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For debate

Silent coronary artery disease in diabetes – a feature of autonomic neuropathy or accelerated atherosclerosis?

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Abstract

Asymptomatic coronary artery disease and myocardial infarctions are common in diabetic subjects. The available clinical and epidemiological data suggest that the increased incidence of asymptomatic myocardial infarctions and coronary artery disease in diabetic patients mainly reflects accelerated coronary atherosclerosis and the proportion of silent disease relative to symptomatic disease or episodes is not increased in diabetes. In spite of the theoretical background, there is no convincing clinical or epidemiological evidence that diabetic autonomic neuropathy plays a major part in the lack of ischaemic pain. This is not surprising because the mechanisms of silent myocardial ischaemia are complex and controversial even without diabetes. [Diabetologia (2001) 44: 259–266]

Keywords Atherosclerosis, autonomic nervous function, coronary artery disease, diabetes mellitus, exercise testing, heart rate, myocardial infarction, myocardial ischaemia, neuropathy, pain perception.

It is generally accepted that diabetic patients with acute myocardial infarction often present with atypical symptoms and the infarction can be completely painless. Autonomic damage is regarded as the cause for the blunted appreciation of pain during acute coronary events, but both of these contentions are open to discussion. The purpose of this paper is to evaluate critically the information available on these relations.

Silent myocardial infarction in patients with diabetes

The concept that silent myocardial infarction is a characteristic of coronary artery disease in the presence of diabetes was originally based on the early report of Bradley and Schonfeld [l]. They found that diabetic patients who were admitted to hospital for myocardial infarction more often had little or no pain during infarction than non-diabetic patients. There is also a necropsy study of 61 patients suggesting that unrecognized myocardial infarction is more common in diabetic subjects [2]. These studies based on hospital and necropsy records cannot definitely prove, however, that painless myocardial infarction is more common in the whole diabetic population because the results could be modified by selection bias. It is reasonable to assume that diabetic patients have a closer medical follow-up and are admitted more readily to hospital for symptoms related to their diabetic status [3], e. g. uncontrolled diabetes, nausea or general weakness. These circumstances could erroneously increase the proportion of painless and atypical infarctions in hospital patients who are diabetic compared with these who are non-diabetic but later reports based on hospital records have failed to show any difference in the frequency of painless acute myocardial infarction between diabetic and non-diabetic patients [3–5].

Population-based epidemiological studies are likely to provide more reliable information on the incidence of unrecognized myocardial infarctions in dia-

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Table 1. Prevalence of signs of myocardial ischaemia in asymptomatic diabetic and non-diabetic subjects

Reference	Diagnosis of ischaemia/CAD	Diabetic subjects	Non-diabetic control subjects	Comments
Rubler et al. [16]	Th-201	48% (31 of 65)	–	All were middle-aged men
Langer et al. [17]	Ex-ECG + Holter + Th-201	17% (10 of 58)	–	All were middle-aged men
Valensi et al. [18]	Ex-ECG + Th-201 + Holter	30% (28 of 92)	–	9 of 24 patients with positive tests had CAD
MiSAD Group [19]	Ex-ECG	12% (112 of 925)	–	Th-201 positive in 59 of 112 patients with positiv ex-ECG
Janand-Delenne et al. [20]	Ex-ECG + Th-201	16% (32 of 203)	–	19 of 26 patients with positive tests had CAD
Rutter et al. [21]	Ex-ECG	65% (28 of 43)	–	All had microalbuminuria
Nesto et al. [22]	Th-201	57% (17 of 30)	–	All had peripheral vascular disease
Camp et al. [23]	Th-201	43% (17 of 40)	–	All had end-stage renal failure
Weinrauch et al. [24]	Coronary angiography	38% (8 of 20)	–	All had end-stage renal failure
Abrenavoli et al. [25]	Th-201	42% (5 of 12)	9% (1 of 11)	
Storstein et al. [26]	Ex-ECG	23% (5 of 22)	5% (1 of 21)	
Koistinen [27]	Ex-ECG	13% (17 of 136)	5% (4 of 80)	
	Th-201	23% (31 of 136)	–	11 of 25 (44%) patients with positive tests had CAD
Naka et al. [28]	Ex-ECG	31% (41 of 132)	30% (42 of 140)	
	CAD in angiography	39% (14 of 36)	18% (6 of 34)	

