Ischaemic heart disease in young hypertensive women

A MACKAY, A M M CUMMING, J J BROWN, A F LEVER,
J I S ROBERTSON

From the Medical Research Council Blood Pressure Unit, Western Infirmary, Glasgow

SUMMARY The association between hypertension and ischaemic heart disease was explored in a retrospective analysis of 50 severely hypertensive premenopausal women (presenting diastolic pressure ≥ 120 mmHg) under 45 years of age who were seen over a seven-year period. Twenty-two per cent of these patients had angina pectoris, and 38 per cent had Minnesota code 4-1 or 5-1 changes on the resting electrocardiogram. The contribution of other risk factors, including smoking habits, was assessed: 72 per cent of the patients smoked; significantly less smoking was found among two groups of age-matched women with less severe hypertension [diastolic pressures of 90 to 104 mmHg ($n=50$) and 105 to 119 mmHg ($n=50$)]. In these latter groups, only one patient had angina pectoris and none had 4-1 or 5-1 changes on the electrocardiogram.

Coronary heart disease is rare in premenopausal women under 45 years of age.^{1 2} In the 20-year follow-up of the Framingham study¹ only one case of ischaemic heart disease was reported in premenopausal women under 45 years of age. Oliver,³ over an 18-year period, collected a personal series of 145 female patients who were under 45 and who had electrocardiographic abnormalities supporting a diagnosis of coronary heart disease; 64 had angina pectoris and 81 had suffered a myocardial infarction. He identified three major risk factors—raised serum cholesterol, hypertension, and excessive cigarette smoking. Variable importance has also been attached to other possible influences, including oral contraceptives,⁴ diabetes mellitus,⁵ and a history among first degree relatives of ischaemic heart disease, hypertension, or diabetes mellitus.⁶

The present study explores the relation between hypertension and ischaemic heart disease in 150 young women.

Patients

All patients were premenopausal (menopause is defined as absence of the menses for at least one year¹) and under 45 years of age at presentation. The first group of 50 patients were consecutive referrals to the MRC Blood Pressure Unit between 1972 and 1978. Recumbent diastolic blood pressures (fifth phase) as outpatients off treatment were equal to or greater than 120 mmHg on two occasions before admission, and mean values did not drop

below 120 mmHg for the first three days in the ward. Thus these were examples of severe hypertension since blood pressure usually falls after admission to hospital.^{7 8}

Two other groups of 50 patients, also premenopausal and age-matched to within four years of the inpatient group, were drawn from the files of the Glasgow Blood Pressure Clinic.⁹ In 50 women diastolic blood pressures measured under the same outpatient conditions as above were in the range 105 to 119 mmHg and in 50 diastolic pressures ranged from 90 to 104 mmHg.

AETIOLOGY OF HYPERTENSION

In the group of severely hypertensive women (diastolic blood pressure ≥ 120 mmHg) a possible cause for the hypertension was identifiable in 39 of the 50 patients (78%). Renal artery stenosis or occlusion was the commonest cause (23 instances). Eleven of these 23 women had arteriographic evidence of fibromuscular hyperplasia of at least one major renal artery, but no fibromuscular changes were seen in other major arteries from the level of the coeliac axis distally. Atheroma was the apparent cause of the renal artery stenosis in the other 12 patients. Five patients had, on intravenous urography, irregularly scarred kidneys suggesting chronic pyelonephritis. Four patients had chronic renal failure (serum creatinine consistently greater than $250 \mu\text{mol/l}$). Three other patients had an aldosterone-secreting adenoma, three had a pheochromocytoma, and one suffered from systemic lupus erythematosus. Eleven of the 50 patients in

this group were in the malignant phase of hypertension at the time of admission (bilateral fundal haemorrhages, exudates, and papilloedema).

By contrast in the 50 patients with diastolic pressures of 105 to 119 mmHg only nine patients had possible secondary hypertension (five had radiological appearances of chronic pyelonephritis, and four were taking a combined oestrogen-progesterone oral contraceptive pill with 50 µg ethinyloestradiol.¹⁰) In the group with diastolic pressures of 90 to 104 mmHg seven patients had a possible cause (two with radiological evidence of chronic pyelonephritis, five taking an oral contraceptive). No patient in the two groups with milder hypertension had retinal haemorrhages, exudates, or papilloedema.

