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Title

Electrocardiographic detection of hypertensive left atrial enlargement in the presence of obesity: re-calibration against cardiac magnetic resonance.

Running Title

Obesity and detecting left atrial enlargement

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Key words: Obesity, ECG; Electrocardiograph; Left atrial enlargement; Hypertension; Cardiac magnetic resonance

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Abstract

Left atrial enlargement (LAE) has adverse prognostic implications in hypertension. We sought to determine the accuracy of 5 ECG criteria for LAE in hypertension relative to cardiac magnetic resonance (CMR) gold-standard, and investigate the effect of concomitant obesity. 130 consecutive patients (age: 51.4 ± 15.1 years, 47% male, 51% obese, systolic blood pressure: 171 ± 29mmHg, diastolic blood pressure: 97 ± 15mmHg) referred for CMR (1.5T) from a tertiary hypertension clinic were included. Patients with concomitant cardiac pathology were excluded. ECGs were assessed blindly for: 1) P wave >110ms, 2) P mitrale, 3) P wave axis <30°, 4) Area of negative P terminal force in V1 >40ms·mm and 5) Positive P terminal force in aVL >0.5mm. LA volume ≥55ml/m^2, measured blindly by CMR, was defined as LAE. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy and area under the receiver operator curve were calculated. The prevalence of LAE by CMR was 26%. All the individual ECG LAE criteria were more specific than sensitive, with specificities ranging from 70% (P axis <30^o) to 99% (P mitrale). Obesity attenuated the specificity of most of the individual ECG LAE criteria. Obesity correlated with significant lower specificity (48% vs 65%, P < 0.05) and a trend towards lower sensitivity (59% vs 43%, P = 0.119) when ≥1 ECG LAE criteria were present. Individual ECG criteria of LAE in hypertension are specific, but not sensitive, at identifying LAE. The ECG should not be used to excluded LAE in hypertension, particularly in obese subjects.

Introduction

The 2013 joint European Society of Cardiology and European Society of Hypertension guidelines for the management of arterial hypertension advise that a 12-lead electrocardiogram (ECG) should be acquired for all patients with hypertension(1). The ECG can show evidence of left atrial enlargement (LAE), which is an important predictor of cardiovascular mortality and morbidity. Indeed, performing an ECG in all subjects with hypertension is advised by the American Society of Hypertension and International Society of Hypertension (ASH/ISH) in their joint clinical practice guidelines, at least in part to assess for LAE(2). LAE has been demonstrated to be a marker of left ventricular (LV) diastolic dysfunction(3) and a predictor of the development of atrial fibrillation(4), congestive heart failure(5), stroke(6), myocardial infarction(7) and cardiac mortality(8). Detecting of LAE is therefore important in subjects with hypertension. All subjects with hypertension should have an ECG performed. LAE can be demonstrated on ECG. The first line imaging modality to structurally assess the heart in hypertension is the echocardiogram and this can be used to gauge the left atrial size. To date, LAE ECG criteria have been assessed against two-dimensional (2D) echocardiography reference standards(9)(10) (11)(12). However, echocardiographic measurements may be inaccurate due to limited acoustic windows and variation in image acquisition planes. This may be particularly troublesome in obesity subjects, with is a common comorbidity in subjects with hypertension. Furthermore, since the left atrium (LA) is not spherical, the assumption of a constant radius necessary for the M-mode or some 2D echocardiography measurements, e.g. the ellipsoid method, does not hold true, limiting the accuracy(13). Cardiac magnetic resonance imaging (CMR) has superior

spatial resolution compared to echocardiography and can consistently acquire LA images regardless of patient body habitus and, for these reasons, CMR is considered gold-standard for atrial assessment. Yet, there are few studies investigating the diagnostic performance of ECG LAE criteria against CMR. Furthermore, those existing studies were either in unselected subjects undergoing CMR and not in the context of hypertension(14) or have used an indexed LA volume of >28ml/m^2 to define LAE(15), which is from the echocardiogram literature(16) and is significantly lower than LA volume of 55ml/m^2 which is 2 standard deviation measurements above the mean of normal, healthy subjects from published CMR studies(17)(18)(19)(20). Thus, to date, ECG LAE criteria appear to have been validated against a variety of reference standards. As the ECG is often the first diagnostic investigation performed when assessing for LAE in hypertensive patients, and treatment decisions may be made on its results, understanding the diagnostic performance of the ECG at detecting LAE relative to CMR gold-standard in a cohort of hypertensive subjects is important.

Obesity and hypertension are common co-morbidities. The former has also been associated with LAE(21). However, to the best of our knowledge, no previous study has investigated the impact of obesity on the diagnostic performance of the ECG at detecting LAE. Consequently, our aim was to comprehensively evaluate the diagnostic performance of 5 ECG criteria for the detection of LAE, in a cohort of hypertensive patients with high LAE prevalence, relative to CMR derived measurements of LA volume. Additionally, we sought to determine the effect of obesity on the diagnostic performance of the ECG at detecting LAE.

