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A Sub-study of the ASCOT Trial

Left ventricular hypertrophy and silent ischaemia: a pilot study to examine the relationship in hypertensive patients

E O'Brien[1], C Gribbin[1], A Stanton[2], N Atkins[1] and S Lyons[1]
[1]*The Blood Pressure Unit, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland;* [2]*Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland*

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Introduction

Hypertension is a well-known risk factor that predisposes to the development of left ventricular hypertrophy (LVH), coronary heart disease and systolic and diastolic dysfunction. This complex of abnormalities is known as hypertensive heart disease and eventually leads to heart failure. Clinically, hypertensive heart disease manifests itself by anginal complaints and sometimes by silent ischaemia, arrhythmias and sudden death.[1] Ischaemic heart disease, once limited to a number of well-defined entities such as angina of effort, unstable angina, and myocardial infarction, must now be regarded as a much more complex and elusive entity. Silent ischaemia was one of the first of the new ischaemic syndromes to be described and its significance remains unclear.[2]

Patients who participate in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) are hypertensive and have not suffered a primary cardiac event, nor do they suffer from current symptomatic angina. Thus, ASCOT provides us with an opportunity to examine the relationship between silent ischaemia (without symptomatic ischaemia) and hypertensive heart disease, specifically left ventricular hypertrophy.

Background rationale

ST segment depression on ambulatory electrocardiography without patient awareness is a marker of what has been termed 'silent ischaemia'.[3] It can be described as real ischaemia without angina pain or other ischaemic symptoms in patients with coronary disease or coronary artery spasm.[4] There are two types of 'silent ischaemia',[5] type I (no previous myocardial infarction or angina pectoris) and type II (previous myocardid infarction or current angina pectoris).

Transient 'silent' ST depressions are associated with left ventricular hypertrophy in end-stage renal disease and diabetes mellitus.[3,6] We hypothesise that hypertensive patients with LVH have an increased incidence of 'silent ischaemia' when compared with hypertensive patients without LVH. This may result from various mechanisms, for example decreased coronary flow reserve, disease of small intramuscular arteries, 'inadequate' size of coronary arteries relative to hypertrophied myocardium, diminution of coronary flow during systole, compression of septal perforator arteries during systole, coronary artery spasm, and co-existent atherosclerotic coronary artery disease.[7]

The risk of infarction and sudden death is considerable in patients with 'silent ischaemia'.[8] It is not yet clear whether treatment improves outcome, although the limited available data suggest that it does.[8] Agents used to treat 'silent ischaemia' have included nitrates, beta-blockers and calcium channel blockers.[9] The Atenolol Silent Ischemia Study (ASIST) showed that atenolol treatment reduced daily life ischaemia and was associated with reduced risk for adverse outcome in asymptomatic patients compared with placebo.[10] The Canadian Amlodipine/Atenolol Silent Ischemia Study (CASIS) concluded that asymptomatic ischaemia during treadmill testing was more effectively suppressed by amlodipine, whereas ischaemia during

Correspondence: Prof Eoin O'Brien, The Blood Pressure Unit, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland

ambulatory monitoring was more effectively suppressed by atenolol. The combination was more effective than either single drug in both settings.[11]

Ambulatory ECG (Holter) monitoring is an effective way of measuring ischaemic events over a 24-h period. It has advantages over exercise testing in identifying the circadian distribution of silent ischaemia. Circadian distribution shows two peaks: on awakening and in the late afternoon periods.[12,13] It has been suggested that blood pressure variations, mainly elevations, may play an important role in triggering episodes of ST-segment depression.[13] Thus, the ideal way to record 'silent ischaemia' and its possible triggers (blood pressure elevation, heart rate variability) is using a combined ambulatory blood pressure and ECG monitor.

Objectives

- To demonstrate that hypertensive patients with left ventricular hypertrophy have an increased incidence of 'silent ischaemia' compared to hypertensive patients without LVH.
- To examine suggested triggers of 'silent ischaemia'; namely blood pressure and heart rate variations.

Study methods/design

A sample of patients from the ASCOT population at the Beaumont hospital site will be studied. In this pilot study 40 patients will be included. Twenty patients with severe LVH and 20 patients with no evidence of LVH will be selected. Patients in both groups will be matched for race, sex, age ±5 years, medications, and systolic blood pressure ±5 mm Hg.

Left ventricular hypertrophy will be assessed during echocardiography examination using the estimation of left ventricular mass equation.[14] Using the Echo data of 500 patients taking part in the phenotyping sub-study, we will assess patients according to left ventricular mass index (LVMI). We will select 20 patients for the no-LVH group and 20 patients for the severe LVH group.

All 40 patients will undergo 24-h-combined ambulatory blood pressure and ECG monitoring with heart rate variability analysis on a single occasion following year 1 echocardiography. We propose to use the CardioTens device. This device allows for recording of ischaemic events on ECG while simultaneously triggering an extra sequential blood pressure measurement, thus providing EGG data relating to the ischaemic event and corresponding blood pressure data.

The most generally accepted definition of an ischaemic event within the context of ambulatory ECG monitoring is the 'rule of 3×1" which is recommended by the American Heart Association. A transient ischaemic event, during ambulatory ECG monitoring, is said to have occurred if a horizontal or descending ST depression occurs with a measure $\geqslant 1$ mm (0.1 mV) within the interval of 60 to 80 ms from the J point, if it lasts at least 1 min, and if there is a duration of at least 1 min between two events. The ischaemic event begins when ST depression reaches 1 mm, while the event is considered finished when the value falls below 1 mm.

To be included in this sub-study patients must have already met the inclusion criteria for the main ASCOT study; male patients with $\leqslant 80\ gm^{-2}$ and female patients with $\leqslant 70\ gms^{-2}$ as assessed during echocardiography examination will be suitable for the no-LVH group. Male patients with LVMI $\geqslant 150\ gm^{-2}$ and female patients with $\geqslant 130\ gm^{-2}$ will be suitable for the severe LVH group. Patients with borderline/mild/moderate LVH (LVMJ between 81 and 149 for males and between 71 and 129 for females) will not be included in this pilot study.

This sub-study is designed to have minimal impact on the main ASCOT study. Participating patients will undergo 24-h combined ambulatory blood pressure and Holter monitoring on a single occasion. This should result in little discomfort or inconvenience and the only additional expense is an extra clinic visit to return the monitor. No additional blood sampling or a drug-free period is required. There are no discrete ethical implications. The 40 participating patients will be asked to sign a modification of the standard ASCOT documentation which will include reference to the ambulatory monitoring procedure and the risk of discomfort and inconvenience.

Discussion

The natural course of silent ischaemia, type I (no previous myocardial infarction or angina pectoris) is poorly defined. We hypothesise that patients with hypertensive LVH have an increased incidence of silent ischaemic episodes. The CardioTens device provides us with the ability to record all episodes of transient ischaemia, over a 24-h period while also examining the possible triggers of ischaemia namely, blood pressure elevation and heart rate variability.

Hypertensive patients with LVH are at increased risk of cardiovascular complications and sudden death, as are patients with silent ischaemia.[2] This sub-study is a unique opportunity to examine a possible relationship and assess the significance of any association.

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