Methods

CLINICAL DATA

All data were collected retrospectively from case records. Histories were scrutinised for details of chest pain and all mentioned its presence or absence. Attention was focused on details of its character, situation, radiation, duration, frequency, relation to physical exercise, and response to drugs, though information on all of these aspects was not always recorded (see Table 1). Before presentation two patients had a history consistent with a myocardial infarction: in both, changes in the serum levels of cardiac enzymes and in the electrocardiogram (Minnesota code 1-1 or 1-2¹¹) confirmed the clinical diagnosis.

Further data abstracted from all records included: past medical history—history of ischaemic heart disease or of hypertension in first degree relatives; drug history including oral contraceptives; smoking habits—people who had abstained from smoking for at least six months were classified as non-smokers; details of the underlying disease process

where investigation had revealed a cause of the hypertension; subsequent medical or surgical treatment and its efficacy; mortality between presentation and February 1979; details of coronary angiography (one patient only, with triple vessel disease). No patient had cardiac surgery.

ANGINA PECTORIS

We have employed the strict criteria for angina pectoris as laid down by Rose.¹² Angina pectoris was defined by him as 'a chest pain or discomfort with these characteristics:

- (1) The site must include either the sternum (any level) or the left arm and left anterior chest (defined as the anterior chest wall between the levels of clavicle and lower end of sternum).
- (2) It must be provoked by either hurrying or walking uphill (or by walking on the level, for those who never attempt more).
- (3) When it occurs on walking, it must make the subject either stop or slacken pace, unless glyceryl trinitrate is taken.
- (4) It must disappear on a majority of occasions in 10 minutes or less from the time when the subject stands still.'

It must be emphasised that the above definition is a rigid one and excludes several well-known variants of otherwise unequivocal angina. However, there were no patients with less typical angina in the present study.

Eleven patients have thus been classified as having angina pectoris: all satisfy the first two of Rose's criteria,¹² and nine satisfy the fourth. Data about the third criterion were not routinely recorded in this retrospective analysis, but the features listed in Table 1 are considered to justify the diagnosis of angina pectoris.

ELECTROCARDIOGRAMS

Resting electrocardiograms of all patients at

Table 1 Characteristics of chest pain in 11 women with angina pectoris

Case no.	Site	Radiation	Character	Duration	Related to increased cardiac work	Relieved by
1	Praecordium	No	Tight	10 min	Exercise	GTN
2	Arms	Jaw	Severe heavy	10 min	Mild exercise	GTN
3	Left side of chest	Left arm	Cramplike	NS	Exercise	Rest
4	Retrosternal	No	Heavy	5 min	Exercise	GTN
5	Central chest	Right arm	Crushing	20 min	Exercise, emotion	GTN
6	Chest	No	Tightness	10 min	Exercise	Rest
7	Retrosternal	NS	Heaviness	10 min	Exercise	NS
8	Chest	Left arm	Tightness	10 min	Walking	Rest
9	Retrosternal	No	Tightness	5-10 min	Exercise	GTN
10	Retrosternal	Left arm	Heaviness	10 min	Exercise	GTN, rest
11*	Chest	Left arm	Choking	5-10 min	Exercise	GTN, rest

* Case 11 had no electrocardiographic abnormalities of ischaemia. NS, not stated in case records. GTN, glyceryl trinitrate.

presentation were re-examined and classified according to the Minnesota code.¹³ Abnormalities classifiable as 4-1 (ST depression ≥ 1 mm) or 5-1 (T wave inversion ≥ 5 mm), the criteria adopted by Oliver,³ were taken as indices of myocardial ischaemia in this study. It is recognised, however (see Discussion), that false-positive and false-negative findings may result from this classification. Considerable difficulties also surround the interpretation of ST and T wave changes in exercise electrocardiograms^{14 15}; these tests had not been routinely performed in patients and are not considered further.