Methods

Study population

In our institution, CMR is used routinely in the tertiary hypertension clinic setting to detect hypertensive end-organ damage and screen for potential secondary causes of hypertension(22). In this prospective study, we included all eligible, consecutive hypertensive patients referred for a CMR from the Bristol Heart Institute tertiary hypertension clinic, which has a catchment area of the South West of England, between January 2011 and February 2015 (**Figure 1**). Subjects were excluded from analysis if they exhibited any concomitant cardiac pathology, which could confound the aetiology of LAE, such as previous myocardial infarction, other cardiomyopathy and/or moderate-severe valvular heart disease.

Demographic and baseline clinical data were documented. The World Health Organization definition of obesity of body mass index (BMI) > 30kg/m^2 was used(23). The mean office systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were from repeated readings from both arms, where available, recorded with an appropriately-sized BP cuff at the time of ECG acquisition, following a period of 5 minutes seated rest.

Subjects provided written consent for their images to be used for research.
The study conformed to the governance arrangements for research ethics committees (REC).

ECG

A standard 12-lead ECG (scale: 10mm = 1mV, speed: 25 mm/s) was recorded supine, during quiet respiration. The analyzing clinician was blinded to all other CMR and clinical data. The presence of complete bundle branch block was an exclusion criterion. The 5 ECG LAE criteria evaluated were: 1) P wave >110ms, 2) P mitrale (notched P wave with inter-peak duration >40ms), 3) P wave axis <30°, 4) Area of negative P terminal force in lead V1 (NPTF-V1) > 40ms·mm and 5) Positive P terminal force in aVL (PPTF-aVL) >0.5mm(9)(24)(12)(25).

CMR protocol

CMR was performed with the subjects lying supine at 1.5T (Avanto, Siemens, Erlangen, Germany), with anterior 8-element and posterior 8-element body-array coils. Steady state free precession (SSFP) cines were acquired (Time to echo 1.07ms, temporal resolution 38.1ms, in-plane pixel size 2.0 x 2.0mm, matrix 156 x 192) with retrospective ECG-gating and breath-holding. The entire LV was imaged with short axis SSFP with slice thickness of 8mm and no slice gap. The standard 3 long-axis cines (4-chamber, 2-chamber and 3-chamber) were acquired at 60 degrees from each other. Additionally, late gadolinium myocardial enhancement (LGE) imaging was routinely acquired using an inversion-recovery fast gradient echo sequence, as well as a phase-sensitive inversion-recovery sequence, 10-15 minutes following 0.1mmol/kg intravenous gadobutrol (Gadovist, Bayer Pharma AG, Germany). Inversion times were optimized in each patient to ensure adequate nulling of normal myocardium. Subjects with subendocardial LGE consistent with previous MI were excluded.

CMR analysis

All CMR analysis was performed blinded to all other clinical and ECG data by an experienced CMR reader using dedicated CMR post-processing software (CMR42, Circle Cardiovascular Imaging Inc., Calgary, Canada). Maximum left atrial (LA) volume was measured at maximal atrial dilatation at left ventricular end-systole, as previously described (**Figure 2**)(14)(26). Briefly, maximum LA volume was defined as the image immediately preceding the opening of the mitral valves on SSFP cines. LA length was measured at maximum atrial dilatation from the posterior LA wall to the level of the mitral valve plane, parallel to the long-axis of the heart, in the 2-chamber and 4-chamber SSFP cines. The endocardial board of the LA was manually contoured at maximum atrial diastole in the apical 2-chamber and 4-chamber SSFP cines. The confluence of the pulmonary veins and LA appendage were excluded from planimetry measurements. The left atrial borders were delimited at the planes of the AV annulus and the junctions of venous inflow. LA volume was then calculated according to the biplane area-length method and then indexed to body surface area (BSA)(16)(27)(28), calculated using the Mosteller formula. LAE was defined as $\geq 55 ml/m^2$ which is 2 standard deviation measurements above the mean of normal, healthy subjects from published CMR studies(17)(18)(19)(20).

LVM was measured as described previously(29)(30). In brief, LV endocardial contours were generated on the short axis SSFP cines stack at end-diastole using previously validated(31) blood-pool threshold detection software (CMR42, Circle Cardiovascular Imaging Inc., Calgary, Canada). Epicardial contours were manually plotted. LVM was

derived by multiplying total myocardial volume, inclusive of trabeculae and papillary muscles, by myocardial specific gravity (1.05 g/ml), as previously described(29). LVM was indexed to BSA. Left ventricular hypertrophy (LVH) was defined as LVM/BSA >95th percentile of established CMR reference ranges (women = 77-78g/m^2 and men = 89-93g/m^2)(29).

