 % (6.3-9.8) ns

D=dippers; E/e'= the ratio of early (E) peak of mitral inflow velocity to early (e') peak mitral annular velocity; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction;

LVMI=left ventricular mass index; LV=left ventricular; ND=non-dippers; RWT=relative wall thickness.

Data are presented as absolute numbers, percentage, mean±SD, and confidence intervals. * < 0.05 ; ** < 0.01

Figure 1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Screening
Eligibility
Inclusion
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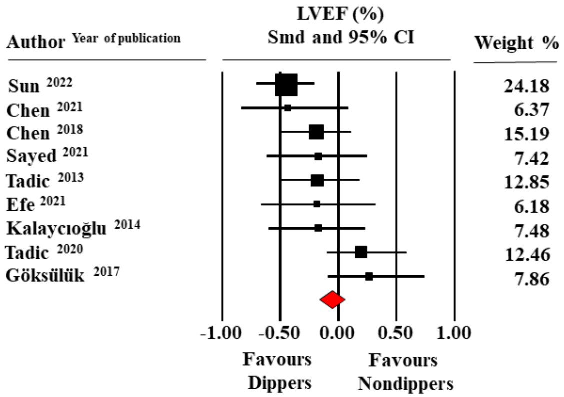
PUBMED = 1015
CHOCRANE Library = 0
Duplicates records removed (N= 307)
Records screened (N= 1206)
Records excluded after reading title and abstract because not related to the topic (N= 1135)
Full-text articles assessed for eligibility (N= 71)
Records excluded after full-text assessment because:
- No data on myocardial mechanics (N= 40)
- No separate data for dippers and non-dippers (N= 11)
- Review, commentary, editorial (N= 11)
Studies included in the final review (N= 9)

Figure 2



LVEF (%)
Smd and 95% CI
Author Year of publication
Weight %
Sun 2022
Chen 2021
Chen 2018
Sayed 2021
Tadic 2013
Efe 2021
Kalaycıoğlu 2014
Tadic 2020
Göksülük 2017
24.18
6.37
15.19
7.42
12.85
6.18
7.48
12.46
7.86
-1.00
-0.50
0.00
0.50
1.00
Favours Dippers
Favours Nondippers

Figure 3

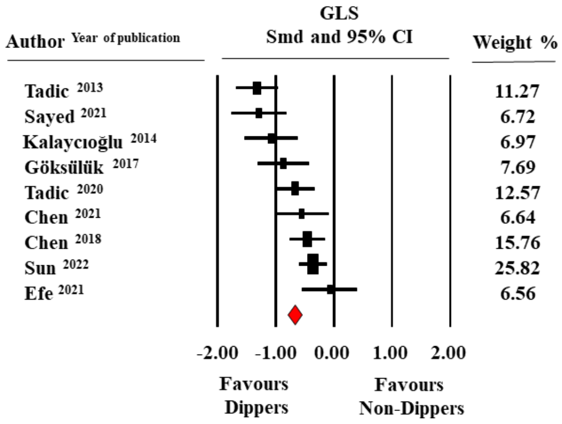
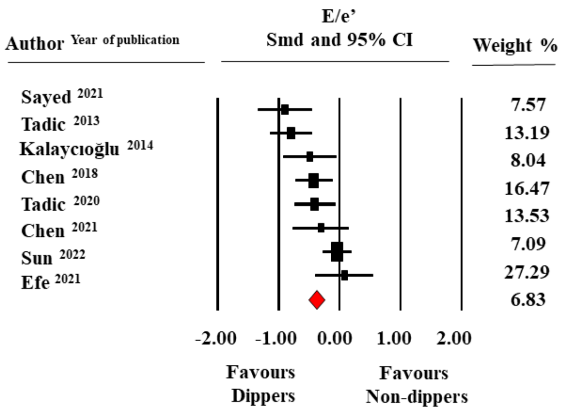
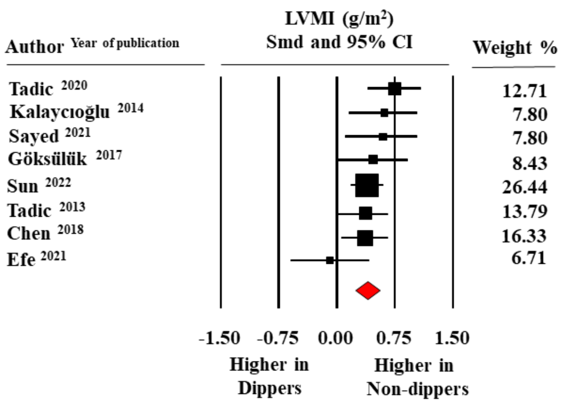