OTHER INVESTIGATIONS

An analysis was made of the following investigations which were carried out on all patients at presentation: haemoglobin, serum electrolytes, urea and creatinine, fasting cholesterol (inpatients only). Thyroid function tests when available were also noted. Peripheral venous plasma renin and angiotensin II concentrations were measured on the majority of inpatients. Samples were collected between 8.30 and 9.30 a.m. after overnight recumbency and fasting in untreated patients who were taking either a fixed diet containing known and normal quantities of sodium and potassium, or a normal ward diet. Plasma total renin concentration was measured according to the method of Brown *et al.*¹⁶ (20 patients) or active renin concentration according to the method of Millar *et al.*¹⁷ (24 patients). Plasma angiotensin II concentrations were measured according to the method of Düsterdieck and McElwee.¹⁸

Results

(1) PATIENTS WITH DIASTOLIC BLOOD PRESSURE ≥ 120 mmHg

On the basis of their clinical histories (Table 1) and electrocardiographic appearances (Table 2) the 50 severely hypertensive women have been divided into four groups. Ten patients (20%) had angina pectoris and electrocardiographic abnormalities of ischaemia (AP+, ECG+); one patient had classical angina but no ischaemia on electrocardiographic evidence (AP+, ECG-); nine patients (18%) had ischaemia on the electrocardiogram in the absence of angina pectoris (AP-, ECG+). Thirty patients (60%) were both asymptomatic and without electrocardiographic abnormalities of ischaemia (AP-, ECG-). Thus, overall, 40 per cent of these severely hypertensive women had either angina pectoris or ischaemic changes on their resting electrocardiograms or both. Mean diastolic pressures were similar in the four groups (138, 130, 139, and 134 mmHg, respectively).

Electrocardiographic abnormalities (at rest) (Table 2) ST depression of ≥ 1 mm (code 4-1) was present in all patients considered to have electrocardiographic ischaemia. T wave inversion of ≥ 5 mm (code 5-1) was also present in one-quarter of these patients. Ninety-one per cent of patients with angina pectoris had ischaemic changes; 53 per cent of patients with ischaemia on the electrocardiogram had angina pectoris.

Less pronounced T wave abnormalities (code 5-2 or 5-3) were commonly present (Table 2). Had the criteria for electrocardiographic ischaemia included 5-2 changes,¹⁹⁻²¹ five more patients would have fallen into the asymptomatic group with ischaemic electrocardiograms (Table 2). On this basis, 50 per cent of the severely hypertensive women would then have had either ischaemic electrocardiograms or symptoms of angina pectoris.

Taking an R wave of > 26 mm in the lateral chest leads (code 3-1) as an index of left ventricular hypertrophy, more women with ischaemic changes had left ventricular hypertrophy than those without ischaemic changes ($\chi^2=11.76$; $P<0.001$). Overall, 24 patients (48%) had 3-1 changes present.

Fifteen patients (30%) had no electrocardiographic abnormality according to the code.¹¹

Risk factors (Table 3)

(i) *Smoking*: Ten out of 11 symptomatic patients (91%) smoked cigarettes and 15 out of 19 patients with electrocardiographic ischaemia (79%) smoked, compared with 20 out of 30 asymptomatic patients with normal electrocardiograms (67%). The difference between symptomatic and asymptomatic patients did not reach significance ($\chi^2=2.69$; $P>0.05$) nor did that between patients with ischaemic and non-ischaemic electrocardiograms

Table 2 *Electrocardiogram abnormalities in 50 women with diastolic blood pressure ≥ 120 mmHg*

Code	Meaning	AP+ ECG+ n=10	AP+ ECG- n=1	AP- ECG+ n=9	AP- ECG- n=30	All groups n=50
1-0	No abnormality reported	0	0	0	15	15
1-1 or 2	Q waves	2	0	0	0	2
3-1	Left ventricular hypertrophy	8	1	7	8	24
4-1	ST depression ≥ 1 mm	10	0	9	0	19
4-2 or 3	Lesser ST changes	0	0	0	4	4
5-1	T inversion ≥ 5 mm	2	0	3	0	5
5-2	T inversion 1-5 mm	6	0	5	5	16
5-3	T flat or diphasic	1	0	1	7	9

