ASSOCIATION OF DIABETIC AUTONOMIC NEUROPATHY WITH PAINLESS MYOCARDIAL ISCHAEMIA INDUCED BY EXERCISE

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ABSTRACT

Silent myocardial ischaemia is now well-recognised in patients with symptomatic coronary artery disease. Its pathogenesis remains speculative, though diminished sensitivity to pain is thought to be one of the mechanisms involved. Because cardiovascular autonomic dysfunction occurs frequently in diabetic patients, we postulate that it contributes towards painless myocardial ischaemia among them.

Forty consecutive diabetic (type II) male patients and ten normal volunteers were studied. Using 5 previously-validated noninvasive tests for autonomic dysfunction, 14 of these diabetic men had definite autonomic neuropathy (at least 2 abnormal tests). All 50 subjects were then exercised on a motor-driven treadmill to either exhaustion or chest pains. Thirty-three diabetic subjects were tested positive, with significant (> 1 mm) ST segment depression over at least 2 contiguous leads. Of these, 18 were associated with typical angina but the other 15 stopped because of fatigue or exhaustion (ie painless). Thirteen subjects who had definite autonomic neuropathy (AN+) had positive exercise ECG tests - 10 had painless ischaemia, and only 3 had angina. This contrasted with 15 patients who had painful ischaemia and 5 who had painless ischaemia among the group without (AN-) autonomic dysfunction ($p = 0.0047$, Fisher's exact test). There were no significant differences among the various groups for peak rate-pressure-product, all subjects attaining similar maximal oxygen consumption states during which ischaemic ST segment changes were noted (painful AN+: 21917±4753; painless AN+: 20117±6752; painful AN-: 16544±4063; painless AN-: 22220±4341, p=NS). There were also no differences in the exercise duration (440±141s; 460±168s; 443±99s; 570±111s, respectively; p=NS).

In 18 patients who had coronary arteriography, all had significant coronary artery disease (CAD), ie 2 LMS disease, 13 3-vessel CAD, and 3 2-vessel CAD. Thus, some degree of cardiac denervation secondary to autonomic neuropathy, may be the cause of this defective pain perception in long-standing diabetic men.

Keywords: autonomic neuropathy, diabetic neuropathy, painless myocardial ischaemia.

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INTRODUCTION

Coronary heart disease is a major cause of morbidity and death in diabetic patients[1,2]. It has been suggested that painless myocardial infarction occurs more frequently among diabetic patients than in the general population [3,4], and that this may be due to cardiac denervation as a result of diabetic neuropathy[5]. Certainly, it has become widely accepted that variable degrees of silent myocardial ischaemia occur in almost every patient with symptomatic coronary heart disease [6-9].

Furthermore, an abnormal exercise ECG is more common in diabetic patients without cardiac symptoms than in nondiabetic controls [10-13]. Such reports whilst suggesting that asymptomatic myocardial ischaemia was commoner among diabetic subjects, however, did not address the issue of whether diabetic neuropathy contributed to this high incidence. A recent study by Hume et al[14], reported that a positive stress ECG test was no more common in patients with diabetic neuropathy; but their number of patients with abnormal exercise tests was only 14, among whom only 5 had autonomic neuropathy (9 others with evidence of autonomic neuropathy, did not have an abnormal exercise test).

Our objective for this study was therefore, to show whether autonomic neuropathy contributes significantly to painless exercise-induced myocardial ischaemia among a group of high-risk diabetic patients attending our Cardiology and Endocrine clinics.

MATERIALS AND METHODS

Patient Selection

Forty consecutive diabetic (type II) male patients and 10 normal volunteers above the age of 40 years were recruited from our Cardiology and Endocrine clinics. Five among the diabetic men had a previous myocardial infarction, and another 12 were referred for further cardiac evaluation for either chest pains or abnormal electrocardiograms (ECG), the other 23 were asymptomatic. No women were studied because the results of exercise ECG are unreliable in women[15].