GLS
Smd and 95% CI
Author Year of publication
Weight %
Tadic 2013
Sayed 2021
Kalaycıoğlu 2014
Göksülük 2017
Tadic 2020
Chen 2021
Chen 2018
Sun 2022
Efe 2021
11.27
6.72
6.97
7.69
12.57
6.64
15.76
25.82
6.56
-2.00
-1.00
0.00
1.00
2.00
Favours Dippers
Favours Non-Dippers

Figure 4



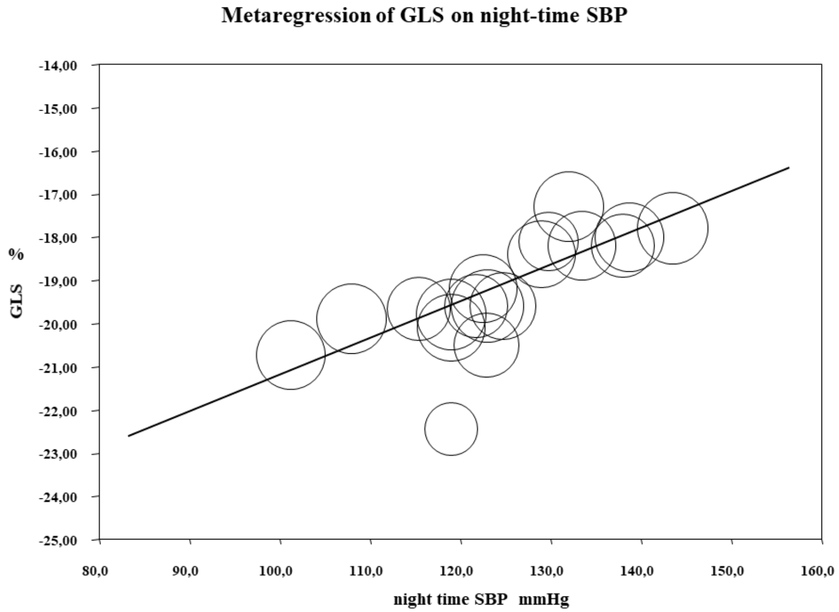
E/e'
Author Year of publication
Smd and 95% CI
Weight %
Sayed 2021
Tadic 2013
Kalaycıoğlu 2014
Chen 2018
Tadic 2020
Chen 2021
Sun 2022
Efe 2021
7.57
13.19
8.04
16.47
13.53
7.09
27.29
6.83
-2.00
-1.00
0.00
1.00
2.00
Favours Dippers
Favours Non-dippers

Figure 5



Author Year of publication
LVMI (g/m²)
Smd and 95% CI
Weight %
Tadic 2020
Kalaycıoğlu 2014
Sayed 2021
Göksülük 2017
Sun 2022
Tadic 2013
Chen 2018
Efe 2021
12.71
7.80
7.80
8.43
26.44
13.79
16.33
6.71
-1.50
-0.75
0.00
0.75
1.50
Higher in Dippers
Higher in Non-dippers

Figure 6



Metaregression of GLS on night-time SBP
-14,00
-15,00
-16,00
-17,00
-18,00
-19,00
-20,00
-21,00
-22,00
-23,00
-24,00
-25,00
GLS %
80,0
90,0
100,0
110,0
120,0
130,0
140,0
150,0
160,0
night time SBP mmHg