Table 3 Risk factors

Classification of patients	No. of patients	Cigarette smoking			Serum cholesterol			Oral contraceptives			Family history Of IHD or hypertension
		Non- or ex-	<20/day	≥20/day	Normal	High	Not measured	Present use (within 6 mth)	Use in past	No use admitted	
AP+ ECG+	10	1	5	4	9	0	1	1	3	6	5
AP+ ECG-	1	0	1	0	1	0	0	0	0	1	1
AP- ECG+	9	3	2	4	5	2	2	3	0	6	6
AP- ECG-	30	10	12	8	24	5	1	11	4	15	12
All patients	50	14	20	16	39	7	4	15	7	28	24

($\chi^2=0.73$; $P>0.05$). Forty-two per cent of patients with ischaemic changes smoked heavily (≥ 20 cigarettes per day) but so did 26 per cent of patients with non-ischaemic electrocardiograms and the difference was not significant ($\chi^2=1.44$, $P>0.05$).

(ii) *Cholesterol, oral contraceptives, family history*: Data regarding these factors show abnormalities no more frequently in the symptomatic or electrocardiographically abnormal groups than among those who were asymptomatic or had normal electrocardiograms (Table 3).

(iii) *Renin and angiotensin II* (Table 4): 88 per cent of patients had peripheral venous plasma renin concentration measured when untreated, shortly after admission, and 86 per cent also had measurements of peripheral plasma angiotensin II levels. No statistical difference between symptomatic/asymptomatic or ischaemic/non-ischaemic groups was found. When renin and angiotensin II levels at presentation were related to subsequent morbid events, one patient who subsequently suffered a myocardial infarction had high peripheral plasma renin and angiotensin II levels but two others suffering a myocardial infarction and four suffering strokes had values within the normal range.

(iv) *Fibromuscular hyperplasia*: Fibromuscular hyperplasia of the coronary arteries was unlikely since changes in the renal arteries were not found more frequently among those with angina pectoris or electrocardiographic abnormalities than among those who were asymptomatic and had normal electrocardiograms (21% compared with 23%).

(v) *Malignant-phase hypertension*: Malignant-phase hypertension was present in 11 patients. Two patients had angina pectoris and ischaemic electrocardiograms; three had abnormal electrocardiograms but were asymptomatic; six did not have angina pectoris or electrocardiographic abnormalities of ischaemia. There was thus no excess of symptomatic patients among those admitted with malignant-phase hypertension.

(vi) *Others*: There were no differences in obesity, parity, or haemoglobin levels between the four groups. No patient was clinically hypothyroid, but this was only checked and confirmed biochemically in nine. Three patients had glycosuria on routine testing at presentation: in two a subsequent oral glucose tolerance test was normal, as were repeated urine estimations, and in the third renal glycosuria was shown. Thus no patient had diabetes mellitus.

(vii) *Multiple risk factors*: At least one risk factor (smoking, hypercholesterolaemia, family history, oral contraceptives) in addition to high blood pressure was present in 94 per cent of patients. Additional factors were equally common among symptomatic and asymptomatic patients.

Table 4a and b 50 women with diastolic blood pressure ≥ 120 mmHg: renin and angiotensin II

Table a	Peripheral plasma renin concentrations				
	AP+ ECG+ n=10	AP+ ECG- n=1	AP- ECG+ n=9	AP- ECG- n=30	All groups n=50
Low renin	1	0	1	4	6
Normal renin	5	1	4	20	30
High renin	3	0	1	4	8
No result available	1	0	3	2	6

Table b	Peripheral plasma angiotensin II concentrations				
	AP+ ECG+ n=10	AP+ ECG- n=1	AP- ECG+ n=9	AP- ECG- n=30	All groups n=50
<10	0	0	0	2	2
10-19	2	0	2	8	12
20-29	2	1	1	8	12
30-39	1	0	0	5	6
40-49	2	0	1	0	3
>50	2	0	2	4	8
No result available	1	0	3	3	7

Twenty of the renin samples were measured according to the method of Brown *et al.*¹⁶, 24 samples according to the method of Millar *et al.*¹⁷. Results have been classified as low, normal, or high in relation to the respective normal ranges of these methods. Angiotensin II levels were estimated according to the method of Dusterdieck and McElwee¹⁸ (normal range 5 to 35 pg/ml).

