Association Between Silent Coronary Artery Disease, Diabetes, and Autonomic Neuropathy

Fact or Fallacy?

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It is generally accepted that the incidence of both asymptomatic and symptomatic coronary artery disease is increased in diabetic patients. Many of us have also been taught that diabetic patients with myocardial infarction present with atypical symptoms of acute infarction and are frequently admitted to hospital with painless myocardial infarction. Another easily accepted notion is that autonomic damage is responsible for the increased frequency of painless ischemic episodes. However, all of these contentions are open to discussion. The purpose of this article is to make a critical review of the available information on these relationships.

SILENT MYOCARDIAL INFARCTION AND DIABETES — Bradley and Schonfeld (1) demonstrated that diabetic patients hospitalized for myocardial infarction more often had little or no pain during infarction than did nondiabetic patients. This result does not definitely mean that painless or atypical myocardial infarction is abnormally common in the whole diabetic population, although it was more common in the proportion of patients who were hospitalized at the time of infarction. Selection bias may modify results, which are based on hospital records. It is possible that the diabetic patients had a closer medical follow-up, including closer electrocardiographic surveillance, or that they sought medical attention and were hospitalized more readily because of symptoms related to their diabetic status, e.g., uncontrolled diabetes, nausea, or general weakness. These circumstances could have erroneously increased the frequency of painless and atypical infarctions in the hospitalized diabetic patients compared with hospitalized nondiabetic patients. Population-based epidemiological studies are likely to give a more reliable picture of the incidence of unrecognized myocardial infarctions in diabetic populations, although the electrocardiographic criteria of infarction and the interval between the recordings may affect the incidence.

The first population-based assessment of the association between diabetes and silent myocardial infarction was the Framingham Study (2). In the 18-yr follow-up, a higher proportion of myocardial infarctions were silent or unrecognized not only in diabetic but also in hypertensive subjects (2). However the fact that these differences were not statistically significant has often been ignored. In the less-frequently-referred-to 30-yr follow-up, hypertension and female gender were associated with an excessive occurrence of unrecognized infarctions but not diabetes (3). In the Israeli study, the incidence of unrecognized infarctions was related to age, left ventricular hypertrophy, and high blood pressure but not to diabetes (4), whereas a prevalence survey in Malta showed that 1.8% of 656 nondiabetic patients with myocardial infarction and 2.8% of 283 diabetic patients had no chest pain (5). Similarly, pain as a presenting symptom was no less common in diabetic patients enrolled in the Multicenter Postinfarction Program (6). The Western Collaborative Group Study has often been thought to support the association between silent myocardial infarctions and diabetes mellitus (7), but this investigation compared patients with unrecognized myocardial infarctions with subjects with no clinical coronary artery disease. Naturally, a trend toward a preponderance of diabetic subjects in the former group was found. This relationship may nevertheless reflect only the effect of diabetes mellitus in promoting atherosclerosis. A similar relationship was found with respect to other common risk factors. In summary, the above observations suggest that even if diabetic subjects have silent myocardial infarctions more often than nondiabetic subjects, silent or unrecognized infarctions

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Table 1—*Prevalence of diabetes mellitus in patients with silent and painful ischemia*

Ref.	N	Detection of ischemia	Coronary angiography (%)	Prevalence of diabetes (%)	
				Silent ischemia	Painful ischemia
Mark et al. (22)	842	ex-ECG	100	9 (22 of 242)	9 (54 of 600)
Falcone et al. (23)	473	ex-ECG	100	4 (10 of 269)	6 (12 of 204)
Chipkin et al. (24)	211	ex-ECG	48	14 (14 of 101)	11 (12 of 110)
deBelder et al. (25)	104	ex-ECG	88	16 (11 of 67)	8 (3 of 37)
Ouyang et al. (26)	60	ex-ECG	100	24 (9 of 38)	0 (0 of 22)*
Kurata et al. (27)	173	Th-201	66	24 (26 of 108)	34 (22 of 65)
Hecht et al. (28)	112	Th-201	100	13 (11 of 84)	32 (9 of 28)*
Gasperetti et al. (29)	103	Th-201	69	24 (14 of 59)	23 (10 of 44)
Total	2078			12 (117 of 968)	11 (122 of 1110)

ex-ECG, exercise electrocardiography; Th-201, exercise thallium scintigraphy.
*$P < 0.05$.

relative to all episodes do not seem to be significantly increased in diabetic compared with nondiabetic patients.