Cardiovascular Autonomic Function Testing

All 50 subjects were then evaluated for autonomic dysfunction using 5 standard non-invasive tests:

1. immediate heart rate response to standing (30:15 ratio),
2. beat-to-beat heart rate variation during deep breathing (E:I ratio),
3. Valsalva ratio,
4. resting heart rate, and
5. blood pressure response to standing.

These tests were conducted by a single investigator (PGK) so as to reduce interobserver variation. The full text of the methodology and validation has been reported [16]. Diabetic autonomic neuropathy was considered to be present if at least two of these tests were abnormal[17].

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Exercise ECG Testing

The subjects were exercised on a motor-driven treadmill following the modified Bruce protocol with continuous monitoring of the ECG leads V_{4-6}, using the conventional 12-lead system. Baseline supine, standing and voluntary hyperventilation ECG recordings were obtained prior to commencement of the exercise test. During the test, cuffed-blood pressures were obtained using an aneroid manometer. Further ECG recordings were made immediately after exercise and after 1, 3, 5, 10 minutes. Each exercise was terminated when either the target heart rate was achieved, or when chest pains or anginal equivalents or exhaustion occurred, or when grossly abnormal ECG changes occurred. The exercise test was considered positive when development of horizontal or down-sloping ST segment depression > 1 mm lasting > 80 ms after the J point occurred[18].

Other Tests

Peripheral neuropathy was assessed clinically: typical glove-stocking hypaesthesiae, absent tendon reflexes, typical neuritic symptoms. Retinopathy was considered positive when definite background or proliferative changes were detected on ophthalmic referral. Nephropathy was considered present when recurrent proteinuria was associated with elevated serum creatinine levels > 200 umol/l.

Coronary Arteriography

For patients who had a positive exercise ECG test, coronary arteriography was recommended. However, only 18 consented to this investigation. Significant coronary artery disease was diagnosed when > 50% diameter stenosis was consistently detected on at least two angiographic views.

Other Risk Factors

The other major coronary risk factors were also looked at, namely, history of hypertension (blood pressure > 160/90 mmHg), and fasting serum lipid profiles.

Statistical Analysis

The χ^2 - test or the Fisher's exact test was used to analyse the differences between the groups. Numerical values and data were computed for their means with their standard deviation. The Abstat version II programme was used to analyse the data. A p value of less than 5% was considered significant.

The nature and purpose of the study was explained to each patient and informed consent was obtained. The study was approved by the University's Research and Ethical Committee.

RESULTS

Subjects

The ten normal men had a mean age of 47±3 years (range 42-53 years); they were volunteers from working staff members. This was different from our consecutive sample of diabetic men whose mean age was 10 years older, ie 57±7 years (range 46-72). The mean duration of their known history of diabetes mellitus (type II) was 13.7±6.6 years (4-29 years). Table I shows the overall characteristics of our study group.

Cardiovascular Autonomic Function Tests

All the 10 normal volunteers had normal autonomic function when tested. This was in contrast to 14 of our 40 diabetic men who had 2 or more abnormal autonomic function tests and therefore had definite autonomic neuropathy. The most sensitive tests were:

1. immediate heart rate response to standing (30:15 ratio < 1.00),
2. beat-to-beat heart rate variation during deep breathing (E:I ratio < 1.10), and
3. the Valsalva ratio (< 1.10) where 11,13, and 10 subjects had abnormal responses, respectively. The details of these results have been reported [16].

In this study, those with borderline autonomic dysfunction (1 abnormal test result) were considered as not having autonomic neuropathy.

