

Blood pressure lowering in patients with central hypertension: a randomized clinical trial

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Short title: Central hypertension clinical trial

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Total word count: 6888

Abstract

Background. Cuff blood pressure (BP) is recommended for guiding hypertension management. However, central BP has been proposed as a superior clinical measurement. This study aimed to determine whether controlling hypertension as measured by central BP was beneficial in reducing left ventricular mass index (LVMI) beyond control of standard cuff hypertension.

Methods. This multi-center, open-label, blinded-endpoint trial was conducted in individuals treated for uncomplicated hypertension with controlled cuff BP ($<140/90$ mmHg) but elevated central BP (≥ 0.5 SD above age- and sex-specific normal values). Participants were randomized to 24-months intervention with spironolactone 25 mg/day ($n=148$) or usual care control ($n=153$). The primary outcome was change in LVMI measured by cardiac MRI. Cuff and central BPs were measured by clinic, 7-day home and 24-hour ambulatory BPs.

Results. At 24-months, there was a greater reduction in LVMI (-3.2 [95%CI $-5.0, -1.3$] g/m^2 ; $p=0.001$) with intervention compared to control. Cuff and central BPs were lowered by a similar magnitude across all BP measurement modes (e.g., clinic cuff systolic BP -6.16 [$-9.60, -2.72$] mmHg and clinic central systolic BP -4.96 [$-8.06, -1.86$] mmHg; $p \geq 0.48$ all). Secondary analyses found that changes in LVMI correlated to changes in BP, with the magnitude of effect nearly identical for BP measured by cuff (e.g., 24-hour systolic BP $\beta=0.17$ [$0.02, 0.31$] g/m^2) or centrally (24-hour systolic BP $\beta=0.16$ [$0.01, 0.32$] g/m^2).

Conclusions. Among individuals with central hypertension, spironolactone had beneficial effects in reducing LV mass. Secondary analyses showed that changes in LV mass were equally well associated with lower measured standard cuff BP and central BP.

Clinical Trial Registration: <https://www.anzctr.org.au/> ACTRN12613000053729

Keywords: Blood Pressure; Hypertension; Arterial Pressure; Hemodynamics; Randomized Controlled Trial.

Nonstandard abbreviations

CMR, cardiac magnetic resonance imaging

LV, left ventricular

LVMi, left ventricular mass index

MRI, magnetic resonance imaging

Introduction

Standard upper arm cuff measured blood pressure (BP) is the principal method used for hypertension management.¹ However, this method does not always reflect the true intra-arterial BP,² nor always have sufficient sensitivity to detect BP changes in response to therapy at the level of the central aorta.³ Consequently, non-invasive methods based on analysis of peripheral BP pressure waveforms (e.g. from the radial or brachial arteries) and derivation of central BP⁴ were developed; the aspiration being to provide more sensitive measures of individual risk related to BP, as well as responses to antihypertensive therapy.⁵

Individuals with central hypertension have greater risk for cardiovascular events and death.⁶ Meta-analysis of cross-sectional data has also shown stronger associations between central systolic BP and markers of preclinical end-organ damage (i.e. LV mass index [LVMI] and carotid intima media thickness) compared with cuff systolic BP (e.g. pooled correlation coefficients for LVMI $r=0.30$ for central systolic BP versus $r=0.26$ for cuff systolic BP; $p<0.01$ for difference).⁷ The selective reduction of central BP might provide a means to discriminate the roles of cuff BP- and central BP-based treatment effects. This is notionally achievable by reducing aortic stiffness, which lowers LV afterload (central systolic BP) and reduces hypertensive LV hypertrophy, independent from standard cuff BP.⁸⁻¹⁰ Several studies have suggested that such effects may be possible by aldosterone blockade using spironolactone.¹¹⁻¹⁵ By lowering excess aldosterone, this agent could improve large artery wall stiffness through reduction in fibrosis that is independent from cuff BP lowering effects.^{12, 16}

In this trial we aimed to determine whether central BP lowering with spironolactone has cardiovascular benefits beyond that which can be explained by standard cuff BP. The study population were individuals being treated for hypertension who had controlled cuff BP but with elevated central BP according to population norms.¹⁷ Thus they represent a ‘central

hypertension' phenotype, theoretically at greater cardiovascular risk. Recently there has been a call for clinical trials to determine if controlling central hypertension with optimized antihypertensive therapy will be 'beneficial beyond the control of brachial [cuff] measured hypertension.'¹⁸ To date, three small, uncontrolled studies have reported stronger associations between changes in echocardiographic LV mass to changes in central BP, compared with standard cuff BP.¹⁹⁻²¹ The primary hypothesis for which this study is powered was that spironolactone treatment will be associated with significantly lower LVMI (a clinical outcome in which changes reflect the efficacy of antihypertensive treatment)^{22, 23} compared with a control group on standard treatment. Secondary hypotheses were that any observed reduction in LVMI will be associated with a parallel reduction in central, but not cuff, BP, and that central BP lowering will be associated with reduced aortic stiffness.