Ex-ECG = exercise electrocardiography, Th-201 = thallium scintigraphy, CAD = significant coronary artery disease in coronary angiography

[a] $p < 0.05$ for the comparison between the groups

betic populations. In the 18-year follow-up of the Framingham Study, a higher proportion of myocardial infarctions were silent or unrecognized in diabetic and hypertensive subjects [6]. That these differences were not statistically significant has often been ignored and in the less frequently referred to 30-year follow-up, female sex but not diabetes was associated with an excessive occurrence of unrecognized infarctions [7, 8]. In smaller studies from Israel and Hawaii, the incidence of unrecognized infarctions was not related to diabetes [9, 10]. Similarly, prevalence surveys in Malta, New York and Reykjavik and the Multicenter Postinfarction Program showed that similar proportions of diabetic and non-diabetic patients had no chest pain during myocardial infarction [11–14]. The Western Collaborative Group Study found a trend towards a preponderance of diabetic subjects among patients with unrecognized myocardial infarctions compared with subjects with no clinical coronary artery disease [15]. This finding does not, however, support any association between silent myocardial infarctions and diabetes mellitus but possibly reflects only the effect of diabetes mellitus in promoting atherosclerosis.

In summary, although early clinical studies suggest that diabetics with acute myocardial infarction is more often present with atypical symptoms or remain unrecognized, later clinical studies have not confirmed this association. The statistical power of epidemiological data is limited and does not provide proof of an association between diabetes and silent myocardial infarction.

Asymptomatic coronary artery disease and myocardial ischaemia in diabetes

Asymptomatic coronary artery disease in diabetes. Because diabetes accelerates coronary atherosclerosis, all clinical manifestations of coronary artery disease are excessively common in diabetic subjects. From this viewpoint it is obvious that the asymptomatic forms of the disease should also be more common in diabetic subjects than in non-diabetic ones. In line with this reasoning, several studies have shown a high prevalence of abnormalities in exercise electrocardiography and perfusion studies in middle-aged diabetic patients [16–20], especially in certain high-risk subgroups [21–24] (Table 1). There are also a few reports which have compared the prevalence of exercise-induced myocardial ischaemia between presumably healthy diabetic and non-diabetic young and middle-aged subjects [25–28] (Table 1). The scope for interpreting each individual study can be limited by small sample size, selection bias or lack of specificity of the tests but, taken together, they show that asymptomatic coronary artery disease is more common in diabetic patients than in similar groups of non-diabetic subjects [29–30]. It is, however, not certain that the excess of asymptomatic disease is ab-

Table 2. Prevalence of silent ischaemia in diabetic and non-diabetic patients with coronary artery disease

Reference	Diagnosis of ischaemia	Coronary angiography (%)	Diabetic patients	Non-diabetic patients
Callaham et al. [31]	Ex-ECG	19%	62% (112 of 180)	60% (940 of 1567)
Weiner et al. [32]	Ex-ECG	100%	40% (45 of 113)	33% (429 of 1321)
Aronow et al. [33]	Ex-ECG	NA	38% (52 of 136)	33% (120 of 365)
Deedwania et al. [34]	Holter	NA	39% (11 of 28)	44% (35 of 79)
Total			48% (220 of 457)	46% (1524 of 3332)

Ex-ECG = exercise electrocardiography, Th-201 = exercise thallium scintigraphy, Holter = ambulatory electrocardiogram monitoring, NA = not available

Table 3. Prevelance of diabetes mellitus in patients with silent and painful ischaemia