SILENT CORONARY ARTERY DISEASE AND DIABETES — The current literature cannot give a direct answer to the question of whether the proportion of asymptomatic coronary artery disease compared with symptomatic disease is abnormally high in diabetic subjects. There are three ways, with their inherent limitations, to analyze this question. *1*) Do epidemiological studies reveal any differences in the relative risks of angina pectoris (symptomatic disease) and electrocardiographic changes? 2) Is exercise-induced silent myocardial ischemia abnormally common in presumably healthy diabetic subjects? 3) Do diabetic patients with documented coronary artery disease have more often silent ischemia than nondiabetic patients?

In the Israel Ischemic Heart Disease Study, the incidence of new angina pectoris was 3.2 times higher in previously diagnosed diabetic than nondiabetic patients whereas that of myocardial infarction (electrocardiographic diagnosis) was only 1.5 times higher (8). Similarly, in the diabetic subjects of the Framingham cohort, the relative risk of angina pectoris was comparable to the risk of other manifestations of coronary artery disease (9). In a cross-sectional study from California, resting electrocardiographic abnormalities suggestive of asymptomatic ischemic heart disease were associated with non-insulin-dependent diabetes mellitus (10). On the other hand, there are at least three other large studies suggesting that the increase in the prevalence or incidence of symptomatic coronary artery disease is similar to that in ischemic electrocardiographic abnormalities in the diabetic population (11–13). One limitation of epidemiological studies is that electrocardiographic diagnosis of coronary artery disease suffers from low sensitivity and specificity. Registration of subjective symptoms is also sensitive e.g., to verbal skills of the patient.

Exercise electrocardiography has been used to assess the prevalence of asymptomatic coronary artery disease in small series of presumably healthy diabetic subjects. The frequency of positive exercise electrocardiograms in asymptomatic middle-aged diabetic subjects has varied from 14 to 23% (14–16) compared with a prevalence of 6–12% (17–19) in asymptomatic nondiabetic subjects of similar age. Although exercise electrocardiogram is a more sensitive method than resting electrocardiogram, its reliability in totally asymptomatic subjects has been questioned because according to Bayes's theorem, the probability of false positive findings is high (20). The lack of specificity is also a problem in thallium imaging. In two studies, 38–52% of patients with abnormal scans had no significant coronary artery disease (16,21). Therefore, it would be ideal if the positive findings of noninvasive tests could be ascertained with coronary arteriography. Wide application of invasive studies in asymptomatic subjects may result in ethical problems. Despite these limitations, the excess of asymptomatic disease seems to be quite comparable to the reported overall excess of coronary artery disease in diabetic populations.

Silent ischemia is common in patients with coronary artery disease, especially after myocardial infarction. There are several studies that have compared the clinical characteristics of patients with angiographically documented coronary artery disease who have either silent or painful myocardial ischemia (Table 1; 22–29). Although potential bias in the selection of patients for noninvasive testing cannot be excluded, these studies have not revealed any significant preponderance of diabetic subjects in the group with silent myocardial ischemia. In addition to these studies, there are two studies that

have compared the prevalence of silent ischemia in diabetic and nondiabetic patients with probable coronary artery disease. Nesto et al. (30) studied 50 diabetic and 50 nondiabetic patients. Silent ischemia was more common in the diabetic group (72 vs. 32%, respectively). On the other hand, Callaham et al. (31) reported the results of 1747 patients, of whom 180 were diabetic and 317 had asymptomatic ischemia, and found that the prevalence of silent ischemia was similar in diabetic and nondiabetic patients (62 vs. 60%). Angiographic data was available only in 18% of the study patients and Nesto et al. did not include angiographic data. Taken together, all the above-mentioned results suggest indirectly that the increase in silent coronary artery disease is quite similar to that in painful and overall coronary artery disease in the diabetic population.

DIABETIC AUTONOMIC NEUROPATHY AND SILENT MYOCARDIAL INFARCTION AND ISCHEMIA — The afferent fibers running through the cardiac sympathetic nerves form the essential pathway for the transmission of cardiac pain (32). It is reasonable to assume that diabetic autonomic neuropathy may interfere with the afferent cardiac sensory impulses in view of the abnormalities encountered in efferent parasympathetic and sympathetic cardiac control. The idea that autonomic damage is responsible for the increased frequency of painless infarctions and ischemia in diabetes is based primarily on the small autopsy series of Faerman et al. (33), who found various degrees of neuropathic change in the visceral pericardial nerve fibers of five diabetic patients with silent myocardial infarction but not in five patients with painful infarctions. Only three of the patients with painless myocardial infarction had clinical neuropathy. No data on the extent of myocardial damage or coronary atherosclerosis were available.