Exercise ECG

None of the 10 volunteers had a positive exercise test. However, 33/40 diabetic patients had a positive exercise ECG test,

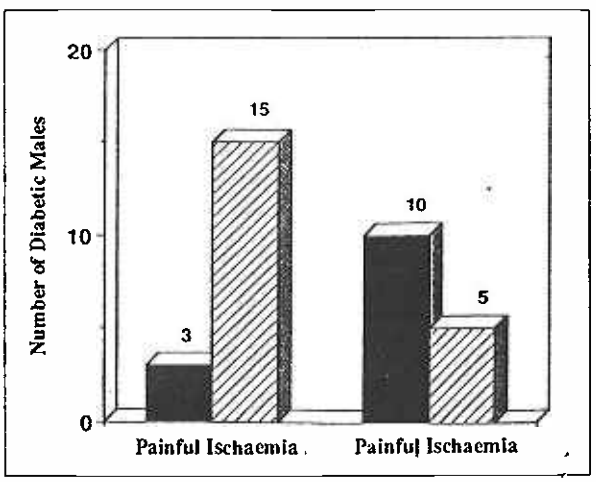
Table I - Subject Characteristics

Variable	Exercise ECG Negative	Test Result Total (%)	Overall Positive
Normal Volunteers	0	10	10
Age (years)			47±3
Diabetic Subjects (no.)	33	7	40
Age (years)	57±7	57±8	57±7
Duration of diabetes (years)	13±7	12±5	13±6
Ischaemic Heart Disease	17	0	17(42.5)
Past Myocardial Infarction	5	0	5(12.5)
Hypertension	4	3	7(17.5)
Cigarette Smoking	26	4	30 (75)
Total cholesterol > 6.4 mmol/l	20	2	22 (55)
LDL-cholesterol > 3.6 mmol/l	25	2	27(67.5)
HDL-Cholesterol < 1.0 mmol/l	10	5	15(37.5)
TC/HDLC ratio > 4.5	27	4	31(77.5)
Retinopathy	15	4	19(47.5)
Nephropathy	4	2	6 (15)
Peripheral Neuropathy	9	3	12 (30)
Autonomic Neuropathy	13	1	14 (35)
Painless ischaemia	10	0	10
No Autonomic Neuropathy	20	6	26 (65)
Painless ischaemia	5	0	5

LDL: low density lipoprotein; HDL: high density lipoprotein;
TC: total cholesterol

18 of whom had painful, and 15 had painless myocardial ischaemia. Among those with autonomic neuropathy (AN+), 10 had painless ischaemia and only 3 had angina of exercise. This contrasted with 15 who had painful myocardial ischaemia and 5 painless, among those without autonomic neuropathy (AN-). This difference was statistically significant, p = 0.0047 (Fisher's exact test). Fig 1 shows this relationship.

Fig 1 - Bar chart showing the frequency distribution of patients with painless positive exercise ECG in association with the presence or absence of diabetic autonomic neuropathy



■ AN+ = Definite autonomic neuropathy
☑ AN - = Diabetic neuropathy absent
* P < 0.047 (Fisher's test)
P = 0.0047 indicates the significance level of the statistical difference between 2 groups.

Table II - Diabetic Autonomic Dysfunction, Age, Duration of Diabetes & Exercise ECG Tests

Exercise ECG	Autonomic Neuropathy	Painful Ischaemia	No.	Age(yr)	Duration of Diabetes (yr)	Maximal RPP	Peak HR (bpm)	Exercise Time (s)
Positive	Yes	Yes	3†	60±9§	5.3±0.9§	21917±4753#	120±25#	440±141#
Positive	Yes	No	10†	59±8#	18.6±5.6§	20117±6752#	132±23#	460±169#
Positive	No	Yes	15†	55±5§	14.6±6.1#	16544±4663#	119±16#	443±99#
Positive	No	No	5†	54±4#	11.0±3.5#	22220±4391#	119±12#	570±111#
Negative	Normal*	No	10	47±3§	---	32183±3903#	161±11#	797±93#
Negative	No	No	7	57±8#	11.6±4.6#	20029±2941#	119±15#	531±140#

RPP: Rate Pressure Product (Heart Rate x Systolic Blood Pressure); HR: Heart Rate; * Normal Volunteers
† $p = 0.0047$; § $p < 0.05$ #: Not significant, $p > 0.05$

Table II shows the various characteristics of the study sample. It appeared that those subjects who had autonomic neuropathy were older (59 vs 54 years, $p<0.05$). Also those with painless myocardial ischaemia and autonomic neuropathy had had longer duration of diabetes (18 vs 5 to 14 years, $p<0.05$). However there were no differences in the exercise time to ischaemia or attainment of peak rate-pressure-product among all the subjects who had a positive exercise ECG test. (Our normal volunteers were able to achieve higher mets and longer exercise duration to exhaustion when compared with the diabetic subjects.)