Statistical analysis

All statistical analyses were performed in SPSS (v.21, Armonk, NY, USA: IBM Corp). Using the pooled prevalence of LAE of 32% from a recent systematic review of 10,141 subjects assessed by echocardiogram(32), an alpha error of 0.05 and a statistical power of 90%, the sample size for our study, accounting for the fact that CMR has been demonstrated to reduce the sample sizes by 6-fold compared to 2D echocardiogram when a power of 90% is employed(33), should be 100. Consequently, our final sample size of 130 subjects, from an initial 160 subjects who were screened, was sufficient for this study. Normally-distributed continuous variables were expressed as mean ± standard deviation and compared using unpaired Student's T test or one-way analysis of variance with *post-hoc* correction for multiple testing as appropriate. Categorical variables were expressed as percentages and interrogated with the Fisher's exact test. Specificity, sensitivity, negative predictive value (NPV), positive predictive valve (PPV) and accuracy were also calculated. Area under the receiver-operating curve (AUC-ROC) analysis was performed and to compare the diagnostic performance of the various ECG criteria. R values are for Pearson's correlation coefficient. Multivariate logistic regression

analysis was performed to identify independent predictors of ECG false positives and false negatives of LAE relative to CMR. Statistical significant was set at $P < 0.05$.

Results

Demographics

One hundred and sixty consecutive patients referred for CMR were assessed for eligibility. Thirty patients met the exclusion criteria (**Figure 1**), resulting in a final sample size of 130 (men: 47%, age: 51 ± 15 years). CMR evidence of LAE was present in 26% (n = 34) and obesity was present in 51% (n = 67) of the cohort. There were no significant differences between non -obese and obese cohorts for the following variables: age, gender, office SBP, office DBP, treatment with angiotensin converting enzyme inhibitor / angiotensin II receptor blocker or calcium channel blocker (**Table 1**).

Diagnostic performance of ECG criteria of LAE

Specificity was higher than sensitivity for all ECG LAE criteria (**Table 2**). Specificities ranged from 70% to 99% for the individual ECG criteria of LAE. However, the sensitivities ranged from 0% to 18% and the best performance on AUC-ROC was 0.502 (95^{th} CI: 0.389 – 0.616) for PPTF-aVL > 0.5 mm. A composite ECG criterion consisting of any positive individual ECG criteria for LAE had the highest sensitivity of 29% but a specificity of 48% and accuracy of 43%.

Obesity subgroup analysis of diagnostic performance of ECG criteria for LAE

The specificity was significantly lower in obese subjects compared to non-obese subjects for P wave < 30^{o} (non-obese: 83% vs obese: 64%, P < 0.05) and for the composite ECG criterion consisting of any positive individual ECG criteria (non-obese: 65% vs obese: 48%, P < 0.05) (**Table 3**). There were non-significant trends for lower specificity for NPTF-V1 > 40 ms.mm (non-obese: 89% vs obese: 78%, P = 0.06) and PPTF-aVL > 0.5 mm (non-obese: 96% vs obese: 88%, P = 0.07) for obese compared to non-obese subjects.

The AUC-ROC values were lower for all ECG criteria of LAE and for the composite ECG criterion consisting of any positive individual ECG criteria for obese subjects compared to non-obese subjects (**Table 3**).

Indexed LA size in subjects with positive ECG criteria

The mean indexed LAV were not significantly different between those subjects with positive ECGs compared to negative ECGs for all the ECG criteria for LAE investigated (**Table 4**). There was no correlation between the number of positive ECG criteria and absolute LAV (R = -0.05, P = 0.66) or index LAV (R = -0.09, P = 0.4). However, in obesity subgroup analysis, there were consistent trends towards larger absolute and indexed LAV in obese subjects who did not fulfill ECG criteria for LAE compared to obese subjects who did fulfill ECG criteria for LAE. In addition, obese subjects who did not fulfill ECG criteria for LAE had significantly large absolute LAV compared to similar non-obese subjects but these significant differences no longer persisted after indexing the LAV to BSA.

Prevalence of LAE in subjects without hypertensive left ventricular hypertrophy

Of the 130 hypertensive subjects, 35% (46/130) had LVH and 65% (84/130) did not have LVH. LAE occurred in 19% (16/84) of subjects without LVH. However, the prevalence of LAE amongst subjects with LVH (39%, 18/46) was significantly higher than amongst subjects without LVH (LAE and LVH: 39% vs LAE and no LVH: 19%, $P < 0.05$).

Predictors of false positive ECG criteria for LAE

Multivariate logistic regression analyses, accounting for age, gender and BMI, were performed to identify predictors of false positive and false negative ECGs for LAE (**Table 5**). For P wave axis < 30^{o}, female gender and increasing BMI were significant independent predictors of false positive ECGs for LAE relative to CMR gold-standard. Age, gender and BMI were not predictors of false negative ECGs for LAE.

Discussion

For the first time, we investigate the impact of obesity on the diagnostic performance of the ECG at detecting LAE as compared to CMR gold-standard in subjects with arterial hypertension.