Methods

Study design. The data that support the findings of this study are available from the corresponding author upon reasonable request. The study rationale and design has been published previously.²⁴ The online supplement provides additional information to this section. Briefly, this was a multicentre, prospective, open-label, blinded-endpoint, parallel arm trial involving individuals with stable treated hypertension randomized to spironolactone 25 mg daily (intervention) or usual care (control) over 24 months at three Australian study sites (University of Tasmania, Hobart; The University of Queensland, Brisbane; The Australian National University, Canberra). Usual care was according to the standard practice of each participant's usual doctor. The primary outcome was LVMI measured by cardiac magnetic resonance imaging (CMR) at baseline and 24-months. Participants had standard cuff BP and central BP recorded at baseline, 6, 12, 18 and 24 months. These included research-grade 'clinic' BP, 7-day home BP and 24-hour ambulatory BP. Investigators were

blinded to the primary outcome variable and all other measures were recorded using automated methods with electronic data transfer. LV mass index was assessed by an expert blinded to the treatment allocation. Randomization was web based, centrally controlled, permuted block, and stratified by the site, two-dimensional echocardiographic LV mass (men $\geq 49\text{g/m}^{2.7}$ and women $\geq 45\text{g/m}^{2.7}$), sex and age (≥ 60 years and < 60 years). Participants were enrolled and assigned to interventions by research staff. The study was ethically approved (H0012445) and prospectively registered (ACTRN12613000053729). All participants provided written informed consent.

Study population. Full inclusion and exclusion criteria, as well as screening and monitoring protocols are presented in the supplemental material. Instructions to each participant's doctor regarding antihypertensive medication titration (other than for spironolactone) were only provided to ensure appropriate management of BP control (see supplement). Participants were individuals with uncomplicated hypertension screened and recruited from the general community. All were on stable therapy with controlled cuff BP ($< 140/90$ mmHg) but with relatively raised central systolic BP (SBP), deemed as central hypertension. Criteria for central hypertension were defined as seated central systolic BP ≥ 0.5 SD above age- and sex-specific normal values according to the largest published dataset of non-invasive central BP at the time the study was designed (see supplemental material criteria for raised central BP and Table S1).¹⁷ Screening for BP eligibility was undertaken using SphygmoCor XCEL device (AtCor Medical, Sydney, NSW).^{25, 26} Duplicate measures were acquired after 5, 10 and 15 minutes of seated rest and the average of any two consecutive measurements were used to determine BP eligibility.

LV mass index. CMR images were acquired using a 1.5T (Sonata Symphony, Siemens) or 3T (Signaexcite, GE) scanner using a standardized protocol. Serial contiguous short axis cine images were piloted from the vertical long axis and horizontal long axis of the right and left

ventricle (ECG gated, steady-state free precession imaging [True-FISP]; with temporal resolution 40 to 50 ms, repetition time 3.2 ms, echo time 1.6 ms, flip angle 60°, using 14 to 20 slices, thickness 7 mm) as per validated methods.^{27, 28} Analysis was performed off-line (Medis software, Leiden, The Netherlands and CVi42, Circle CVI, Calgary, Alberta) for the assessment of ventricular volumes (end-diastole, end-systole, stroke volume), ejection fraction and LV mass by an expert blinded to group allocation.

Standard cuff BP and central BP. Baseline and follow up visits of seated cuff BP and central BP were recorded with both SphygmoCor 8.1 radial tonometry (calibrated with XCEL cuff SBP and DBP) and SphygmoCor XCEL cuff-based methods. XCEL measures were recorded immediately on seating, and at 2, 5, 8 and 10 minutes. Radial tonometry was also recorded at 8 and 10 minutes, with the average of these duplicate measures used for analysis. Mobil-O-Graph BP monitors (I.E.M. Industrielle Entwicklung Medizintechnik GmbH, Aachen)²⁹ were used to record cuff and central BP over 24 hours (every 20 minutes during the day and 30 minutes overnight) according to recommended protocols.³⁰ Night-time was defined from patient diaries of sleep and wake times. In addition to ambulatory BP, each participant was provided with a Mobil-O-Graph BP monitor and instructions on how to measure home BP over 7-days, three times daily where possible (morning, midday and evening). Both the XCEL and Mobil-O-Graph methods record cuff BP using a standard, non-invasive automated technique in which BP is estimated using proprietary algorithms during a single cuff inflation and deflation cycle.³¹ Immediately after measurement of standard cuff BP, each device reinflates the cuff to record peripheral pressure waveforms and estimate central BP by application of proprietary generalized transfer functions. All BP data was electronically downloaded from the BP monitors. Central BP using the SphygmoCor devices were derived with calibration using SBP and DBP from the XCEL device (C1). Central BP using the Mobil-O-Graph device was derived with two calibration techniques: C1 using SBP

and DBP from the Mobil-O-Graph device; and C2 using mean arterial pressure and DBP from the Mobil-O-Graph device. C1 calibration is classified as type I device operation which always provides central SBP values lower than cuff SBP, whereas C2 calibration is classified as type II device operation which sometimes provides central SBP values higher than cuff SBP.³²

Aortic stiffness. Supine carotid-to-femoral artery pulse wave velocity was measured as per recommendations³³ using a SphygmoCor XCEL device (AtCor Medical, Sydney, NSW), which records femoral pulse waveforms by thigh cuff simultaneous with carotid pulse waveforms by handheld tonometry. The average of duplicate measures after 10 minutes supine rest was analyzed.

