Silent myocardial ischaemia in treated hypertensives with and without left ventricular hypertrophy

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Background **Silent ischaemia has been reported to be associated with an increased risk of myocardial infarction and sudden death in a wide range of patient groups. The aim of this study was to examine the prevalence of silent ischaemia in hypertensive patients with and without left ventricular hypertrophy (LVH).**

Methods **Twenty hypertensive patients participating in the Anglo-Scandinavian Cardiac Outcomes Trial with echocardiographic LVH (11 males, nine females), and 20 age, sex, blood pressure, and drug treatment-matched hypertensive patients without LVH underwent 24-h combined ambulatory blood pressure and electrocardiographic (ECG) monitoring. Ischaemic events were defined by the 'rule of $3 \times 1'$—asymptomatic ST-depression ≥ 1 mm (0.1 mV), lasting at least 1 min, and with a duration of at least 1 min between two events.**

Results **Thirteen patients with LVH had ischaemic events, whilst only four without LVH demonstrated ischaemia. Median numbers of events (seven versus zero; $P < 0.01$) and median total ischaemic area (0.25 versus 0 mV*min/day; $P < 0.01$) were significantly increased amongst hypertensive patients with LVH by comparison to those without LVH.**

Conclusion **Despite similar levels of established risk factors for atherosclerotic coronary artery disease, the prevalence of silent ischaemia was markedly increased amongst hypertensive patients with LVH by comparison to those with normal left ventricular dimensions. Ambulatory ECG monitoring may have a use in the identification of those at greatest risk of cardiovascular complications and sudden death, amongst hypertensive patients with persistent cardiac hypertrophy despite anti-hypertensive therapy.** ***Blood Press Monit*** **8:45–51 © 2003 Lippincott Williams & Wilkins.**

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Introduction

Left ventricular hypertrophy (LVH) is strongly associated with elevated blood pressure (BP) [1]. Hypertensive patients with LVH are at increased risk of all manifestations of coronary heart disease [2]; myocardial infarction, stable and unstable angina are all more common in these patients. This relationship persists even after correction for the contribution of hypertension and other risk factors for atherosclerosis [3].

Silent myocardial ischaemia, an ischaemic episode of the myocardium of which the patient is unaware, has been recognized as a clinical entity since the beginning of the last century ('angina sine dolore) [4]. Silent ischaemia, like angina pectoris, occurs where there is a discrepancy between myocardial oxygen demand and supply. In the vast majority of cases it is believed to be caused by atherosclerotic changes in the coronary vessels [5]. Studies, in both asymptomatic individuals and in patients known to have coronary artery disease, have shown that asymptomatic ischaemia, detected by ambulatory electrocardiographic monitoring, is associated with a worse clinical outcome [6,7]. Similarly in hypertensive patients, the prognostic value of ST-segment depression has been shown by Zehender and colleagues [8]. In this study hypertensive patients with transient ST-segment changes at baseline were four times as likely to suffer death or myocardial infarction, over a 36-month period, as were patients without ST-segment changes.

The prevalence of silent ischaemia in hypertensive populations without proven coronary artery disease has been reported to vary from 15–57% [9]. Both severity of hypertension and level of blood pressure control have been shown to influence prevalence rates [10]. It seems logical that those with LVH would also be more likely to demonstrate myocardial ischaemia, due to increased myocardial oxygen demand (greater mass of muscle) and reduced oxygen delivery (impaired vasodilator reserve [11], and elevated left ventricular intra-cavity diastolic pressures [12]). However studies to date, concerning the relationship between hypertrophy and

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ischaemia, have yielded conflicting results [13–17]. Hence the primary aim of this study was to compare the prevalence and severity of silent myocardial ischaemia in treated hypertensive patients with LVH, with that of well-matched hypertensive patients without LVH.

Methods

Participants

The study cohort consisted of 40 males and females, aged 40–80 years who were already participating in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [18]. ASCOT is a randomized trial comparing the long-term effects of a standard antihypertensive regimen (beta-blocker ± diuretic) with a more contemporary regimen (calcium antagonist ± angiotensin converting enzyme) on myocardial infarction and fatal coronary heart disease. Patients recruited to ASCOT were required to have essential hypertension (off-treatment BP $\geq$140/90). These patients are at high cardiovascular risk due to the requirement for additional risks, such as smoking, dyslipidaemia, diabetes mellitus, left ventricular hypertrophy, cerebral or peripheral vascular disease. Patients with a previous diagnosis of angina or myocardial infarction were excluded from the ASCOT study.