We demonstrate that all the ECG criteria for LAE are poor at excluding LAE relative to CMR. Consequently, a normal ECG in a hypertensive patient has a high chance of being falsely reassuring for an absence of LAE, and is less specific for LAE in the presence of obesity. LAE is a marker of left ventricular (LV) diastolic dysfunction(3)

and a predictor for the development of atrial fibrillation(4), congestive heart failure(5), stroke(6), myocardial infarction(7) and cardiac mortality(8). Failing to identify LAE may alter an individual's cardiovascular risk estimation and theoretically could have treatment implications(1). Furthermore, in subgroup analysis of the LIFE study, Wachtell et al. found that prevention of AF during antihypertensive treatment may be improved by antihypertensive therapy that reduces LA size in addition to controlling blood pressure(34) and the effect of different antihypertensive agents on LA size has been previously been investigated(35).

The sensitivity of the ECG at excluding LAE has varied from 6 to 69% relative to echocardiography in previous studies(9)(10)(11)(12)(36). Regarding individual ECG criteria, we found higher sensitivity for P wave >110ms compared to previous echocardiographic studies(9)(10)(12)(25). We demonstrate higher sensitivity for P mitrale and NPTF-V1 > 40ms·mm compared to the most recent echocardiographic study of 261 randomly selected patients, which calculated LAV using a similar bi-plane atrial volume analysis from 2-dimensional echocardiography(36). Our findings are similar to those of Tsao et al. who performed ECG-CMR correlation, albeit in unselected patients(14).

However, it should be realized that a direct comparison between existing echocardiography studies and our work is prone to discrepancy. Estimation of atrial size with echocardiography, both by M-mode and 2-dimensional techniques, may be limited by poor acoustic windows and limited spatial resolution, which may underestimate left atrial dimensions. Indeed, the atrial size measured by CMR

measurement are recognized to exceed echocardiograph measurements of LAV by 14-37%(37)(38). As a result, the thresholds and accuracy for defining LAE will differ between studies using CMR and echocardiography as the gold-standard for LAV and, therefore, the proportion of individuals classified as having LAE will also differ which will impact on sensitivity and specificity analyses. Furthermore, differing allometric scaling of LAV between studies may be another important variable.

Whilst the ECG criteria generally have a high specificity for identifying LAE, we show for the first time that the diagnostic performance falls in the presence of obesity. This is potentially an important finding with clinical implications. The MONIC/KORA (monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg) study of 1,212 participants demonstrated that whilst both hypertension and obesity were predictors of LAE, obesity was numerically stronger(39). Furthermore, obesity hypertensive subjects had the largest indexed LAV(39). The lower specificity of the ECG at identifying LAE relative to CMR in our study in obese subjects to non-obese subjects means that the ECG risks missing LAE in subjects are at a particular high risk for LAE. A putative reason why the ECG is less able to detect enlarged atria in obese subjects is due to electrical insulating effects of excess subcutaneous adipose tissue, a phenomenon which has previously been postulated to explain the effect of obesity on reducing the diagnostic performs of the ECG at detecting left ventricular hypertrophy(40)(41). Imaging obese hypertensive subjects with echocardiography to establish a diagnosis of LAE may also be difficult because adipose tissue can attenuate the ultrasonic beam and reduce the diagnostic quality of the study.

In terms of the clinical implications of our study, we suggest that the ECG should still remain the initial investigation of choice for assessing for LAE as advised in International guidelines(1)(2). However, clinicians should take into account the patient's BMI when interrogating the ECG for LAE. For example, we show that the positive predictive value is significantly lower in obese hypertensive subjects compared to non-obese subjects for P axis < 30^{o} and PPTF-aVL > 0.5mm. The sensitivity of the investigation is also poor for both obese and non-obese subjects. It is clearly not practicable to perform CMR in all subjects with hypertension. Clinicians should consider investigating hypertensive patients with an additional modality, such as echocardiography in the first instance, to confirm the presence of LAE in obese subjects with positive P axis < 30^{o} and PPTF-aVL > 0.5mm criteria and in subjects where exclusion of LAE is important and may have therapeutic implications, for example in subjects with no other evidence of end-target damage where the demonstration of LAE would alter the cardiovascular risk sufficiently to alter treatment(1).

Finally, it is important to recognize that abnormalities in atrial conduction, and hence the electric sign recorded from the atria on the ECG in the form of the P wave can be independent of atrial size(42)(43). Multiple aetiologies may manifest with similar P wave abnormalities on ECG. As a result, in unselected populations, the ECG is unlikely to have good specificity for LAE as the changes may simply represent atrial abnormality rather than enlargement.

Limitations

Our clinical cohort study had a modest sample size of 130 patients. However, the increased accuracy and reproducibility of CMR relative to echocardiography increases the statistical power of the study. Furthermore, our study was in a selected population of well-characterised hypertensive subjects, and excluded patients with other concomitant cardiac pathology. Consequently, our results are more applicable to the hypertension community than most of the previous studies that have been in unselected populations.

We do not routinely estimate total body fat mass in our clinical practice and this variable could not be investigated. BMI has been used as a routinely recorded clinical surrogate. Theoretically, an increase in lean muscle mass could yield a BMI value in the obesity range but this is unlikely to have occurred in our cohort of patients.

In this non-invasive study, we were unable to adjust for certain variables that may alter P wave morphology, e.g. atrial pressure(43). The diagnostic accuracy of the ECG at detecting left ventricular hypertrophy in hypertension was not investigated in this study, but has been recently described(30).