Niakan et al. (34) found that diabetic patients with an abnormal Valsalva ratio, which was suggested to reflect autonomic neuropathy, more often had a history of silent myocardial infarction than those with normal Valsalva ratio, i.e., normal autonomic nervous function. At first, this finding seems to support an association between autonomic damage and silent myocardial infarction. However, it must be remembered that autonomic neuropathy cannot be diagnosed on the basis of one abnormal cardiovascular reflex. Furthermore, myocardial infarction is associated with autonomic dysfunction (35–38), which may cause similar alterations in Valsalva ratio as diabetic autonomic neuropathy (35). Therefore, in a critical interpretation the findings described by Niakan et al. may only reflect the often disregarded effect of myocardial infarction on autonomic nervous function. Note that the proportions of episodes of myocardial infarctions that were silent were comparable in the patients with abnormal and normal Valsalva ratios.

Interest has turned to the potential association between diabetic autonomic neuropathy and silent myocardial ischemia. Ambepityia et al. (39) studied diabetic and nondiabetic patients with angina pectoris (i.e., symptomatic disease) with exercise electrocardiography and found that the diabetic patients experienced chest pain later after the onset of ST depression than did nondiabetic patients. Those patients with the most prominent abnormality, i.e., six nondiabetic and eight diabetic patients who failed to develop chest pain during testing, despite diagnostic ST segment depressions, were, however, excluded from analysis and the data on the severity of coronary artery disease were incomplete. The delay in the perception of pain was related to the impairment of autonomic nervous function, i.e., heart rate variation during deep breathing and the Valsalva ratio. However, it was significant that a similar relationship was also noted in the nondiabetic group, who are unlikely to have autonomic neuropathy but rather autonomic dysfunction related to the severe coronary artery disease (35–38,40,41).

Nesto et al. (30) assessed the reliability of angina pectoris as a sign of coronary artery disease in consecutive diabetic patients referred for exercise thallium scintigraphy. As previously discussed, they found that diabetic patients were more often asymptomatic than nondiabetic patients. However, the lack of symptoms was not related to the presence of neuropathy.

The findings of Nesto et al. (30) are in agreement with those of Hume et al. (15), who demonstrated that an abnormal exercise electrocardiogram is no more common in asymptomatic diabetic patients with peripheral or autonomic neuropathy than in those without.

Koistinen et al. (16) recently screened a large population-based group of middle-aged diabetic subjects and found 14 patients with asymptomatic coronary artery disease and exercise-induced myocardial ischemia (42). Their autonomic function was compared with that of a group of consecutive diabetic patients catheterized in the same institution because of severe chest pain. The groups did not differ in regard to the autonomic function tests. Detailed data were also obtained on the coronary anatomy of the patients, showing the asymptomatic diabetic patients to have a milder coronary artery disease compared with the symptomatic ones. Unfortunately, the above-mentioned investigations into silent ischemia in diabetic patients had no data on the coronary anatomy (15,30,39).

The question of the potential association between diabetic autonomic neuropathy and silent myocardial infarction and ischemia is difficult to answer. Cardiac sympathetic afferent fibers constitute the main pathway for the transmission of cardiac pain (32). One limitation on any clinical evaluation of the association of autonomic

neuropathy with the lack of cardiac pain is that this part of autonomic function is difficult to assess. The heart-rate responses used for the conventional diagnosis of autonomic neuropathy mainly reflect the integrity of cardiac parasympathetic activity, and an additional problem with the heart-rate tests is the confounding effect of coronary artery disease and myocardial infarction (35–38,40,41). Preliminary studies suggest that the distribution of myocardial sympathetic nerves may be assessed with radiolabeled metaiodobenzylguanidine (43). The technique has not been used in the evaluation of silent myocardial ischemia or infarction.

It is not known how severe the autonomic neuropathy must be to interfere significantly with pain perception. This question is important, because if an advanced and infrequently encountered damage is required, its influence would be easily obscured in epidemiological studies. Note that even patients with advanced autonomic neuropathy may develop severe pain during acute myocardial infarction (44).

The mechanisms of silent myocardial ischemia are complex and controversial even in nondiabetic patients. Less-severe ischemia, i.e., less myocardium at jeopardy, milder or shorter ischemic episodes, 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 may contribute to the differences between silent and painful myocardial ischemia (45).

CONCLUSIONS — In summary, we believe that there is nothing mysterious in the silent coronary artery disease of diabetic patients. Diabetic subjects have accelerated coronary atherosclerosis; all clinical manifestations of coronary artery disease are abnormally common in diabetic subjects; it is quite natural also that the milder preclinical and asymptomatic forms of the disease are more common. Similarly, if we assessed asymptomatic middle-aged patients with familial hypercholesterolemia, we would not be surprised to find asymptomatic coronary artery disease to be common. No study shows that asymptomatic coronary artery disease or myocardial infarction is more severe (assessed by cardiac catheterization and degree of ischemia) in diabetic subjects compared with nondiabetic patients. The association of autonomic neuropathy to unrecognized myocardial infarctions or silent myocardial ischemia is still unsubstantiated, although the theoretical background of the association may capture the imagination of investigators and physicians.