Treatment

Symptomatic improvement occurred after beta-blockade in seven of the 11 women with angina pectoris, but the possible direct antianginal effect of the beta-blockers could not be separated from the possible antianginal effect of blood pressure reduction by beta-blockers and other drugs. In six out of seven patients with symptomatic improvement the diastolic blood pressure was reduced by treatment to below 100 mmHg. The four remaining symptomatic patients continued to experience attacks of chest pain with the same frequency and one suffered a myocardial infarction; blood pressure control was poor in three of these patients with diastolic values ≥ 110 mmHg despite treatment.

Morbidity and mortality

Patients were followed up for from six months to six years after presentation. Morbidity (three patients with myocardial infarction, two with strokes, and three with intermittent claudication) was much commoner in patients who were symptomatic or had electrocardiographic signs of ischaemia—92 patient-years follow-up—than in patients who had initially normal electrocardiograms and were asymptomatic (two patients suffered a stroke)—122 patient-years follow-up. Mortality was also commoner but not significantly so in patients with symptoms or with positive electrocardiograms (three died—15% mortality) than in the asymptomatic group with normal electrocardiograms (one died—3% mortality). The fatal events were stroke (two) and myocardial infarction in the former group, and fungal peritonitis after peritoneal dialysis in the latter.

(2) PATIENTS WITH DIASTOLIC BLOOD PRESSURE < 120 mmHg

Table 5 shows the increase in angina pectoris and electrocardiographic abnormalities of ischaemia in relation to the height of the mean diastolic blood pressure at presentation. Minor ST and T wave changes were present in four patients with diastolic pressures in the range 105 to 119 mmHg and in one patient in the range 90 to 104 mmHg, but no patient in either group had the 4-1 or 5-1 changes

which we have taken as indicative of ischaemia.

One patient only in the 105 to 119 mmHg group had a history of angina pectoris, and satisfied all four of Rose's criteria.¹² No fatality occurred during the follow-up period (410 patient-years follow-up) in the 100 patients with a diastolic pressure less than 120 mmHg. One patient, however, developed intermittent claudication and another had transient cerebral ischaemia during follow-up; both were in the 105 to 119 mmHg group.

Of the risk factors (smoking, family history, oral contraceptive usage) which it was possible to analyse in the 100 less severely hypertensive women, only smoking habits varied, and appeared to be related to the height of the diastolic pressure at presentation (Fig.). It was thus not possible to dissociate the adverse effects of smoking and hypertension. Seventy-two per cent of those with diastolic readings of ≥ 120 mmHg smoked compared

Fig. Smoking habits in 150 premenopausal women with varying diastolic blood pressure at presentation.

Table 5 Angina pectoris and electrocardiographic abnormalities in 150 women with varying diastolic blood pressures at presentation

Diastolic blood pressure (mmHg)	Mean diastolic blood pressure (± 1 SD)	No. of patients	History of angina pectoris	ECG ischaemia (Code 4-1; 5-1)
90-104	96 $\pm$ 3.5	50	0	0
105-119	109 $\pm$ 4.7	50	1	0
≥ 120	137 $\pm$ 16.6	50	11	19

with 40 per cent of the 105 to 119 mmHg group and 24 per cent of the 90 to 104 mmHg group. Comparable percentages of heavy smokers (≥ 20 cigarettes per day) were 32, 16, and 10, respectively. When smoking habits among the 50 severely hypertensive women were compared with those among the 100 women with diastolic pressures < 120 mmHg the difference was highly significant ($\chi^2 = 21.52$, $P < 0.001$).