Conclusion

We have recalibrated 5 ECG criteria for LAE against current non-invasive gold-standard CMR. The individual ECG criteria are more specific than sensitive at identifying anatomical LAE relative to CMR. However, the concomitant presence of obesity reduces the specificity for most ECG criteria for LAE. Clinicians need to be

aware of these differences when interpreting the ESC/ESH and ASH/ISH guidelines and tailor the ECG criteria they use accordingly taking into account the patient's BMI. Whilst the ECG may identify LAE, it has poor sensitivity and therefore the ECG should not be used in isolation to exclude LAE where this could have treatment implications. Obese hypertensive subjects are at risk of false positive and false negative results if the ECG is used to screen of LAE.

Conflicts of interest

None to declare

Summary Table

What is known about the topic

- 1) Detecting LAE in hypertension has prognostic and treatment implications.
- 2) The ECG can detect LAE and it has been validated against echocardiographic assessment of LA size.
- 3) The impact of obesity on the ECG detection of LAE has not previously been investigated.

What this study adds

- 1) We recalibrate 5 ECG criteria for LAE against non-invasive gold-standard CMR.
- 2) We show the ECG is more specific than sensitive at detecting LAE and that obesity reduces ECG specificity at detecting LAE.
- 3) We identify predictors of false positive and false negative ECG results with multivariate logistic regression analysis.
- 4) In hypertension, the ECG should not be used to exclude LAE

LAE = left atrial enlargement. ECG = electrocardiograph. LA = left atrial M = left ventricular mass. CMR = cardiac magnetic resonance.

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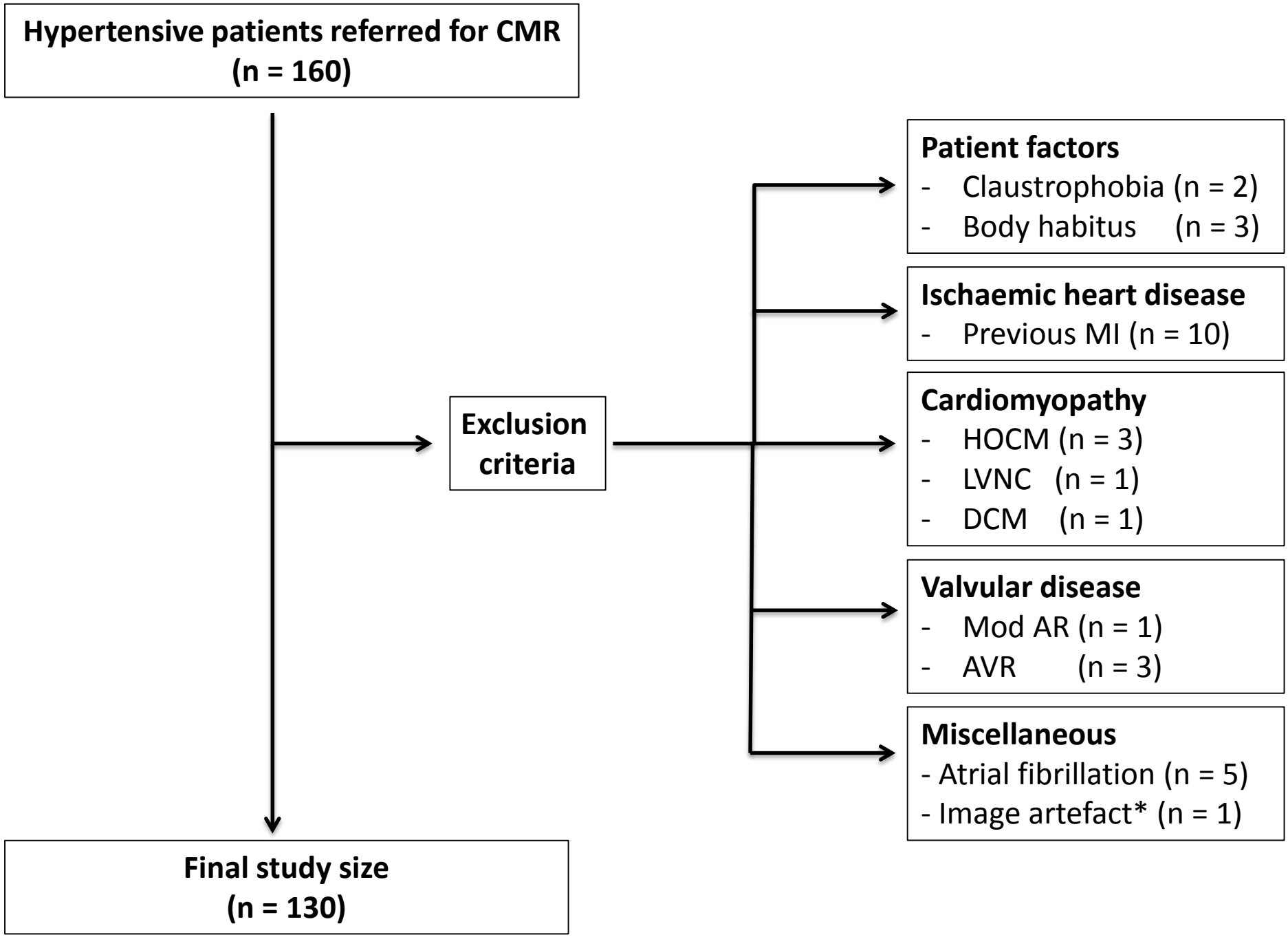
Figure legends