Reference	Diagnosis of ischaemia	Coronary angiography (%)	Silent ischaemia	Painful ischaemia
Nesto et al. [35]	Ex-ECG + Th-201	NA	69% (36 of 52)	29% (14 of 48)[b]
Mark et al. [36]	Ex-ECG	100%	9% (22 of 242)	9% (54 of 600)
Falcone et al. [37]	Ex-ECG	100%	4% (10 of 269)	6% (12 of 204)
Chipkin et al. [38]	Ex-ECG	48%	14% (14 of 101)	11% (12 of 110)
DeBelder et al. [39]	Ex-ECG	88%	16% (11 of 67)	8% (3 of 37)
Ouyang et al. [40]	Ex-ECG	100%	24% (9 of 38)	0% (0 of 22)[a]
Kurata et al. [41]	Th-201	66%	24% (26 of 108)	34% (of 65)
Hecht et al. [42]	Th-201	100%	13% (11 of 84)	32% (9 of 28)[a]
Gasperetti et al. [43]	Th-201	69%	24% (14 of 59)	23% (10 of 44)
Travin et al. [44]	Th-201	64%	11% (15 of 134)	10% (14 of 134)
Chiariello et al. [45]	Ex-ECG	NA	56% (18 of 32)	47% (7 of 15)
Caracciolo et al. [46]	Ex-ECG	100%	14% (39 of 271)	14% (33 of 240)
Marchant et al. [47]	Ex-ECG	100%	63% (10 of 16)	33% (12 of 36)
Total			14% (163 of 1136)	12% (148 of 1194)

Ex-ECG = exercise electrocardiography, Th-201 = thallium scintigraphy, NA = not available
[a] $p < 0.05$ and [b] $p < 0.001$ for the comparison between the groups

normal when the reported overall excess of coronary artery disease in diabetic populations is taken into account.

Silent myocardial ischaemia in diabetic patients with coronary artery disease. Patients with documented coronary artery disease often have episodes of silent myocardial ischaemia, but do diabetic patients of this kind have asymptomatic myocardial ischaemia more often than non-diabetic ones? There are two large studies which have compared the prevalence of silent ischaemia in diabetic and non-diabetic patients with documented coronary artery disease. Neither of them could find significant differences between the groups. One found that the prevalence of silent ischaemia in 1747 patients, of whom 180 were diabetic and 317 had asymptomatic ischaemia during exercise testing, was similar in the diabetic and non-diabetic groups [31]. Concordant results were obtained from the Coronary Artery Surgery Study Registry when analysing 113 diabetic and 1321 non-diabetic patients with documented coronary artery disease [32]. In addition, there are at least two smaller studies [33, 34] which could not show any effect of diabetes on the prevalence of silent ischaemia (Table 2).

Another, and perhaps more relevant question is whether the proportion of silent ischaemia compared with symptomatic ischaemia is higher in diabetic patients. The most often cited work in this respect is that of Nesto et al. [35], who studied 50 diabetic and 50 non-diabetic patients, all of whom had myocardial ischaemia in exercise thallium scintigraphy. Of these, 34 non-diabetic subjects, but only 14 diabetic ones ($p < 0.001$), had chest pain during exercise. Notably there were no differences in the magnitude of ischaemia as defined on the basis of the maximum ST depression or the size of the reversible perfusion defects. The picture is, however, not so clear because there are several other studies [36–47] which have assessed the clinical characteristics of patients with angiographically documented coronary artery disease involving either silent or painful myocardial ischaemia (Table 3). One of the most noteworthy of these is the Asymptomatic Cardiac Ischemia Pilot Study [46] and in line with most such reports [36–39,41,43–45,47], it did not find any significant difference in the prevalence of diabetes between these groups. Although potential bias in the selection of patients for non-invasive testing cannot be excluded, these studies have not found any significant preponderance of diabetic subjects in the group with silent myocardial ischaemia.