Further detailed cardiovascular assessments including, echocardiography, carotid wall ultrasonography, radial artery applanation tonometry, retinal photography, urine sampling and blood sampling, are being performed, after 1 and 3 years of ASCOT therapy, on 1000 patients recruited into ASCOT at two trial centres (St. Mary's Hospital, London and Beaumont Hospital, Dublin) [19]. From the patients who underwent these additional assessments in Dublin, 20 subjects with severe LVH [11 male, left ventricular mass index (LVMI) $\geq$ 145 g/m^2, and nine female LVMI $\geq$ 135 g/m^2] were identified. These were individually matched for race, sex, age ± 5 years, ASCOT drug treatment, and clinic systolic blood pressure ± 5 mmHg, with 20 patients, in whom there was no evidence of LVH (males LVMI $\leq$ 120 g/m^2 and females LVMI $\leq$ 115 gm^2). All subjects gave written informed consent. The Irish Medicines Board and the local research ethics committees approved the study protocol. The research was carried out in accordance with the Declaration of Helsinki (1996) of the World Medical Association.

Study design

This was a cross-sectional case–control study. In addition to undergoing echocardiography and applanation tonometry as part of the above-described ASCOT year one assessments, all 40 patients underwent simultaneous ambulatory blood pressure and electrocardiographic monitoring.

Echocardiography

Echocardiography was performed with the patient in the left lateral position, using an Advanced Technology Laboratories HDI-5000 scanner and a 3.5 MHz. transducer. Interventricular septal wall thickness (IVST), posterior wall thickness (PWT), and left ventricular internal diameter (LVID) were measured from the left ventricular short axis view using two-dimensional guided M-mode echocardiography. Measurements were made at end-diastole in accordance with the Penn convention. Three consecutive cardiac cycles were measured and average values obtained. Left ventricular mass (LVM) was calculated using the cubed formula:

$$\mathrm{LVM} = 1.04\times\left([\mathrm{IVST}+\mathrm{LVID}+\mathrm{PWT}]^3-\mathrm{LVID}^3\right) - 14\,\mathrm{g}$$

This was then divided by body surface area to give a value for left ventricular mass index (LVMI g/m^2).

Applanation tonometry

Central aortic pressures, timings of pressure peaks, the augmentation index and the Buckberg ratio were determined by applanation tonometry of the left radial artery using a commercially available computer system linked to the arterial tonometer (Sphygmocor; PWV Medical Ltd, West Ryde, Australia) [20]. Brachial artery blood pressure was measured according to the standard procedure for the ASCOT study [18]. The radial artery waveform was recorded immediately afterwards using the tonometer. This data was then processed by the computer to yield a synthesized central arterial waveform and the following pressure and timing parameters; aortic maximum systolic and minimum diastolic pressures; the duration from the start of waveform to the first peak/shoulder (T_1); the duration from the start of waveform to the second peak/shoulder (T_2); the time to return of the reflection wave of the aortic waveform (Tr); and the ejection duration (ED). Also calculated were the augmentation index (AI), the diastolic pressure time interval (DPTI), the systolic pressure time interval (SPTI), and the Buckberg ratio. The AI is used as a measure of the additional load imposed on the left ventricle as a result of wave reflection [21,22]. The DPTI and SPTI are determinants of myocardial blood supply and left ventricular load or myocardial demand respectively. Hence the Buckberg ratio (DPTI/SPTI) is regarded as an index of subendocardial viability [23,24].