Other Tests

Table III shows the frequency of diabetic complications among the groups studied. Fifteen diabetic subjects had retinopathy, 9 had gross peripheral neuropathy and 4 had impaired renal function, but there was no consistent relationship with the presence of either painful or painless myocardial ischaemia. Although all 3 patients with autonomic neuropathy and painful myocardial ischaemia had no retinopathy, nephropathy or peripheral neuropathy, the numbers were too small to analyse meaningfully.

Table III - Autonomic Dysfunction and Diabetic Complications in Patients with Positive Exercise ECG Tests

Variable	Number	Retinopathy	Nephropathy	Peripheral Neuropathy
Autonomic Neuropathy Present				
Painful Ischaemia	3	0	0	0
Painless Ischaemia	10	6	2	3
Autonomic Neuropathy Absent				
Painful Ischaemia	15	5	2	3
Painless Ischaemia	5	4	0	3
Overall Total	33	15	4	9

Other Coronary Risk Factors

75 percent (30/40) of our diabetic subjects were current cigarette smokers, as compared with 40 percent of our normal volunteers. Seven of 40 subjects had controlled hypertension (17.5%); none in the controls. For the fasting lipid profile, 55% had total cholesterol > 6.4 mmol/l; 35% had triglycerides > 1.7 mmol/l; 66.7% had LDL-cholesterol > 3.6 mmol/l; 36.4% had HDL-cholesterol < 1.0 mmol/l. 77.5% had total cholesterol/HDL-cholesterol ratio (TC/HDLC) > 4.5. The mean values of these parameters were: total cholesterol 6.7±1.4 mmol/l (range 3.9 – 9.3); triglycerides 2.1±1.2 mmol/l (range 0.8 - 6.5); LDL-cholesterol 4.7±1.4 mmol/l (range 2.4 - 7.5); HDL-cholesterol 1.1±0.3 mmol/l (range 0.6 - 2.3); TC/HDLC 6.6±2.2 (range 2.7 - 11.6).

Coronary Arteriography

Coronary arteriography was recommended to all subjects who had a positive exercise ECG tests. But only 18 consented to this investigation. Most of those with painless myocardial ischaemia and who were asymptomatic, were quite reluctant to undergo this test despite full explanation. All 18 had coronary artery diameter stenoses > 50% (equivalent to 75% cross-sectional stenoses), 2 with left main stem disease, 13 with 3-vessel disease and 3 with 2-vessel disease. In this group who agreed to be studied, 12 had painful positive exercise tests and 6 had painless positive tests, 1 and 5 subjects, respectively, had positive autonomic dysfunction.

DISCUSSION

Our study, although small, shows that among a high-risk group of diabetic patients with autonomic neuropathy, exercise-induced myocardial ischaemia was more likely to be painless. In our sample, 10/13 (76.9%) neuropathic patients did not have angina or anginal equivalents when significant electrocardiographic ST segment depression occurred, whereas 15/20 (75.0%) without neuropathy had painful episodes - this was quite highly significant ($p = 0.0047$). This suggests to us that some degree of cardiac denervation may be responsible for the defective pain perception among our diabetic patients. However, there were still 5 subjects without autonomic neuropathy who had painless myocardial ischaemia. This cannot be readily explained, and suggests that other mechanisms may be at play. Two main hypotheses have been expounded to account for painless or silent myocardial ischaemia.