Sample size. Based on our pilot data of 25 mg/day spironolactone intervention,¹³ 300 subjects would offer more than 80% power at 2-sided p-value=0.05 to identify clinically significant regression of $\geq 9\%$ in LV mass ($82 \pm 20 \text{ g/m}^{2.7}$ vs $90 \pm 20 \text{ g/m}^{2.7}$) based on 2D echocardiography. However, CMR has greater accuracy and precision than echocardiography.³⁴ Therefore, we chose a conservative estimate of LV mass effect size based on CMR changes with 25 mg/day spironolactone reported by Edwards et al¹¹ where 145 participants per group would provide 80% power to detect a change in LV mass of 4 g (SD 13 g). We sought to randomize at least 145 participants for each group.

Statistical analysis. All analysis was performed on an intention-to-treat basis. Descriptive statistics were presented as mean (standard deviation) or n (percentage). Between-group differences over time were assessed by mixed regression analysis to account for repeated measures on individual subjects, adjusted for baseline age, sex, diabetes and the change in antihypertensive medications (using a random intercept for person; we had also *a priori* specified adjustment by duration of hypertension, but this could not be reliably determined from participants and was not included; diabetes was not a prespecified covariate but

included due to baseline imbalance between groups; **Table 1**). This model uses full information maximum likelihood estimation, which includes all available information for each participant. Specifically, the observed baseline data effectively corrects for the missing follow-up data. The assumption is that any missingness in the follow-up data is related to the baseline variables included in the model. The estimates produced are analogous to those produced from a multiple imputation model which includes the same variables.³⁵ The model included an interaction term of treatment x time (as a categorical variable), the coefficient from this interaction represents the difference in change from baseline to follow up between groups over 24-months. Marginal least-squared means are additionally presented for the primary outcome (LVMI). The same model was also used for analysis of hypothesis-generating secondary outcomes relating to LV mass, aortic stiffness, cuff BP and central BP variables (as outlined in **Table 2**). To assess whether there was a difference in the magnitude of effects in terms of changes in cuff BP and central BP, these measures were pooled and a further interaction was added to the above model. This expanded model contained the three-way (and all subsequent two-way) treatment by time by BP measure interaction term to indicate whether changes differed by BP measure. Additional analyses using derived variables for change from baseline to 24 months was undertaken for change-on-change analysis using linear regression analysis adjusted for baseline age, sex, diabetes and change in antihypertensive medications. These analyses were conducted for each group separately using LV mass index (Table S2) and aortic stiffness (Table S3) with the cuff BP and central BP predictor variables. Regression diagnostics were assessed for all linear and mixed-effects models. Due to missing data for the primary outcome (reasons detailed in results section) a sensitivity analysis for the primary outcome, LVMI, was conducted using multiple imputation with the following additional auxiliary variables: seated cuff SBP and DBP, body surface area and body mass index. This model used 15 imputed datasets and LVMI was passively

imputed from LV mass and body surface area. Analyses were conducted in R, version 4.0 (R Core Team (2021)).

Results

Recruitment and baseline measurements were conducted between 25th February 2013 and 11th March 2016, during which time 1409 individuals were screened for eligibility. Most were ineligible because they failed to meet BP inclusion criteria (n=802). Baseline data was missing for LVMi among 35 participants (18 control, 17 intervention) due to image quality issues and inability to calculate LVMi. Primary analysis was conducted for 131 intervention participants and 135 control participants who were randomized (**Figure 1**). From these, 91.4% completed 12-month assessments (90.5% intervention, 92.2% control) and 86.7% completed 24-month assessment (87.1% intervention, 86.3% control).

Mean age of all participants was 58 ± 9 years and 49% were women. Baseline characteristics of study participants are presented in **Table 1**. There was balance in baseline variables between groups, with the exception of higher prevalence of diabetes mellitus in the control group. There were two participants (1 per treatment arm) with left ventricular hypertrophy at baseline on the basis of CMR imaging. **Table 2** presents the between-group comparisons for the change in outcome variables from baseline to 24-months follow up. Compared to the control group, the study intervention was associated with a significantly greater reduction in LVMi. The adjusted values for LVMi from baseline to 24-months were 54.6 and 54.4 g/m² for controls and 54.2 and 50.9 g/m² for intervention, respectively. Intervention was also associated with greater reductions in BP levels. The magnitude of BP reduction within the intervention group were similar for cuff BP and central BP across all measurement methods (clinic, 7-day home and 24-hour ambulatory BPs; all comparisons $p \geq 0.48$). Results of the sensitivity analysis using multiple imputation were consistent with the primary analysis in

which there was a greater reduction in LVMI with intervention compared to control (-2.7 [95%CI -0.19,-5.19] g/m²; p=0.037). The **graphic abstract** provides a summary representation of the study findings. An example of similar changes is presented in Figure S1 across tertiles of the change in seated central systolic BP. There was no between-group difference for aortic stiffness from baseline to 24-months.