Since malignant phase hypertension is known to be associated with excess smoking,^{22 23} patients presenting in this way and matched patients with diastolic pressures < 120 mmHg were removed from the analysis. Smoking was still significantly commoner in patients with diastolic pressures ≥ 120 mmHg than in those < 120 mmHg ($\chi^2 = 18.93$, $P < 0.001$).

Discussion

The most notable inference which may be drawn from this study is that ischaemic heart disease, which is very rare among young women generally,²⁴ is common, with an incidence of one in five for angina pectoris and two in five for electrocardiographic abnormalities,³ in a highly selected population of severely hypertensive young women.

Differing criteria in the Minnesota coded resting electrocardiogram have been applied to myocardial ischaemia in various studies. Epstein *et al.*,¹⁹ Welborn *et al.*,²⁰ Bengtsson²¹ and others accepted 4-1; 5-1; 5-2-6-1 or 7-1 changes as indicative of a 'coronary electrocardiogram',²¹ where 5-2 represents T wave inversion of 1 to 5 mm, 6-1 represents complete atrioventricular block, and 7-1 left bundle-branch block. Oliver,³ on the other hand, chose stricter criteria for ischaemia, namely, 4-1 or 5-1 changes, which we have adopted. Had we extended our electrocardiographic criteria of ischaemia to include 5-2 changes, 48 per cent of the women with diastolic pressures of ≥ 120 mmHg would have been so affected.

Bengtsson²¹ has raised the question whether 'coronary electrocardiograms' or left ventricular 'strain'²⁵ truly mirror ischaemia, having discovered that 29 of 1462 women in his population study had a history of angina pectoris and 23 had ischaemic electrocardiograms, but that only three had both angina pectoris and an ischaemic electrocardiogram. Our results cannot confirm this trend. Of 11 women with angina pectoris, 10 had ischaemic electrocardiographic changes, ST depression of ≥ 1 mm being the most consistent abnormality. Also, 10 out of 19 women with ischaemic changes had angina pectoris, and two of the women with electrocardiographic changes only later went on to have myo-

cardial infarctions. While significantly more women with myocardial ischaemia had left ventricular hypertrophy, this does not necessarily imply that ST depression is an effect of hypertension on the myocardium independent of ischaemia but suggests that hypertension probably predisposes to the development of ischaemia.

There are difficulties in the identification and classification of myocardial ischaemia. ST and T wave changes need not be associated with demonstrable abnormalities on coronary arteriography either in the presence of angina pectoris^{26 27} or in asymptomatic patients.²⁸ Even myocardial ischaemia, identified by isotopic scanning²⁹ or by lactate extraction³⁰ may occur in the absence of arteriographic narrowing of the main coronary arteries. On the other hand, patients with 'typical prolonged myocardial ischaemic pain'³¹ may not have 4-1 or 5-1 changes on their resting electrocardiograms.³²

Selective referral of patients in the group with diastolic blood pressures ≥ 120 mmHg might have biased results in favour of a high incidence of ischaemic heart disease. Twelve patients (24%) in this group had atheromatous stenoses of their renal arteries, and excess deposition of atheroma at other arterial sites would not be unexpected. However, only two symptomatic patients and two asymptomatic patients with ischaemia on the electrocardiogram could be accounted for in this way.

Multiple risk factors in young women with ischaemic heart disease have been found in many studies, including the present one.^{2 4 6} However, by selecting premenopausal women for this study one risk factor has been removed. In the present study only the prevalence of cigarette smoking was observed to change throughout the groups with different diastolic pressures at presentation. This may in part reflect the number of patients with malignant-phase hypertension and/or renal artery stenosis in the group with diastolic pressures ≥ 120 mmHg, since cigarette smoking, which has been associated with excess atheroma formation in men,³³ has also been shown to be a feature of both malignant phase hypertension^{22 23} and renal artery stenosis.³⁴ However, Sammel *et al.*³⁵ have observed excess smoking (73% smokers) in a series of young women with coronary artery disease who were compared with healthy controls (21% smokers)—only 18 per cent of coronary patients in their series had diastolic blood pressures of > 94 mmHg. Thus smoking has been independently associated with angina pectoris, malignant phase hypertension, and renal artery stenosis, and in this study it is difficult to separate the different associations.