Figure 1. A flow chart demonstrating the study exclusion criteria and final sample size (n = 130). *Image artifact from implantable loop recorder device precluding volumetric assessment from LV short axis SSFP cine stack. CMR = cardiac magnetic resonance, MI = myocardial infarction (defined as subendocardial late gadolinium

enhancement on CMR), HOCM = hypertrophic obstructive cardiomyopathy (clinical and/or CMR diagnosis), LVNC = left ventricular non-compaction cardiomyopathy (CMR diagnosis), DCM = idiopathic dilated cardiomyopathy (CMR diagnosis), Mod AR = moderate aortic regurgitation, AVR = aortic valve replacement.

Figure 2. Cardiac magnetic resonance measurements from steady state free precession cine images of the maximal left atrial area (A1) and the length of LA (L1) on 4C-cine (A) and area (A2) and length (L2) on 2C-cine (B). Left atrial volume=$8/3\pi[(A1)(A2)/L$, where L is the shortest of either L1 or L2.


Hypertensive patients referred for CMR
(n = 160)
Exclusion criteria
Patient factors
- Claustrophobia (n = 2)
- Body habitus (n = 3)
Ischaemic heart disease
- Previous MI (n = 10)
Cardiomyopathy
- HOCM (n = 3)
- LVNC (n = 1)
- DCM (n = 1)
Valvular disease
- Mod AR (n = 1)
- AVR (n = 3)
Miscellaneous
- Atrial fibrillation (n = 5)
- Image artefact* (n = 1)
Final study size
(n = 130)