Table S2 provides a summary of the regression analyses for the associations between the change in LVMI and the change in cuff systolic BP and central systolic BP measures. For these analyses, the strengths of associations with change in LVMI associated with the study intervention were nearly identical for cuff and central systolic BPs, and this was irrespective of central BP calibration methods. Sensitivity and specificity for changes in cuff SBP and central SBP to predict changes in LVMI were similar (18%/70% and 14%/70%, respectively, with categorical cut offs of 5 mmHg and 6 g/m²). The regression analyses for the associations between the change in aortic stiffness and the change in cuff systolic BP and central systolic BP are provided in Table S3. The strength of associations with the change in aortic stiffness were similar between cuff and central systolic BPs. Table S4 provides a summary of correlation coefficients between LVMI and example brachial and central systolic BPs at baseline. In general, the correlations between LVMI and central systolic BP were stronger with C2 calibration, in keeping with other independent analysis of cross-sectional data. Table S5 provides information on adverse events. Participants in the intervention arm reported more adverse events, many of which were attributable to expected effects of spironolactone (for example, symptoms of gynecomastia or gastrointestinal discomfort). Dizziness or hypotension was reported at an intervention/control ratio of 17.5. None of the control group participants reported being prescribed with spironolactone by their doctor throughout the study period.

Discussion

To our knowledge this is the first study to examine the cardiovascular effects of spironolactone 25 mg/day among a selected population of individuals with controlled cuff BP (<140/90 mmHg) but raised central BP relative to expected population norms. Despite cuff BP control, these individuals are suspected to have higher risk for serious cardiovascular events associated with central hypertension,⁶ and thus could benefit with treatment targeted towards additional central BP lowering. As expected, spironolactone led to a significant reduction in LVMI; an endpoint associated with reduced rate of major cardiovascular events.²³ However, secondary analyses showed the intervention was associated with a similar lowering of cuff and central BP across all modes of measurement (clinic BP, 7-day home BP and 24-hour ambulatory BP). These analyses also showed that observed reductions in LVMI were similarly associated with changes in both cuff BP and central BPs regardless of central BP calibration modes. These findings raise the hypothesis that the beneficial effects of antihypertensive therapy on cardiac structure are equally well associated with lowering of standard cuff BP and central BP.

The study of Kampus et al found no significant change in aortic stiffness in spite of BP reduction with beta blockers nebivolol and metoprolol.²¹ This same finding was also observed in our study using spironolactone 25 mg/day, and is concordant with another randomized trial of intervention with higher dose spironolactone (50 mg/day) in people at risk or with type 2 diabetes, where aortic stiffness failed to reduce even with a mean systolic BP reduction of 7 mmHg over 6 months of treatment.³⁶ This lack of effect on aortic stiffness conflicts with the hypothesized 'de-stiffening' action of aldosterone blockade on large central arteries among people with hypertension.¹⁴ To the contrary, a trial of 115 patients with a hypertensive response to exercise found that 3 months spironolactone at 25 mg/d significantly

lowered both LVMI and aortic stiffness, but did not change cuff systolic BP, supporting direct effects of spironolactone on the heart and arteries that are independent of BP lowering.¹³ One other randomized clinical trial with aortic stiffness as an *a priori* outcome variable reported reductions in aortic stiffness that were statistically independent from the change in peripheral BP lowering, and this was in 112 patients with chronic kidney disease treated over 40 weeks with spironolactone 25 mg/day.¹¹ The explanation for the divergent effects of spironolactone on aortic stiffness and cuff BP is not known but could depend on patient characteristics, although this requires further examination.

Stronger associations between LVMI and central systolic BP compared with cuff systolic BP has been shown by meta-analysis of cross-sectional data.⁷ This observation is replicated in the baseline, cross-sectional data of this current study (see Table S4). Albeit noting this study was not powered for these tertiary analyses, the strongest coefficients were for central systolic BP derived using C2 calibration (see Table S4), which is also concordant with previous cross-sectional data on associations with LVMI.³⁷ However, these cross-sectional associations in which central BP appears to have greater clinical relevance, failed to replicate in longitudinal follow up within this current study. The same null effects were recently demonstrated in two other studies where the relationships with cardiovascular events and mortality were similar for central and cuff BP.^{38, 39} This lack of prognostic differentiation (as with this current study) is most likely explained by the high degree of correlation between cuff and central systolic BP when using C1 calibration to derive central systolic BP by the SphygmoCor device (e.g. $r=0.95$ ⁴⁰ as also found in this current study, see Table S4).

The different C2 calibration approach that is possible with the Mobil-O-Graph device used in this study results in lower correlation between cuff and central systolic BP (e.g. $r=0.83$ to 0.88), and central systolic BP from this method has been shown to independently predict mortality in one study of individuals with chronic kidney disease.⁴¹ The logic for C2