Other common factors in the aetiology of the patients' hypertension and ischaemic heart disease

have not been forthcoming in the present study. Fibromuscular hyperplasia of the coronary artery was one possibility considered, but fibromuscular changes of the renal arteries were no commoner in symptomatic or ischaemic patients than in asymptomatic patients. Renin and angiotensin II have been claimed as being implicated in the development of morbid or fatal events in hypertension.³⁶ The present study confirms Brunner's later evidence³⁷ that this association does not hold for ischaemic heart disease.

The effects of sustained hypertension on the myocardium may thus manifest themselves as angina pectoris or as electrocardiographic changes of ischaemia, and the severity of the rise in blood pressure allows definition of a group of premenopausal women at particularly high risk of developing ischaemic heart disease.

References

- ¹Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med* 1976; **85**: 447-52.
- ²Oliver MF, ed. *Coronary heart disease in young women*. Edinburgh: Churchill Livingstone, 1978.
- ³Oliver MF. Ischaemic heart disease in young women. *Br Med J* 1974; **4**: 253-9.
- ⁴Mann JI, Vessey MP, Thorogood M, Doll R. Myocardial infarction in young women with special reference to oral contraceptive practice. *Br Med J* 1975; **2**: 241-5.
- ⁵Jarrett R J. Diabetes and the heart: coronary heart disease. *Clin Endocrinol Metab* 1977; **6**: 389-402.
- ⁶Engel HJ, Page HL Jr, Campbell WB. Coronary artery disease in young women. *JAMA* 1974; **230**: 1531-4.
- ⁷Irving JB, Kerr F, Ewing DJ, Kirkby BJ. Value of prolonged recording of blood pressure in assessment of hypertension. *Br Heart J* 1974; **36**: 859-66.
- ⁸De Leeuw PW, Wester A, Van Soest GAW, Vaarties-Steeleman JEM, Birkenhäger WH. Sodium balance and blood pressure in essential hypertensives during the early phase of hospitalisation. In: *Abstracts of 6th Scientific Meeting of International Society of Hypertension, Goteborg, Sweden, June 1979*; p. 92.
- ⁹Glasgow Blood Pressure Clinic (1972). The Glasgow Blood Pressure Clinic. *J R Coll Physicians Lond* 1972; **7**: 87-97.
- ¹⁰Weir RJ, Briggs E, Mack A, Naismith L, Taylor L, Wilson E. Blood pressure in women taking oral contraceptives. *Br Med J* 1974; **1**: 533-5.
- ¹¹Rose GA, Blackburn H. Cardiovascular survey methods. *WHO Monogr Ser* 1968; No. 56: 137.
- ¹²Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field survey. *Bull WHO* 1962; **27**: 645-58.
- ¹³Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies: a classification system. *Circulation* 1960; **21**: 1160-75.
- ¹⁴Bruce RA. Values and limitations of exercise electrocardiography. *Circulation* 1974; **50**: 1-3.
- ¹⁵Linhardt JW, Laus JG, Satinsky JD. Maximum treadmill exercise electrocardiography in female patients. *Circulation* 1974; **50**: 1173-8.
- ¹⁶Brown JJ, Davies DL, Lever AF, Robertson JIS, Tree M. The estimation of renin in human plasma. *Biochem J* 1964; **93**: 594-600.
- ¹⁷Millar JA, Leckie BJ, Semple PF, Morton JJ, Sonkodi S, Robertson JIS. Active and inactive renin in human plasma: renal arteriovenous differences and relationships with angiotensin and renin substrate. *Circ Res* 1978; **42** and **43**: Suppl I: 120-7.
- ¹⁸Düsterdieck G, McElwee G. Estimation of angiotensin II concentration in human plasma by radioimmunoassay: some applications to physiological and clinical states. *Eur J Clin Invest* 1971; **2**: 32-8.
- ¹⁹Epstein FH, Ostrander LD Jr, Johnson BC, et al. Epidemiological studies of cardiovascular disease in a total community—Tecumseh, Michigan. *Ann Intern Med* 1965; **62**: 1170-87.
- ²⁰Welborn TA, Cumpston GN, Cullen KJ, Curnov DH, McCall MG, Stenhouse NS. The prevalence of coronary artery disease and associated factors in an Australian rural community. *Am J Epidemiol* 1969; **89**: 521-36.
- ²¹Bengtsson C. Ischaemic heart disease in women. *Acta Med Scand* (Suppl) 1973; **549**: 1-128.
- ²²Bloxham CA, Beevers DG, Walker JM. Malignant hypertension and cigarette smoking. *Br Med J* 1979; **1**: 581-3.
- ²³Isles C, Brown JJ, Cumming AMM, et al. Excess smoking in malignant-phase hypertension. *Br Med J* 1979; **1**: 579-81.
- ²⁴Gordon T. Coronary heart disease in young women—incidence and epidemiology. In: Oliver MF, ed. *Coronary heart disease in young women*. Edinburgh: Churchill Livingstone, 1978: 12-23.
- ²⁵Schamroth L. *An introduction to electrocardiography*. 4th ed. Oxford: Blackwell Scientific Publications, 1971: p. 59.
- ²⁶Likoff W, Segal BL, Kasparian H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *N Engl J Med* 1967; **276**: 1063-6.
- ²⁷Kemp HG Jr, Vokonas PS, Cohn PF, Gorlin R. The angina syndrome associated with normal coronary arteriograms. Report of a six-year experience. *Am J Med* 1973; **54**: 735-42.
- ²⁸Taggart P, Carruthers M, Joseph S, et al. Electrocardiographic changes resembling myocardial ischaemia in asymptomatic men with normal coronary arteriograms. *Br Heart J* 1979; **41**: 214-25.
- ²⁹Korhola O, Valle M, Frick MH, Wijasalo M, Riihimäki E. Regional myocardial perfusion abnormalities on xenon-133 imaging in patients with angina pectoris and normal coronary arteries. *Am J Cardiol* 1977; **39**: 355-9.
- ³⁰Boudoulas H, Cobb TC, Leighton RF, Wilt SM. Myocardial lactate production in patients with anginal-like chest pain and angiographically normal coronary