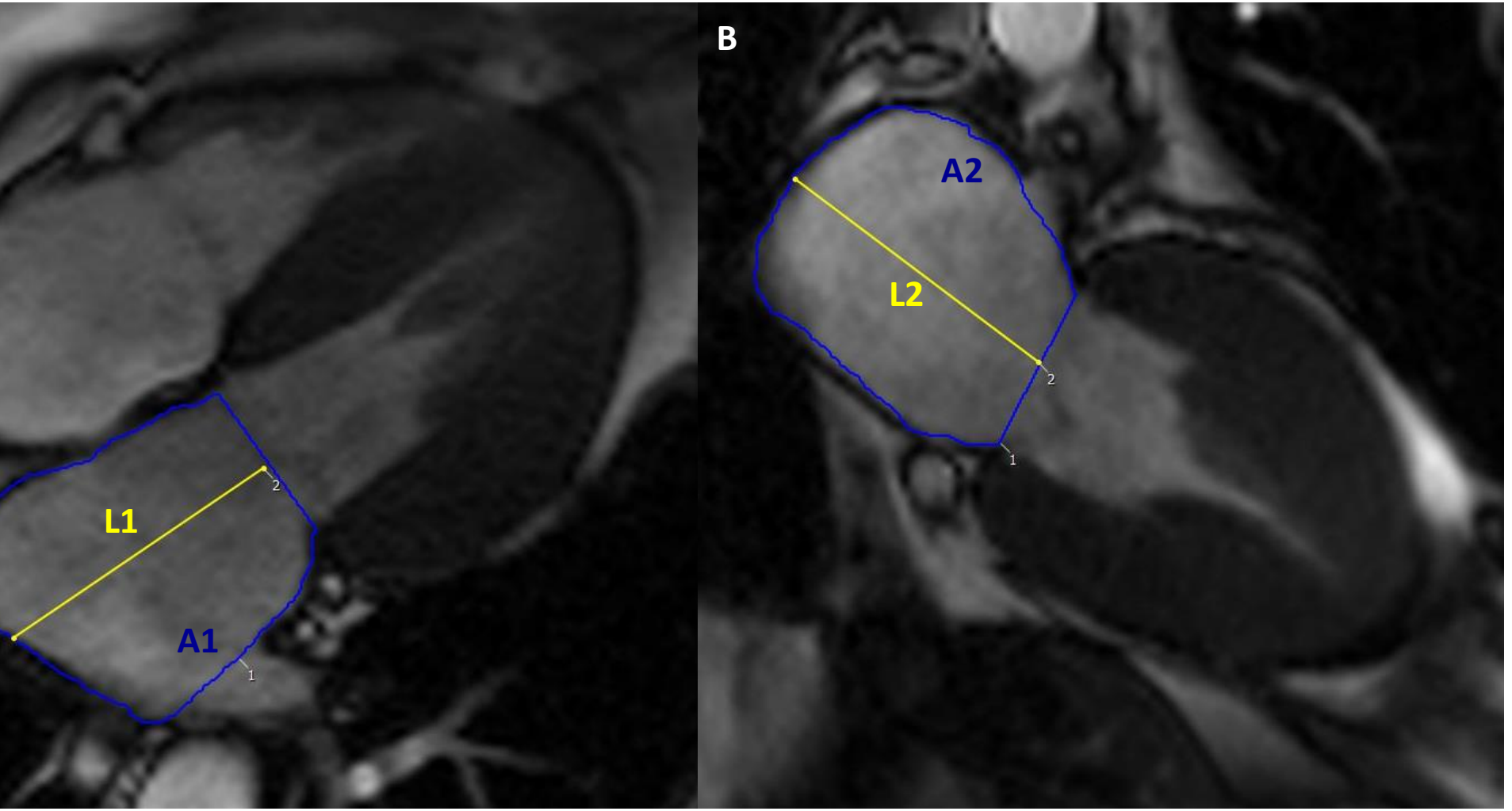

B
A2
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Table 1. Demographic, ECG and left atrial data for all subjects and obesity subgroups

	All (n = 130)	**Non-obese** (n = 63)	**Obese** (n = 67)	**P-value**
Demographic				
Age (year)	51 ± 15	51 ± 17	52 ± 14	= 0.76
Gender (% male)	47	52	42	= 0.23
BMI (kg/m^2)	31 ± 6	27 ± 3	35 ± 5	< 0.0001 *
Office SBP (mmHg)	171 ± 29	173 ± 29	170 ± 30	= 0.57
Office DBP (mmHg)	97 ± 15	98 ± 16	97 ± 14	= 0.73
ESH/ESC BP Grade 1 (%)	20	21	19	= 0.86
ESH/ESC BP Grade 2 (%)	22	22	21	= 0.86
ESH/ESC BP Grade 3 (%)	41	41	40	= 0.91
ACEi / ARB (%)	75	73	76	= 0.69
CCB (%)	53	51	55	= 0.62
ECG data				
P > 110ms (%)	9	10	9	= 0.91
P mitrale (%)	1	2	0	= 0.30
P wave axis < 30^o (%)	27	21	33	= 0.12
NPTF-V1 >40ms.mm (%)	17	11	22	= 0.09
PPTF-aVL >0.5mm (%)	9	6	10	= 0.41
Any ECG LAE criteria (%)	46	41	51	= 0.28
Left atrial size data				
Absolute LA volume (ml)	99 ± 33	93 ± 28	105 ± 14	< 0.05 *
Indexed LA volume (ml/m^2)	49 ± 15	49 ± 14	48 ± 16	= 0.90
LAE (%)	26	27	25	= 0.84

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, ESH / ESC = European society of hypertension / European society of cardiology, ACEi = ACE inhibitor, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker, LA = left atrial, LAE = left atrial enlargement

Table 2. Diagnostic performance of the various ECG parameters at detecting left atrial enlargement. (LAE = left atrial enlargement, ROC-AUC = receiver operator curve-area under curve, CI = confidence interval, PPV = positive predictive value, NPV = negative predictive values, ACC = accuracy)

	Prevalence ECG LAE (%)	ROC-AUC (95^{th} CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)
P > 110 ms	9	0.497 (0.384 – 0.610)	9	91	25	74	69
P mitrale	1	0.495 (0.382 – 0.608)	0	99	0	74	73
P axis < 30°	27	0.437 (0.328 – 0.546)	18	70	17	71	56
NPTF-V1 > 40 ms.mm	17	0.465 (0.355 – 0.576)	12	81	18	72	63
PPTF-aVL > 0.5 mm	8	0.502 (0.389 – 0.616)	9	92	27	74	70
Any ECG criteria for LAE	46	0.387 (0.279 – 0.495)	29	48	17	65	43

Table 3. Obesity subgroup analysis of diagnostic performance of the various ECG parameters at detecting left atrial enlargement. (LAE = left atrial enlargement, ROC-AUC = receiver operator curve-area under curve, CI = confidence interval, PPV = positive predictive value, NPV = negative predictive values, ACC = accuracy)

	Prevalence ECG LAE (%)	ROC-AUC (95th CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)
P > 110 ms							
Non-obese	10	0.515 (0.352 – 0.679)	12	91	33	74	70
Obese	9	0.519 (0.357 – 0.681)	12	92	33	75	72
P mitrale							
Non-obese	2	0.529 (0.364 – 0.695)	0	98	0	74	73
Obese	0	0.500 (0.340 – 0.660)	0	100	0	75	75
P axis < 30^{o}							
Non-obese	21	0.560 (0.395 – 0.725)	29	83 *	38 *	76	68
Obese	34	0.467 (0.309 – 0.625)	29	64	22	73	55
NPTF-V1 > 40 ms.mm							
Non-obese	11	0.504 (0.342 – 0.667)	12	89	29	73	68
Obese	21	0.478 (0.320 – 0.636)	18	78	21	74	63
PPTF-aVL > 0.5 mm							
Non-obese	6	0.537 (0.371 – 0.703)	12	96	50 *	75	73
Obese	10	0.469 (0.314 – 0.625)	6	88	14	73	67
Any ECG criteria for LAE							
Non-obese	41	0.620 (0.462 – 0.778)	59	65 *	38 *	81	63 *
Obese	51	0.475 (0.315 – 0.635)	47	48	24	73	48