The first relates to some altered perception of pain. This might be due to either higher individual thresholds to pain [19], or abnormalities in sensing pain, eg afferent nervous damage or disease [5]. Although individual differences in pain perception thresholds have been reported to account for some people with silent myocardial ischaemia [20,21], these higher pain thresholds have not been consistently shown. Low sensitivity to pain in patients with silent ischaemia may be related to both a neural pain inhibitory system and the release of endogenous opiates, the endorphins. For example, it has been shown that patients with asymptomatic ischaemia had higher beta-endorphin release at rest and during exercise [22]. Differing endorphin regulatory systems may account for the variable severity and duration of painful or painless ischaemia.

It appears that the essential pathway for the transmission of cardiac pain requires the integrity of the afferent fibres running through the cardiac sympathetic nerves [23,24]. It is reasonable to assume that diabetic neuropathy may interfere with afferent cardiac sensory impulses, given the well-recognised disturbances in sympathetic and parasympathetic control of cardiac function due to diabetes-induced neuropathy of efferent fibres [25]. Such cardiac denervation from diabetic disease affecting the autonomic nervous system could certainly ac-

count for the lack of angina perception in our patients. In fact, Faerman et al [5] had described morphologic changes of diabetic neuropathy of the sympathetic and parasympathetic nerves in 5 diabetic patients who died of painless myocardial infarction. Beaded hyperargentophilic thickenings of the nerves, spindle-shaped nerve fibres, fibre fragmentation and decreased number of fibres were described. Interestingly, peripheral neuropathy, nephropathy, retinopathy and duration of treatment of diabetes did not correlate with the presence of myocardial autonomic neuropathy.

Our results appear to differ from that reported by Hume et al[14] when they found no relationship between diabetic neuropathy and the presence or absence of pain during exercise-induced myocardial ischaemia. However, in their study, they were evaluating mainly neuropathy as a whole, cardiovascular autonomic neuropathy was found in only 5 subjects with a positive exercise test. This led to the statistical inference that it was not more common for diabetic subjects to have asymptomatic myocardial ischaemia whether neuropathy was present or otherwise. It is well-known that diabetic peripheral neuropathy does not always correlate with the severity or distribution or even presence of autonomic dysfunction [5,25].

A recent review by Chipkin et al[26] found that among 211 patients who had a positive exercise-induced ischaemia, 101 (48%) did not have pain. Of these, 26 had diabetes (24 with type II diabetes). They found no difference in the frequency of painless myocardial ischaemia between patients with or without diabetes mellitus (54% vs 47%). However, they did not include diabetic neuropathy in their data analysis. Thus it is possible that if neuropathy was present, the prevalence of painless ischaemia could have conceivably been much more.

In our study, we looked particularly at the autonomic nervous system in a group of higher risk subjects for cardiovascular disease. Undoubtedly our subject sample of 40 diabetic men with 82.5% prevalence of higher probable ischaemic heart disease represents a higher than usual risk. Most epidemiological surveys estimated the ischaemic heart disease prevalence rate of between 20 to 40% [11, 27-29]. However, it is certainly evident that our subjects were a higher-than-average risk group, considering that more than two-thirds had high LDL-cholesterol with high unfavourable (> 4.5) total cholesterol/HDL-cholesterol ratios, as well as being smokers. Thus, in this group of long-standing type II diabetic males, where 35% had autonomic dysfunction, nearly all (13/14) had a positive exercise ECG test.

Our data on exercise-induced myocardial ischaemia would have been better strengthened, had we been able to perform exercise-thallium redistribution studies in our subjects. We were unable to pursue this because of lack of facility for radionuclide imaging at our centre.

With respect to exercise thallium, Nesto and colleagues [25] had studied the relationship of angina to exertional ischaemia in some 43 diabetic and 42 control subjects. They found that only 28% of the diabetic group experienced angina compared with 54% in the nondiabetic cohort ($p < 0.01$), despite there being exercise-induced perfusion defects. Interestingly, they failed to show the predictive value of other well-known variables such as age , sex, cigarette smoking, family history, hypertension, previous infarction, size and location of exercise-induced thallium defect, extent of coronary disease and cholesterol levels.