Electrocardiographic changes usually precede chest pain in the course of myocardial ischaemia. One attractive way to evaluate the role of a defective anginal perceptual threshold as the cause of silent

myocardial ischaemia is to measure the time interval from the emergence of ST segment changes to the onset of chest pain during exercise testing. Exercise electrocardiography done on 32 diabetic and 36 non-diabetic patients with angina pectoris showed that the diabetic patients experienced chest pain later after the onset of ST depression than the non-diabetic ones [48]. A similar analysis was carried out later in the Asymptomatic Cardiac Ischaemia Pilot Study [46], where examination of 545 exercise electrocardiograms could not even find a trend towards a later onset of chest pain in the diabetic group. Differences in the selection criteria could contribute to the divergence of the results. It is also noteworthy that those patients with the most prominent abnormality in the former study, i. e. six non-diabetic and eight diabetic patients who failed to develop chest pain during testing despite diagnostic ST segment depressions, were excluded from the analysis.

Epidemiological studies on asymptomatic coronary artery disease in diabetes. Another way to approach the problem is to review epidemiological studies to see whether they reveal any differences in angina pectoris (symptomatic disease) and ischaemic electrocardiographic changes [*f* (silent + symptomatic disease)] between diabetic and non-diabetic populations. The major limitation of this approach is that the electrocardiographic diagnosis of coronary artery disease suffers from low sensitivity and specificity. In the Israel Ischemic Heart Disease Study, the incidence of new angina pectoris was 3.2 times higher in previously diagnosed diabetic patients than non-diabetic subjects, whereas the incidence of definite ischaemic electrocardiographic changes was only 1.5 times higher in the diabetic patients [49]. There are at least four other large studies suggesting that the increase in the prevalence or incidence of symptomatic coronary artery disease in diabetic patients is not lower than the increase in ischaemic electrocardiographic abnormalities [50–53]. Only in a cross-sectional study in California were resting electrocardiographic abnormalities suggestive of asymptomatic ischaemic heart disease associated with non-insulin-dependent diabetes mellitus [54].

Thus, indirect evidence from clinical studies and epidemiological surveys suggest that the increase in the prevalence of asymptomatic coronary artery disease in diabetic subjects does not differ significantly from the increase in the symptomatic forms of the disease but could be a consequence of accelerated atherosclerosis in diabetes. Further, there is no convincing evidence that the episodes of silent myocardial ischaemia are more common in diabetic patients with documented coronary artery disease.

Association of diabetic autonomic neuropathy with silent myocardial infarction

The afferent fibres running through the cardiac sympathetic nerves form the essential pathway for the transmission of cardiac pain [55]. It is reasonable to assume that diabetic autonomic neuropathy interferes with the afferent cardiac sensory impulses in view of the frequent abnormalities encountered in efferent parasympathetic and sympathetic cardiac control. The concept that autonomic damage is responsible for the increased frequency of painless infarctions in the presence of diabetes is based primarily on an early autopsy series in which various degrees of neuropathic change in the visceral pericardial nerve fibres of all five diabetic patients with silent myocardial infarction but not in five patients with painful infarctions were found [56]. Another study found that diabetic patients with an abnormal Valsalva ratio more often had a history of silent myocardial infarction than those with a normal Valsalva ratio, i. e. normal autonomic nervous function [57]. This finding seems at first to support an association between autonomic damage and silent myocardial infarction but the proportions of myocardial infarctions that were silent were similar in the patients with abnormal and normal Valsalva ratios. A comparison of diabetic patients with painless and painful myocardial infarction found more abnormalities in heart rate responses reflecting autonomic function in the patients with silent myocardial infarction [58].