- arteries and left ventricle. *Am J Cardiol* 1974; **34**: 501-5.
- ³¹Somerville W. Clinical characteristics and prognosis of angina and myocardial infarction—discussion. In: Oliver MF, ed. *Coronary heart disease in young women*. Edinburgh: Churchill Livingstone, 1978: p. 232.
- ³²Oliver MF, ed. *Coronary heart disease in young women*. Edinburgh: Church Livingstone, 1978: p. 233.
- ³³Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. *Br Med J* 1976; **2**: 1525-36.
- ³⁴Mackay A, Brown JJ, Cumming AMM, Isles C, Lever AF, Robertson JIS. Smoking in renal artery stenosis. *Br Med J* 1979; **2**: 770.
- ³⁵Sammel N, Simons LA, Hickie JB, Gibson JC. Antecedents of coronary artery disease in young Australian women. In: *Abstracts of the Cardiac Society of Australia and New Zealand, Sydney, September 1978*: p. 6.
- ³⁶Brunner HR, Laragh JH, Baer L, *et al.* Essential hypertension: renin and aldosterone, heart attack and stroke. *N Eng J Med* 1972; **286**: 441-9.
- ³⁷Brunner HR, Gavras H, Laragh JH, Harrus G, Sealey JE. The risk of low-renin hypertension: an updated analysis. In: *Abstracts, 9th Annual Meeting of European Society for Clinical Investigation, Rotterdam, April 1975*: p. 53.

Requests for reprints to Dr A Mackay, MRC Blood Pressure Unit, Western Infirmary, Glasgow G11 6NT.