calibration is that the derived central systolic BP is potentially a more accurate reflection of the true central systolic BP if it were to be measured intra-arterially by catheter.³² On this basis we expected stronger associations between changes in C2 calibrated central systolic BP and LVMI in response to therapy, but in fact associations were similar to that of the change in cuff systolic BP as well as C1 calibrated central systolic BP (Table S2). Again, this lack of distinction between treatment effects of cuff BP versus central BP is probably because of high correlation between cuff and central systolic BPs as well as similar responses to therapy, which altogether appears to leave little opportunity for added value of central BP independent from standard cuff BP. Similar conclusions were reported from a post-hoc analysis among 470 older individuals with hypertension participating in the Second Australian National Blood Pressure Trial.⁴² Despite all the above, in special circumstances there may still be a role for central BP assessment.⁴³ An example might be if seeking to titrate antihypertensive therapy to the lowest effective dose,⁴⁴ albeit noting that controlled trials with hard clinical outcomes are yet to be conducted. Study intervention was associated with a relatively small reduction in LVMI (-3.2 g/m^2), but is likely to be clinically meaningful because change in LVMI is linearly related to risk for major cardiovascular events.^{45, 46} Moreover, our demonstration that LVMI was still subject to improved remodelling with additional therapy despite BP control under the 140/90 mmHg threshold is also in support of achieving lower cuff BP targets ($<130/80 \text{ mmHg}$) as recommended by recent hypertension guidelines.^{1, 47}

Study limitations. The study was not designed to detect difference in cuff versus central BP, and these comparisons could be under-powered and non-conclusive. This study used the surrogate cardiovascular endpoint of change in LVMI as the primary outcome over 24 months follow up. It remains uncertain if central BP management could improve longer-term residual risk for cardiovascular events and mortality among those with controlled cuff BP. Such a trial design would require thousands of participants, yet the prevalence of central

hypertension is low (i.e. 1.4 to 3.7%)^{6, 48} and recruitment attainment would be challenging. Indeed, even with less strict criteria to denote central hypertension in this trial, >70% of excluded participants failed to meet the BP inclusion criteria. Using an open-label design may have affected compliance and biased reporting of adverse effects with therapy among intervention participants, and we did not objectively confirm drug adherence using blood biochemistry. Nevertheless, we observed a significant reduction in BPs and LVMi among this group. Study participants were mostly Caucasian and healthy, which limits generalizability across diverse populations and diseases. Study findings may also not be generalized to antihypertensive agents other than spironolactone because different cuff versus central BP treatment responses could occur.⁵ The choice of spironolactone itself may not have been optimal for central BP lowering despite exerting unique effects (i.e., antifibrotic, anti-inflammatory) independent from BP lowering. Furthermore, there is variability in central BP device technology and principles of operation.⁴ Thus, findings may not be applicable to central BP methods other than those used in the trial. Since trial commencement we have learned that the XCEL device underestimates intra-arterial central systolic BP^{25, 26} and has proportional systematic bias with respect to measuring SBP amplification, which is overestimated at lower values.⁴⁹ This latter trait will have led to exclusion of potentially eligible participants at screening if it were to be based on intra-arterial SBP. Also, we did not perform late gadolinium enhancement CMR or T1 mapping to identify areas of fibrosis and responses to spironolactone intervention, which may have yielded important findings. Nor did we undertake diagnostic workup to determine if any participants had heart failure with preserved ejection fraction, a condition where spironolactone can be part of guideline-directed medical therapy. The average of duplicate readings of aortic stiffness were recorded according to standardized conditions recommended by expert consensus at the time of study commencement.³³ Later guidelines recommend taking a third reading and reporting the

median value if there is measurement variability.⁵⁰ The extent to which this different protocol may have yielded different results is unknown. Further, a 2017 update to the hypertension guidelines in the US, recommended targeting a cuff BP of 130/80 mmHg. If this criterion were applied to this study, all participants would have qualified for escalation of antihypertensive therapy and different central BP targets would have applied. Finally, while the mixed effects model accounts for missing data in the follow up outcome predicated on the assumption that the included covariates predict missing outcome values.

Perspectives. Among a cohort of middle-aged individuals (with near equal numbers of men and women) with treated and controlled hypertension but raised central BP, intervention with spironolactone 25 mg/day over 24-months was associated with significantly reduced LVMI and lowered both cuff and central BPs. Secondary, hypothesis-generating analyses showed that observed changes in LVMI were equally well associated with changes in both cuff and centrally measured BP values.

Acknowledgements. The study investigators are immensely grateful to the study participants for their contributions to this project. We also sincerely appreciate the technical and research assistant support during the trial provided from Tim Albion, Deborah Gilroy, Robert Howie, Erin Nash, Kim Kennedy, Wichat Srikusalanukul, Kavitha Velusamy, Megan Forsyth, Alex Vo, Johanne Neill.

Sources of Funding. The study was supported by a project grant from the National Health and Medical Research Council, Canberra, Australia (reference 103787). Some BP monitoring equipment was provided by AtCor Medical, Sydney, Australia and at low cost by I.E.M GmbH, Stolberg, Germany. The authors were solely responsible for study design and conduct; collection, management, analysis and interpretation of data, and; manuscript preparation, review and decision to submit for publication.

Disclosures. JES is principal investigator of a National Health and Medical Research Council of Australia partnership grant (S0026615) that includes a medical technology company that manufactures a central BP device, not referred to in this article. He has no personal financial conflicts relating to BP technology. SS is supported by a National Health and Medical Research Council of Australia Fellowship (GNT 1135894). None of the other authors declare a conflict of interest.

Novelty and Relevance

What is new?

- This study determined whether controlling central hypertension with spironolactone improves LV mass index (LVMI) beyond that which can be explained by cuff BP.