Association of diabetic autonomic neuropathy with silent myocardial ischaemia

During the last 10 years, interest has turned to the possible association between diabetic autonomic neuropathy and silent myocardial ischaemia (Table 4). There are at least three studies which have shown that silent ischaemia is more prevalent in patients with autonomic neuropathy than in those with normal autonomic function [17, 59, 60] and two of these [59, 60] show that the proportion of ischaemic episodes that are silent is higher in patients with autonomic neuropathy. Additional support for an association between autonomic neuropathy and silent myocardial ischaemia is provided by two studies [47, 48] that found diabetic patients experienced chest pain later after the onset of ST depression than non-diabetic patients and this delay was related to impairment in the tests of autonomic nervous function. Another study [61] found a high incidence of silent ischaemia in diabetic patients but the proportion among the diabetic patients with minimal autonomic nervous system dysfunction and those with more extensive autonomic neuropathy was similar. Two other studies [62, 63] failed to show an association between

Table 4. Prevalence of silent infarction and ischaemia in diabetic patients with and without autonomic neuropathy

Reference	Diagnosis of myocardial ischaemia or infarction	Coronary angiography (%)	Autonomic neuropathy	No autonomic neuropathy	Comments
Hume et al. [62]	Ex-ECG	–	36% (5 of 14)	20% (9 of 46)	Asymptomatic middle-aged men
Koistinen et al. [63]	Ex-ECG/Th-201	100%	38% (3 of 8)	38% (11 of 29)	Angiographic confirmation of CAD
Langer et al. [79]	Ex-ECG + Holter	–	38%[a] (8 of 21)	5% (2 of 37)	Asymptomatic middle-aged men
Murray et al. [59]	Ex-ECG	–	92%[a] (11 of 12)	39% (7 of 18)	Patients had known or suspected CAD
O'Sullivan et al. [60]	Holter	–	65%[b] (11 of 17)	4% (1 of 24)	Half of patients had a history of CAD

Ex-ECG = exercise electrocardiography, Th-201 = thallium scintigraphy, Holter = ambulatory electrocardiographic recording, CAD = coronary artery disease
[a] $p < 0.01$ and [b] $p < 0.001$ for the comparison between the groups

abnormalities in conventional autonomic function tests and silent myocardial ischaemia or asymptomatic coronary artery disease but the symptomatic patients had more severe coronary artery disease [63]. Furthermore, Nesto et al. [35] found no association between silent ischaemia and peripheral neuropathy but the development of peripheral and autonomic neuropathy is not always concordant in patients with non-insulin-dependent diabetes [64].

Confounding factors

Interpretation of the above reports on the possible association between autonomic neuropathy and silent myocardial ischaemia is complicated by many confounding factors. One limitation is that the heart-rate responses used for the conventional diagnosis of autonomic neuropathy mainly evaluate cardiac parasympathetic efferent activity (Table 4) and not the integrity of the cardiac sympathetic afferent fibres, the main pathway for the transmission of cardiac pain [55]. Another problem with the heart-rate tests is their inability to separate true diabetic autonomic *neuropathy* from autonomic *dysfunction* related to coronary artery disease, myocardial infarction or congestive heart failure because all these conditions can cause similar abnormalities in the autonomic function tests [65–69]. This information is of particular importance in diabetic patients with acute myocardial infarction because they often develop heart failure which could modify both the clinical presentation (dyspnoea instead of pain) and autonomic function of the patient leading to an "erroneous" association between atypical symptoms and abnormal autonomic function [70]. Similar problems are faced when comparing patients with silent myocardial ischaemia or infarction with healthy subjects. Increased heart rate and reduced heart rate variability, the hallmarks of diabetic autonomic neuropathy, seem to be associated with the rapid progression of coronary atherosclerosis [71], and tachycardia together with impairment of coronary blood flow and blood pressure regulation could help to precipitate attacks of myocardial ischaemia and contribute to its silent incidence in susceptible patients [72].