* Non-obese vs Obese, $P < 0.05$

Table 4: Absolute and index left atrial volume in all subjects, non-obese subjects and obese subjects with positive and negative ECG criteria for LAE. (+ve = positive, -ve = negative, LAV = left atrial volume)

	All (n = 130)			**Non-obese** (n = 63)		**Obese** (n = 67)		
	(+ve) ECG	**(-ve) ECG**	**P-value**	**(+ve) ECG**	**(-ve) ECG**	**(+ve) ECG**	**(-ve) ECG**	**P-value**
P wave > 110ms (n)	12	118		6	57	6	61	
LAV (ml)	96 ± 33	99 ± 33	= 0.70	92 ± 30	93 ± 28	99 ± 39	106 ± 36	< 0.05 *
Index LAV (ml/m^2)	46 ± 15	49 ± 15	= 0.60	49 ± 16	49 ± 14	44 ± 14	49 ± 16	= 0.89
P mitrale (n)	1	129		1	62	0	67	
LAV (ml)	94	99 ± 33	= 0.89	94	93 ± 28	…	105 ± 36	< 0.05 *
Index LAV (ml/m^2)	52	49 ± 15	= 0.82	52	49 ± 14	….	48 ± 16	= 0.97
P wave axis < 30^o (n)	35	95		13	50	22	45	
LAV (ml)	99 ± 31	99 ± 34	= 0.98	98 ± 33	91 ± 27	99 ± 30	108 ± 39	< 0.05 *
Index LAV (ml/m^2)	48 ± 16	49 ± 15	= 0.74	51 ± 17	48 ± 13	46 ± 15	50 ± 16	= 0.72
NPTF-V1 > 40ms.mm (n)	22	108		7	56	15	52	
LAV (ml)	94 ± 32	100 ± 33	= 0.43	87 ± 8	93 ± 30	97 ± 38	107 ± 36	< 0.05 *
Index LAV (ml/m^2)	46 ± 14	49 ± 15	= 0.32	48 ± 8	49 ± 15	45 ± 16	50 ± 15	= 0.74
PPTF-aVL > 0.5 mm (n)	11	119		4	59	7	60	
LAV (ml)	92 ± 32	100 ± 33	= 0.46	90 ± 29	93 ± 28	93 ± 36	106 ± 36	< 0.05 *
Index LAV (ml/m^2)	45 ± 16	49 ± 15	= 0.37	48 ± 18	49 ± 14	43 ± 16	49 ± 16	= 0.78

* Obese (–ve) ECG vs Non-obsese (–ve) ECG P < 0.05

Table 5: Multivariate predictors of false positive and false negative ECGs for left atrial enlargement. (ECG = electrocardiogram, LAE = left atrial enlargement, CI = confidence interval, BMI = body mass index)

	Predictors of false positive ECG for LAE		**Predictors of false negative ECG for LAE**	
	β-coefficient (95% CI)	**P-value**	**β-coefficient 95% CI**	**P-value**
P wave >110ms				
Age (years)	1.03 (0.98 – 1.08)	= 0.23	1.00 (0.90 – 1.11)	= 0.99
Male gender	1.78 (0.41 – 7.64)	= 0.44	0.34 (0.02 – 5.83)	= 0.46
BMI (kg/m^2)	1.02 (0.90 – 1.15)	= 0.80	0.78 (0.57 – 1.07)	= 0.12
P wave axis <30°				
Age (years)	1.03 (1.00 – 1.07)	= 0.05	1.02 (0.95 – 1.08)	= 0.66
Male gender	0.25 (0.09 – 0.67)	< 0.01 *	2.23 (0.32 – 15.76)	= 0.42
BMI (kg/m^2)	1.11 (1.02 – 1.21)	< 0.05 *	1.02 (0.47 – 1.24)	= 0.82
NPTF-V1 > 40ms·mm				
Age (years)	1.00 (0.97 – 1.03)	= 0.89	0.99 (0.90 – 1.09)	= 0.82
Male gender	2.67 (0.86 – 8.25)	= 0.09	0.18 (0.01 – 2.81)	= 0.22
BMI (kg/m^2)	1.02 (0.93 – 1.11)	= 0.68	0.78 (0.59 – 1.05)	= 0.10
PPTF-aVL >0.5mm				
Age (years)	0.98 (0.93 – 1.03)	= 0.49	1.02 (0.93 – 1.11)	= 0.75
Male gender	0.24 (0.04 – 1.33)	= 0.10	2.23 (0.16 – 31.33)	= 0.55
BMI (kg/m^2)	1.05 (0.92 – 1.19)	= 0.31	0.89 (0.70 – 1.14)	= 0.36