What is relevant?

- In patients with central hypertension, spironolactone reduced LVMI, and in secondary analyses these beneficial effects were equally well associated with lower measured standard cuff BP and central BP.

Clinical implications?

- Standard cuff BP using a validated, automated BP device remains the recommended method for hypertension diagnosis and management.

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Figures legend

Figure 1. Flow of study participants. BP, blood pressure; LVMi, left ventricular mass index

Graphic abstract. Intervention with spironolactone compared with usual care reduced left ventricular mass index (LVMi), cuff and central blood pressures, but did not change aortic stiffness. Bar graph show the between-group changes in cuff and central systolic blood pressure (SBP; with C1 calibration), and LVMi from baseline to 24-months (data is mean and 95% confidence intervals). For the secondary analyses, there was no difference in changes between cuff and central SBP responses. Similarly, the corresponding change associations with LVMi for cuff and central SBPs were near to identical (data is β and 95% confidence intervals). All analyses corrected for baseline age, sex, diabetes and change in antihypertensive medications.

Table 1. Baseline characteristics of study participants

Variable	Control (n=153)	Intervention (n=148)
Age (years)	58.0 (9.3)	58.4 (8.9)
Women n (%)	77 (50.3)	72 (48.6)
Caucasian ethnicity (%)	148 (96.7)	138 (93.2)
Body mass index (kg/m ²)	30.4 (5.9)	30.0 (5.3)
Current smokers n (%)	3 (2.0)	4 (2.7)
Diabetes n (%)	16 (10.5)	9 (6.1)
Total antihypertensive medications (daily defined dose)	2.5 (1.6)	2.4 (1.4)
Angiotensin-converting enzyme inhibitors	0.6 (1.1)	0.6 (1.0)
Angiotensin receptor blockers	1.1 (1.1)	1.1 (1.2)
Beta blockers	0.06 (0.3)	0.04 (0.2)
Calcium channel blockers	0.5 (1.0)	0.5 (0.7)
Diuretics	0.04 (0.2)	0.03 (0.1)
Lipid lowering medications n (%)	36 (24)	27 (18)
Screening cuff systolic blood pressure (mmHg)	137 (9)	136 (8)
Screening cuff diastolic blood pressure (mmHg)	80 (8)	80 (7)

Screening central systolic blood pressure (mmHg)	124 (8)	123 (8)
Screening central diastolic blood pressure (mmHg)	81 (10)	81 (7)

Data are mean (standard deviation), n (percentage) or percentage. Screening blood pressures are after 5 minutes seated rest using the SphygmoCor Xcel device.

Table 2. Baseline and 24-month follow up outcome variables between control and intervention participants

Variable	Group	Unadjusted values		Adjusted between-group effects	
		Baseline	24-months	difference in change (95% CI)	p value
Left ventricular mass index (g/m ²)	Control	52.2 (11.8)	51.3 (9.4)	-3.2 (-5.0, -1.3)	0.001
	Intervention	52.5 (12.7)	49.2 (11.6)		
Left ventricular mass (g)	Control	104 (30)	101 (25)	-5.7 (-9.4, -2.0)	0.003
	Intervention	105 (31)	98 (30)		
Aortic stiffness (m/s)	Control	8.17 (1.71)	8.19 (1.56)	-0.18 (-0.51, 0.15)	0.30
	Intervention	8.06 (1.65)	7.96 (1.36)		
Seated clinic cuff SBP (mmHg)	Control	128 (10.7)	129 (13.3)	-6.16 (-9.60, -2.72)	<0.001
	Intervention	128 (12.5)	122 (11.2)		
Seated clinic cuff DBP (mmHg)	Control	77 (9.2)	77 (9.3)	-2.76 (-4.88, -0.65)	0.011
	Intervention	78 (8.1)	74 (8.9)		
Seated clinic C1 central SBP (mmHg)	Control	115 (10.0)	116 (12.0)	-4.96 (-8.06, -1.86)	0.002
	Intervention	115 (11.1)	110 (10.0)		
24-hour cuff SBP (mmHg)	Control	131 (11.1)	129 (11.3)	-3.27 (-5.82, -0.71)	0.012
	Intervention	128 (9.4)	124 (10.4)		
24-hour cuff DBP (mmHg)	Control	80 (9.0)	78 (8.3)	-2.12 (-3.77, -0.47)	0.012
	Intervention	79 (7.7)	76 (7.6)		
24-hour C1 central SBP (mmHg)	Control	120 (10.2)	119 (9.8)	-2.96 (-5.34, -0.58)	0.015