Ambulatory blood pressure and electrocardiography monitoring

Twenty-four-hour combined ambulatory blood pressure monitoring (ABPM) and electrocardiographic ST-segment monitoring was performed with a CardioTens device (Meditech Ltd, Medical Electronics, Budapest, Hungary). This device provides ECG recording with real-time QRS detection and ischaemia analysis, heart rate variability analysis, and synchronized blood pressure monitoring. Blood pressure measurements were

performed at 30-min intervals. Subjects were instructed to keep the arm still and supported whilst blood pressure was being measured. Daytime blood pressure was defined as the average of readings taken between 0800 h to 2200 h and night-time blood pressure as the average of readings taken between 2200 h to 0800 h. For the purposes of ambulatory ST-segment monitoring, two leads were recorded, V2 and V5. The ST-segment shifts were measured within the interval from 60–80 ms from the J point. Ischaemia was defined by the 'rule of 3×1'; a horizontal or down-sloping ST depression of greater than 0.1 mV, that persists for more than 1 min, and is separated from other ischaemic episodes by at least 1 min. The hardcopy printouts of all automatically detected and recorded abnormal ST-segment shifts were later reviewed and verified visually by two doctors. Total ischaemic area (mV*minute/day) is the sum of the products of the magnitude of the ST depressions (mV) and their durations (min).

Statistical methods

Data were expressed as means ± SD, as median (range) or as percentages as appropriate. Analyses were performed with SPSS statistical package (SPSS Inc., Chicago Illinois, USA). A *P*-value < 0.05 was regarded as significant.

The primary objective of this study was to compare the prevalence of silent ischaemia in hypertensive patients with and without left ventricular hypertrophy. As both numbers of ischaemic episodes and total ischaemic area were not normally distributed, these were compared using Mann–Whitney tests. Comparisons of characteristics of those with and without silent ischaemia amongst hypertensives with and without left ventricular hypertrophy were performed by two-way ANOVA for quantitative parameters and by chi-squared tests for qualitative parameters.

Results

Participants

Baseline characteristics of the 40 patients are shown in Table 1. The distributions of gender, age, body mass index, and lifestyle habits were similar for those with and without left ventricular hypertrophy. Numbers of smokers, numbers of patients with diabetes mellitus, total and high-density lipoprotein cholesterol and clinic BP also did not differ between the two groups.

Prevalence of silent ischaemia

Seventeen subjects (eight men and nine women) had one or more silent ischaemic events. Only four (20%) of patients without LVH demonstrated silent ischaemia, and these had a total of 12 events. By contrast 13 [65% (six men and seven women)] with LVH had a total of 248 events of silent ischaemia. Figure 1 clearly illustrates both greater numbers of ischaemic events and greater total ischaemic areas in those with hypertrophy than in those with normal cardiac dimensions ($P < 0.01$).

Table 1 Baseline characteristics of those with and without left ventricular hypertrophy (LVH)

	Patients without LVH ($n = 20$)	Patients with LVH ($n = 20$)
Males	11 (55%)	11 (55%)
Age (years)	58.9 ± 8.3	59.5 ± 8.0
Weight (kg)	78 ± 13.3	81.2 ± 10.2
Height (cm)	166.6 ± 8.3	166.5 ± 9.3
Current smokers	9 (45%)	3 (15%)
Diabetes mellitus	2 (10%)	4 (20%)
Total cholesterol (mmol/l)	5.5 ± 1.4	5.0 ± 1.1
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.4
Clinic systolic BP (mmHg)	144.8 ± 15.4	146.4 ± 15.3
Clinic diastolic BP (mmHg)	85.2 ± 8.2	83.5 ± 7.6
LVMI (g/m^2)	95.3 ± 14.3	174.5 ± 31.1

Values are means ± SD or number of subjects (%). HDL, high-density lipoprotein; LVMI, left ventricular mass index.