In those subjects who had coronary arteriography, we were able to validate that a positive exercise ECG test was indicative of significant coronary artery disease. Thus, it may not be reasonable to expect that most of these subjects did indeed have significant myocardial ischaemia. However, the fact that only 55% (18/33) had angiographic studies, did considerably weaken our ability to extrapolate our analysis to those not so documented. Although in our own series the positive predictive accuracy of a positive exercise ECG test was more than 96% for male subjects (personal observations), we are aware that most treadmill exercise tests provide an overall predictive accuracy of some 70%. But, as we have pointed out, our diabetic cohort appears to be at particularly high risks, by which Bayesian analysis, our sample would achieve much improved post-test probability and positive predictive accuracy[30].

The second hypothesis that myocardial ischaemia was painless because the workload attained during such exercise was lower than that which was accompanied by pain, ie less severe ischaemia insufficient to meet pain thresholds, was not borne out in this study [29,31]. All our diabetic subjects with positive exercise tests, had similar achievement of peak heart rates and rate-pressure products as well as exercise duration when ischaemia occurred. This suggests that our subjects attained similar stages of maximal myocardial oxygen consumption.

Other theories regarding the painless nature of myocardial ischaemia are less developed. For example, it has been suggested that pathophysiologic differences may result in variable patterns of disturbed myocardial blood flow during silent and symptomatic ischaemic. Selwyn et al[32] has shown that symptomatic episodes were accompanied by a larger increase in myocardial blood flow in remote zones and a higher rate pressure product. They suggested that for the same degree of myocardial hypoperfusion, increased demand is a mediating factor in the generation of cardiac pain. In our patients, we have shown that there were no significant differences in the attainment of peak rate pressure product among the groups. Whether increased perfusion demand to remote normal myocardium occurs or not, we cannot comment.

We believe our small preliminary study suggests that, in diabetic men with coronary artery disease, autonomic neuropathy does contribute significantly (though not exclusively) to the painless or asymptomatic myocardial ischaemia. Further systematic study to correlate the presence of cardiovascular autonomic neuropathy with symptomatic or silent myocardial ischaemia, using either radionuclide stress testing or ambulatory ST-segment monitoring should be performed; and confirmed by angiography.

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REFERENCES:

1. Scott RC. Diabetes and the heart. Am Heart J 1975; 90:183-9.
2. Kannel WB, McGee DL. Diabetes and cardiovascular disease. A Framingham study. JAMA 1979; 241:2035-8.
3. Bradley RF, Schofield A. Diminished pain in diabetic patients with acute myocardial infarction. Geriatrics 1962; 17:322-6.
4. Cabin HS, Roberts WC. Quantitative comparison of extent of coronary narrowing and size of healed myocardial infarction in 33 necropsy patients with clinically recognised and in 28 with clinically unrecognised ("silent") previous acute myocardial infarction. Am J Cardiol 1982; 50:677-81.
5. Faerman I, Faccio E, Milei J et al. Autonomic neuropathy and painless myocardial infacrtion in diabetic patients: histologic evidence of their relationship. Diabetes 1977; 226:1147-58.
6. Allen RD, Gettes LS, Phalan C, Avington ND. Painless ST segment depression in patients with angina pectoris: correlation with daily activities and cigarette smoking. Chest 1976; 69:467-73.