	Intervention	118 (8.8)	113 (9.2)		
24-hour C2 central SBP (mmHg)	Control	134 (11.9)	133 (12.2)	-3.38 (-6.14, -0.61)	0.017
	Intervention	132 (10.7)	127 (11.6)		
Daytime cuff SBP (mmHg)	Control	134 (10.9)	133 (11.6)	-3.25 (-5.90, -0.61)	0.016
	Intervention	132 (9.6)	127 (10.9)		
Daytime cuff DBP (mmHg)	Control	83 (9.1)	81 (8.4)	-2.25 (-4.18, -0.32)	0.023
	Intervention	83 (8.1)	79 (7.9)		
Daytime C1 central SBP (mmHg)	Control	123 (10.2)	122 (10.0)	-2.83 (-5.31, -0.35)	0.025
	Intervention	121 (8.8)	116 (9.6)		
Daytime C2 central SBP (mmHg)	Control	136 (11.9)	134 (12.5)	-3.72 (-6.54, -0.90)	0.010
	Intervention	133 (10.6)	129 (11.6)		
Nighttime cuff SBP (mmHg)	Control	121 (13.7)	121 (13.6)	-4.26 (-7.36, -1.17)	0.007
	Intervention	118 (10.8)	113 (10.7)		
Nighttime cuff DBP (mmHg)	Control	72 (10.5)	71 (9.6)	-2.20 (-4.45, -0.05)	0.056
	Intervention	71 (8.2)	67 (7.4)		
Nighttime C1 central SBP (mmHg)	Control	112 (13.0)	111 (12.6)	-3.83 (-6.72, -0.95)	0.009
	Intervention	110 (10.6)	105 (9.7)		
Nighttime C2 central SBP (mmHg)	Control	130 (15.1)	129 (16.4)	-4.92 (-8.83, -1.00)	0.014
	Intervention	127 (14.0)	121 (13.1)		
7-day home cuff SBP (mmHg)	Control	136 (10.1)	135 (9.4)	-3.13 (-5.65, -0.61)	0.015
	Intervention	134 (9.3)	129 (10.6)		

7-day home cuff DBP (mmHg)	Control	83 (9.1)	81 (8.3)	-1.71 (-3.31, -0.11)	0.037
	Intervention	83 (8.1)	79 (7.7)		
7-day home C1 central SBP (mmHg)	Control	125 (9.4)	123 (8.5)	-2.94 (-5.21, -0.68)	0.011
	Intervention	123 (8.4)	118 (9.3)		
7-day home C2 central SBP (mmHg)	Control	139 (11.5)	138 (11.4)	-4.54 (-7.30, -1.79)	0.001
	Intervention	137 (11.6)	132 (12.6)		

Data is mean (SD) or (95% confidence intervals). SBP, systolic blood pressure; DBP, diastolic blood pressure; C1, calibration with cuff SBP and DBP; C2, calibration with mean arterial pressure and DBP using the Mobil-O-Graph device. Clinic BP refers to research grade resting BP. Data not presented for central DBPs as these are similar to the cuff DBPs at the corresponding measurement time. Data analysis corrected for baseline age, sex, diabetes and change in antihypertensive medications. Sample size for left ventricular mass index was n=135 control and n=131 intervention.