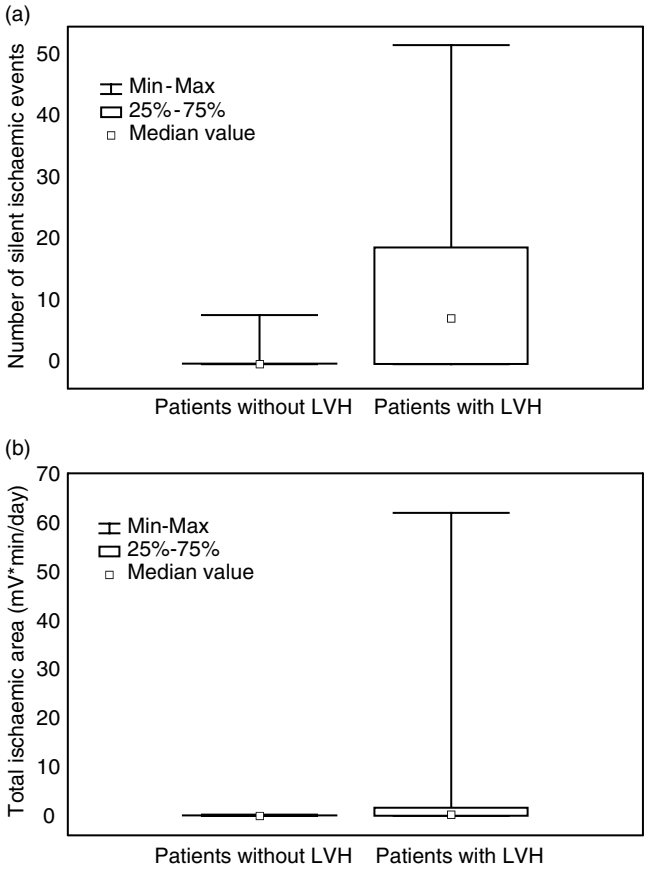
The distribution of silent ischaemia events showed similar circadian variation in both groups—most events occurred during daytime hours. Blood pressure and heart rate values tended to be higher during silent ischaemic events than daytime mean values in those with and without LVH.

Comparisons between patients with and without silent ischaemia

Silent ischaemia was more prevalent in older subjects ($P < 0.05$). Otherwise, there appeared to be no difference in levels of established cardiovascular risk factors between the hypertensive subjects in whom silent ischaemia occurred and those not suffering ischaemia (Table 2). Aspirin usage and numbers of antihypertensive agents used to control BP were similar across the four sub-groups.

Table 3 shows that daytime and night-time ambulatory heart rates were significantly higher in hypertensive subjects demonstrating silent ischaemia. This was observed in both those with and those without LVH. Night-time systolic pressures were elevated amongst those with LVH. Whilst the magnitudes of central aortic systolic and diastolic blood pressures appeared similar in all four groups (Table 4), the timing of the pressure waves did differ between those with and without LVH. Both T_1 and Tr were significantly prolonged in the hypertensives with LVH ($P < 0.01$ and $P < 0.05$ respectively). The augmentation index was significantly smaller in subjects with LVH by comparison with those without ($P < 0.01$). Whilst SPTI tended to be elevated, and the Buckberg tended to be reduced in those with silent ischaemia,

Fig. 1



Panel (a) ~ number of ischaemic events amongst patients with and without left ventricular hypertrophy (LVH). Panel (b) ~ total ischaemic area amongst patients with and without LVH.

Table 2 Lifestyle, medical history, and drug history of hypertensives with and without silent ischaemia

	Patients without LVH		Patients with LVH				
	Without SI	With SI	Without SI	With SI			
	$n = 16$	$n = 4$	$n = 7$	$n = 13$	Chi-squared values (χ^2)		
Males	9 (56.3)	2 (50)	5 (71.4)	6 (46.2)		1.1	
Smokers	6 (37.5)	3 (75)	3 (42.9)	0		1.93	
Diabetes	3 (18.8)	0	0	4 (30.8)		1.5	
Previous PVD	0	0	0	2 (15.4)		2.68	
Previous CVD	2 (12.5)	0	0	0		2	
Aspirin usage	6 (37.5)	1 (25)	3 (42.9)	7 (53.8)		1	
					ANOVA *F* values		
					LVH effect	SI effect	Interaction
Age (years)	57.9 ± 8.6	63.0 ± 6.1	54.9 ± 8.0	61.9 ± 7.2	0.5	4.45*	0.1
BMI (kg/m^2)	27.8 ± 4.1	29.1 ± 2.3	28.9 ± 3.3	29.5 ± 3.4	0.37	0.55	0.06
Total cholesterol (mmol/l)	5.4 ± 1.4	6.1 ± 1.7	5.0 ± 0.8	5.0 ± 1.2	2.31	0.53	0.67
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.3 ± 0.3	1.4 ± 0.4	1.2 ± 0.3	0.18	0.65	0.57
Number of antihypertensive agents	1.9 ± 0.8	2.3 ± 1.5	2.3 ± 0.5	2.3 ± 0.8	0.6	0.43	0.34

Values are means ± SD or number of subjects (%). LVH, left ventricular hypertrophy; SI, silent ischaemia; PVD, peripheral vascular disease; CVD, cardiovascular disease; BMI, body mass index; HDL, high-density lipoprotein. *F*, * $P < 0.05$.