7. Schang SJ, Pepine CJ. Transient asymptomatic ST segment depression during activity. Am J Cardiol 1977; 39:396-402.
8. Deanfield JE, Selwyn AP, Chierchia S et al. Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet 1983; ii:753-8.
9. Cecchi AC, Dovellini EV, Marchi F, Pucci P, Santoro GM, Fazzini PF. Silent myocardial ischaemia during ambulatory electrocardiographic monitoring in patients with effort angina. J Am Coll Cardiol 1983;1:934-9.
10. Karlefors T. Exercise tests in male diabetics. Electrocardiographic study. Acta Med Scand (Suppl) 1966; 449:3-18.
11. Bellet S, Roman L. The exercise test in diabetic patients as studied by radioelectrocardiography. Circulation 1967; 36:245-54.
12. Levitas IM, Kristal JJ. Stress exercise testing of the young diabetic for the detection of unknown coronary artery disease. Isr J Med Sci 1972; 8:845-7.
13 Storstein L, Jervell J. Response to bicycle testing in long-standing juvenile diabetics. Acta Med Scand 1979; 205:227-30.
14. Hume L, Oakley GD, Boulton AJM, Hardisty C, Ward JD. Asymptomatic myocardial ischaemia in diabetes and its relationship to diabetic neuropathy: an exercise electrocardiography study in middle-aged diabetic men. Diabets Care 1986; 9:384-8.
15. McHenry PL. The actual prevalence of false positive ST segment responses to exercise in clinically normal subjects remains undefined. Circulation 1977; 55:683-5.
16. Quek DKL, Khor PG, Ong SBL, Chan PYM, Khalid BAK. Assessment of cardiovascular autonomic neuropathy in diabetic patients - which tests to perform? J ASEAN Fed Endocrin Soc 1987; 6:58-71.
17. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. Br Med J 1982; 285:916-8.
18. Bruce RA, McDonough JR. Stress testing in screening for cardiovascular disease. Bull NY Acad Med 1969; 45:1288-305.
19. Cohn PF. Silent myocardial ischaemia in patients with a defective anginal warning system. Am J Cardiol 1980; 45:697-702.
20. Glazier JJ, Chierchia S, Brown MJU, Maseri A. Importance of generalised defective perception of painful stimuli as a cause of silent myocardial ischemia in chronic stable angina pectoris. Am J Cardiol 1986; 58:667-72.
21. Droste C, Roskamm H. Experimental pain measurement in patients with asymptomatic myocardial ischemia. J Am Coll Cardiol 1983;1:940-5.
22. Droste C, Roskamm H. Silent myocardial ischemia. Am Heart J 1989;118:1087-92.
23. Malliani A, Lombardi F. Consideration of the fundamental mechanisms eliciting cardiac pain. Am Heart J 1982; 103:575-8.
24. Malliani A. The elusive link between transient myocardial ischemia and pain. Circulation 1986; 73:201-4.
25. Nesto RW, Phillips RT. Asymptomatic myocardial ischemia in diabetic patients. Am J Med 1986; 80 (Suppl 4C):40-7.
26. Chipkin SR, Frid D, Alpert JS, Baker SP, Dalen JE, Aronin N. Frequency of painless myocardial ischemia during exercise tolerance testing in patients with and without diabetes mellitus. Am J Cardiol 1987;59:61-5.
27. Bradley RF, Partamian JO. Coronary heart disease in the diabetic patient. Med Clin North Am 1963; 1093-104.
28. Abenavoli T, Rubler S, Fisher VJ, Axelrod HI, Zuckerman KP. Exercise testing with myocardial scintigraphy in asymptomatic diabetic males. Circulation 1981;63:54-64.
29. Chiariello M, Indolfi C, Cotecchia MR, Sifola C, Romano M, Condorelli M. Asymptomatic transient ST changes during ambulatory ECG monitoring in diabetic patients. Am Heart J 1985; 110:529-34.
30. Rozanski A, Bermen DS. Silent myocardial ischemia: I. Pathophysiology, frequency of occurrence, and approaches toward detection. Am Heart J 1987; 114(3):615-26.
31. Chierchia S, Lazzari M, Freedman B, Brunelli C, Maseri A. Impairment of myocardial perfusion and function during painless myocardial ischemia. J Am Coll Cardiol 1983; 1:924-30.
32. Selwyn AP, Deanfield J, Shea M, Jones T. Different pathophysiology of painful and silent myocardial ischemia (Abstr). Circulation 1986;74:11-57.