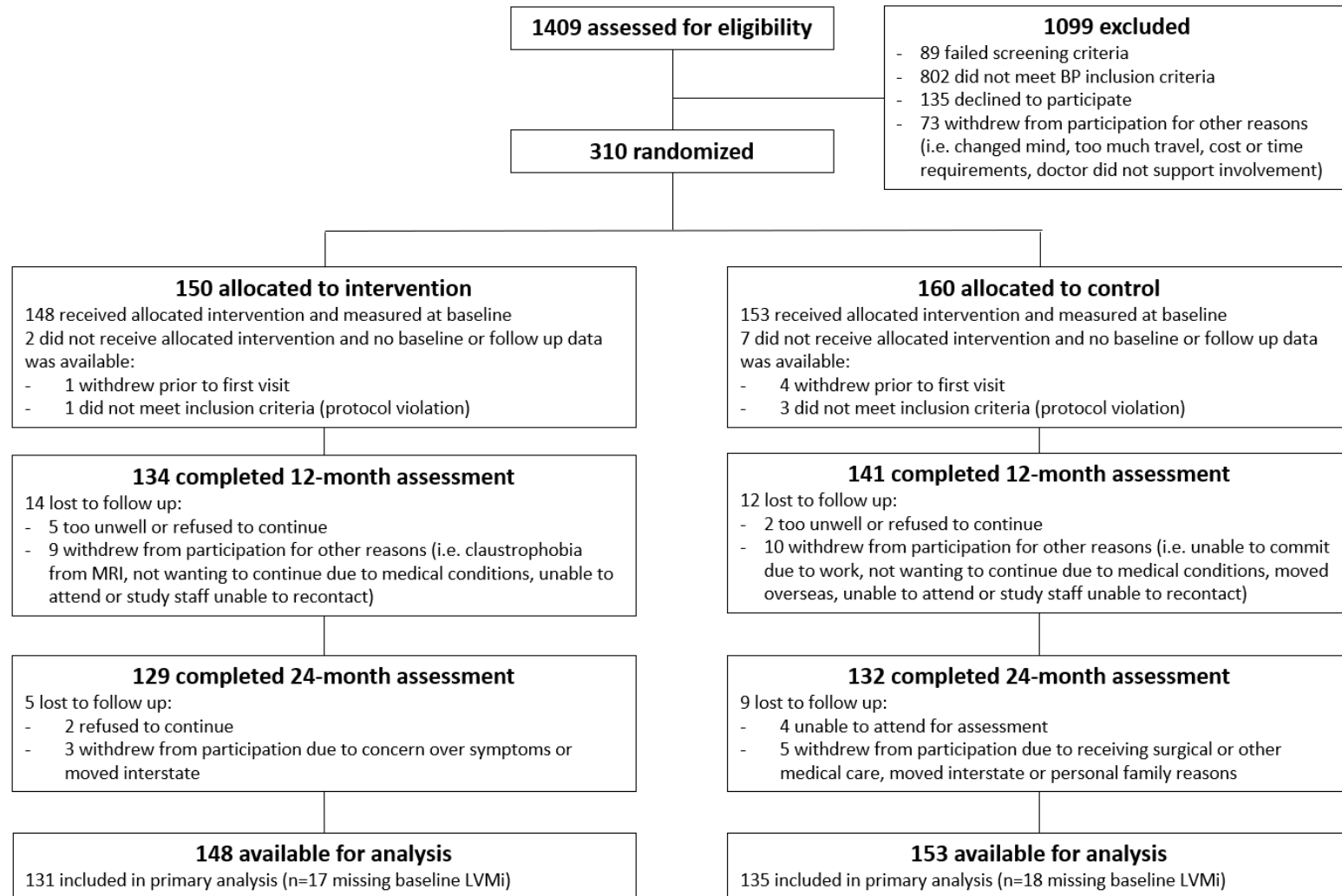
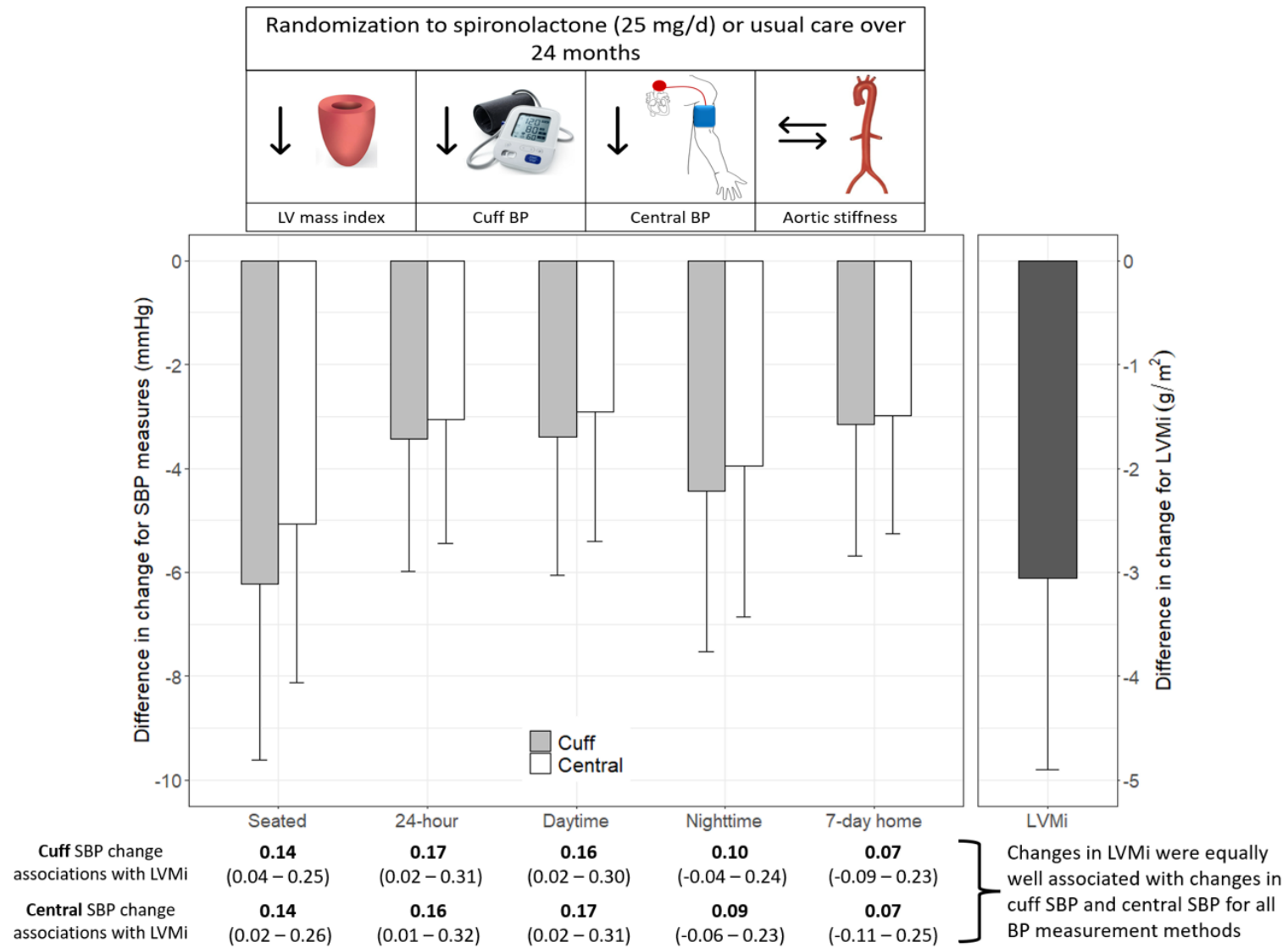


Figure 1



Graphical Abstract