Table 3 Comparison of clinic and ambulatory pressures between groups with and without silent ischaemia

	Patients without LVH		Patients with LVH		ANOVA *F* values		
	Without SI	With SI	Without SI	With SI	LVH effect	SI effect	Interaction
Clinic systolic (mmHg)	143.3 ± 14.2	150.5 ± 20.8	146.1 ± 17.8	146.5 ± 14.5	0.01	0.44	0.35
Clinic diastolic (mmHg)	84.9 ± 7.4	86.0 ± 12.4	85.3 ± 8.4	82.5 ± 7.3	0.28	0.45	0.42
Clinic heart rate (beats/min)	66.0 ± 12.8	66.0 ± 10.5	62.6 ± 10.3	66.0 ± 14.7	0.13	0.13	0.13
Daytime systolic (mmHg)	136.6 ± 10.7	132.6 ± 21.8	135.5 ± 19.7	138.5 ± 5.9	0.18	0.04	0.67
Daytime diastolic (mmHg)	78.5 ± 10.0	78.7 ± 16.3	75.9 ± 12.3	74.5 ± 7.6	1.26	0.48	0.04
Daytime heart rate (beats/min)	65.1 ± 11.1	80.8 ± 8.9	67.9 ± 12.0	70.6 ± 10.2	0.13	4.02*	2.71
Night-time systolic (mmHg)	123.8 ± 12.6	128.0 ± 12.8	131.4 ± 13.7	132.6 ± 14.1	3.33*	1.59	0.1
Night-time diastolic (mmHg)	68.6 ± 8.5	69.1 ± 3.6	71.0 ± 8.0	68.6 ± 5.3	0.12	0.06	0.3
Night-time heart rate (beats/min)	60.2 ± 10.0	71.1 ± 14.7	57.4 ± 9.5	62.6 ± 8.8	0.23	4.8*	0.6

Values are means ± SD; LVH, left ventricular hypertrophy; SI, silent ischaemia; *$P < 0.05$; **$p < 0.01$.

Table 4 Comparison of central aortic haemodynamics between groups with and without silent ischaemia

	Patients without LVH		Patients with LVH		ANOVA *F* values		
	Without SI	With SI	Without SI	With SI	LVH effect	SI effect	Interaction
Aortic systolic (mmHg)	133.3 ± 13.8	139.5 ± 18.9	137.0 ± 16.0	135.8 ± 15.8	0.12	0.21	0.44
Aortic diastolic (mmHg)	83.5 ± 9.4	85.5 ± 13.7	84.1 ± 11.9	81.2 ± 14.8	0.2	0.16	0.31
Ejection duration (ms)	347.0 ± 31.0	338.0 ± 15.2	343.0 ± 13.1	338.5 ± 35.0	0.03	0.40	0.04
T_1 (ms)	101.5 ± 5.4	97.3 ± 12.4	111.3 ± 6.2	109.2 ± 17.6	6.59**	0.55	0.07
T_2 (ms)	248.8 ± 23.0	241.8 ± 11.3	249.0 ± 19.5	237.9 ± 26.5	0.66	0.55	0.07
Tr (ms)	134.0 ± 7.2	126.3 ± 15.2	145.9 ± 8.6	153.1 ± 56.1	3.33*	0.73	0.38
Augmentation index (%)	38.6 ± 5.5	37.0 ± 5.0	32.1 ± 5.9	31.5 ± 9.1	9.35**	2.68	0.04
DPTI (mmHg*ms)	3905.0 ± 488.3	3838.3 ± 600.2	3978.0 ± 620.0	3781.8 ± 774.8	0.01	0.33	0.08
SPTI (mmHg*ms)	2298.3 ± 342.4	2631.5 ± 555.2	2292.3 ± 473.8	2394.5 ± 513.4	0.55	1.78	0.5
Buckberg ratio %	167.8 ± 33.4	149.5 ± 31.3	180.3 ± 49.3	166.3 ± 54.9	0.82	1	0.02