Information on the severity of coronary artery disease and myocardial ischaemia would help to delineate the role of altered pain perception in the lack of cardiac pain during ischaemic episodes. Unfortunately, most of the above-mentioned investigations into silent ischaemia in diabetic patients provide limited data on coronary anatomy or the magnitude of myocardial ischaemia (Tables 2–4). An additional problem for the research is that we do not know how severe the autonomic neuropathy must be to interfere with pain perception because even patients with advanced autonomic neuropathy could develop severe pain during acute myocardial infarction [73]. This question is important, because if an advanced and infrequently encountered level of damage is required, its influence can easily be obscured in epidemiological studies.

Sympathetic innervation of the heart and lack of cardiac pain

The distribution of myocardial sympathetic nerves can be assessed by dual-isotope imaging with radiolabelled metaiodobenzylguanidine, a norepinephrine analogue, or with radiolabelled catecholamines visualized by positron emission tomography [74, 75]. Theoretically, these techniques should add valuable information to the heart-rate based testing of autonomic function, although they cannot distinguish between afferent and efferent nerve endings. A few studies [75–80] have suggested that the global sympathetic

innervation of the heart is disturbed in diabetes, especially in patients with diabetic autonomic neuropathy or non-insulin-dependent disease [78, 79]. Relevant to the present issue is the observation that diabetic patients with silent myocardial ischaemia also seem to have evidence of a diffuse abnormality in metaiodobenzyl guanidine uptake [79]. This was confirmed by a finding of abnormal sympathetic innervation in the areas of myocardial ischaemia in all asymptomatic diabetic patients [81]. Things were made more complicated by the observation in the same study of similar or even more profound abnormalities in all diabetic patients with painful myocardial ischaemia. The results of this study are in agreement with another showing the extent of viable but denervated myocardium to be associated with increased (not decreased) cardiac pain sensitivity in non-diabetic patients with recent myocardial infarction [82]. These findings [63, 82, 83], together with experimental evidence [84], show that sympathetic innervation of the heart is highly sensitive to ischaemia and that this profound effect of ischaemia masks the potential effects of autonomic neuropathy on sympathetic innervation and certainly questions the major role of autonomic neuropathy in the lack of cardiac pain in diabetic patients with coronary artery disease.

Mechanisms of silent myocardial ischaemia

The mechanisms of silent myocardial ischaemia are complex and controversial, even in non-diabetic patients. Less severe ischaemia, i. e. less myocardium at jeopardy, milder or shorter ischaemic episodes that are insufficient to meet the threshold of pain, localized alteration in the pain threshold due to destruction of the nociceptive pathways, e. g. by myocardial infarction, and variation in the general pain threshold could contribute to the differences between silent and painful myocardial ischaemia [85]. Dynamic positron emission tomographic imaging has recently shown that the thalamus, and not the activation of sympathetic afferents, acts as a gate to afferent pain signals from the ischaemic myocardium, with cortical activation being necessary for the sensation of pain [86]. This method could also provide further insights into the pathophysiology of silent myocardial ischaemia in the presence of diabetes.

Conclusions

Due to the wide acceptance of the dogma that diabetic patients with coronary artery disease often present with atypical symptoms, physicians seem to exercise more caution and are more aggressive in their use of tests and procedures in their triage of diabetic patients with chest complaints. It seems, however, that excessive emphasis is placed on the contribution of diabetic autonomic neuropathy to the atypical presentation of coronary artery disease**.** In spite of the theoretical background, there is no convincing evidence that autonomic neuropathy is the major factor responsible for the lack of ischaemic pain in diabetic patients. This is not surprising because the mechanisms of silent myocardial ischaemia are complex and controversial even in non-diabetic patients. The available epidemiological and clinical data suggest that the increased incidence of asymptomatic myocardial infarctions, coronary artery disease and myocardial ischaemia in diabetic patients mainly reflects accelerated coronary atherosclerosis. Even if diabetic subjects do often have asymptomatic coronary artery disease, myocardial infarctions and episodes of myocardial ischaemia, there is no evidence to prove that the proportion of silent disease relative to symptomatic disease or episodes is significantly increased in them.

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