Data are given as mean ± SD. LVH, left ventricular hypertrophy; SI, silent ischaemia; T_1, the duration from the start of waveform to the first peak/shoulder; T_2, the duration from the start of waveform to the second peak/shoulder; Tr, the time to return of the reflection wave of the aortic waveform; DPTI, diastolic pressure time interval; SPTI, systolic pressure time interval: *$P < 0.05$; **$P < 0.01$.

neither trend even approached standard statistical significance.

Discussion

In this study, we have clearly demonstrated a dramatically increased prevalence and also greater severity of silent ischaemia amongst hypertensive patients with LVH by comparison to those with normal left ventricular dimensions. Transient silent ST depressions have been reported to be more common in patients with both end-stage renal disease [16] and diabetes mellitus [17], in the presence of LVH. By contrast a positive correlation between left ventricular mass, as measured by echocardiography, and the occurrence of ischaemia, using Holter monitoring, amongst patients with essential hypertension, has not been found [13–15].

Possible explanations for the disparity between the results of our study and those of previous studies include a different study design, heterogeneity of patient populations and continuation of antihypertensive treatment. We used a case–control design to compare the prevalence of ischaemia in patients at the extremes of the distribution of LVH. We, unlike many of the previous studies, did not exclude patients with baseline ST-segment changes. The coronary arteries of our patients, due to the ASCOT study requirement of additional cardiovascular risk factors, were highly likely to be atherosclerotic. At the time of echocardiography and ambulatory electrocardiography, our patients had received at least 1 year of antihypertensive therapy. Furthermore, we did not withdraw this antihypertensive treatment prior to ambulatory ST monitoring.

We found that age and both daytime and night-time heart rates were higher in those who demonstrated silent ischaemia. This is in agreement with previous studies, which emphasized the important role of heart rate and blood pressure in inducing silent ischaemia [10,24]. The Buckberg ratio, a measure of myocardial supply/demand ratio, and reportedly a useful index of sub-

endocardial ischaemia [23,25], tended to be reduced in those with silent ischaemia. The difference did not achieve statistical significance, perhaps due to small sample size, but it is also pertinent that assessment of central haemodynamics and the Buckberg ratio were performed in resting rather than in ambulant patients.

Given the well-recognized association of non-dipping circadian rhythms and greater BP loads with more severe target organ damage [26,27], it was not surprising to find higher nocturnal systolic pressures in the LVH group. However, the finding of a diminished augmentation index in those with hypertrophy was not anticipated. Large vessel atherosclerosis and cardiac hypertrophy usually occur in parallel [1]. Atherosclerosis leads to arterial stiffening, an increase in pulse wave velocity, early wave reflection, and thus augmentation of the central arterial pressure [21,22]. In this study, slowed left ventricular contraction in the presence of severe LVH, as evidenced by the prolonged T_1 and Tr, may have contributed to the reduced augmentation index of the patients with cardiac hypertrophy. This suggests that the augmentation index may not, in all situations, reliably reflect large vessel compliance.

Data from the Framingham population study suggests that hypertensive patients, in whom LVH reduces with antihypertensive treatment, may have a prognostic advantage over those who do not show a reduction [28]. Our study showed a dramatically increased prevalence of silent ischaemia in hypertensive patients with persistent cardiac hypertrophy after at least 1 year of combination antihypertensive therapy, LVH persisted in these patients despite relatively well-controlled BP. Given the results of the asymptomatic cardiac ischaemia pilot (ACIP) study [29], where mortality and myocardial infarction were significantly reduced through a strategy of revascularization by percutaneous transluminal cardiac angioplasty or coronary artery bypass grafting in patients with stable coronary disease, further studies are needed to address whether hypertensive patients with resistant LVH and with silent ischaemia should be managed by revascularization.

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