References

1. Bradley RF, Schonfield A: Diminished pain in diabetic patients with acute myocardial infarction. *Geriatrics* 17: 322–26, 1962
2. Margolis JR, Kannel WB, Feinleib M, Dawber TR, McNamara PM: Clinical features of unrecognized myocardial infarction—silent and symptomatic. *Am J Cardiol* 32:1–7, 1973
3. Kannel WB: Silent myocardial ischemia and infarction: insights from the Framingham study. *Cardiol Clin* 4:583–91, 1986
4. Medalie JH, Goldbourt U: Unrecognized myocardial infarction: five-year incidence, mortality and risk factors. *Ann Intern Med* 84:526–31, 1976
5. Zammet Maempel JV: Effect of diabetes in the course of acute myocardial infarction in Malta. *Isr J Med Sci* 14:424–31, 1978
6. Smith JW, Buckels LJ, Carlson K, Marcus FI: Clinical characteristics and results of noninvasive tests in 60 diabetic patients after acute myocardial infarction. *Am J Med* 75:217–24, 1983
7. Rosenman RH, Friedman M, Jenkins CD, Straus R, Wurm M, Kositchek R: Clinically unrecognized myocardial infarction in the Western Collaborative Group Study. *Am J Cardiol* 19:776–82, 1967
8. Herman JB, Medalie JH, Goldbourt U: Differences in cardiovascular morbidity and mortality between previously known and newly diagnosed adult diabetics. *Diabetologia* 13:229–34, 1977
9. Kannel WB: Role of diabetes in cardiac disease: conclusions from population studies. In *Diabetes and the Heart*. Zoneraich S, Ed. Springfield, IL, Thomas, 1978, p. 97–112
10. Scheidt-Nave C, Barrett-Connor E, Wingard DL: Resting electrocardiographic abnormalities suggestive of asymptomatic ischemic heart disease associated with non-insulin-dependent diabetes mellitus in a defined population. *Circulation* 81:899–906, 1990
11. Reunanen A, Pyörälä K, Aromaa A, Maatela J, Knekt P: Glucose tolerance and coronary heart disease in middle-aged Finnish men: social insurance institution's coronary heart disease study. *J Chronic Dis* 32:747–58, 1979
12. Uusitupa M, Siitonen O, Aro A, Pyörälä K: Prevalence of coronary heart disease, left ventricular failure and hypertension in middle-aged, newly diagnosed type 2 (non-insulin-dependent) diabetic subjects. *Diabetologia* 28:22–27, 1985
13. Laakso M, Rönnemaa T, Pyörälä K, Kallio V, Puukka P, Penttilä I: Atherosclerotic vascular disease and its risk factors in non-insulin-dependent diabetic and nondiabetic subjects in Finland. *Diabetes Care* 11:449–63, 1988
14. Bellet S, Roman L: The exercise test in diabetic patients as studied by radioelectrocardiography. *Circulation* 36: 245–54, 1967
15. Hume L, Oakley GD, Boulton JM, Hardisty C, Ward JD: Asymptomatic myocardial ischemia in diabetes and its relationship to diabetic neuropathy: an exercise electrocardiography study in middle-aged diabetic men. *Diabetes Care* 9:384–88, 1986
16. Koistinen MJ, Huikuri HV, Pirttiaho H, Linnaluoto MK, Takkunen JT: Evaluation of exercise electrocardiography and thallium tomographic imaging in detecting asymptomatic coronary artery disease in diabetic patients. *Br Heart J* 63:7–11, 1990
17. Eriksen J, Enge I, Forfang K, Storstein

O: False positive diagnostic tests and coronary angiographic findings in 105 presumably healthy males. *Circulation* 54:371–76, 1976
18. Cummings GR, Samm J, Borsyk L, Kich L: Electrocardiographic changes during exercise in asymptomatic men: 3-year follow-up. *Can Med Assoc J* 112:578–81, 1975
19. Bruce RA, McDonough JR: Stress testing in screening for cardiovascular disease. *Bull NY Acad Med* 45:1288–305, 1969
20. Froelicher VF, Thompson AJ, Longo MR Jr, Triebwasser JH, Lancaster MC: Value of exercise testing for screening asymptomatic men for latent coronary artery disease. *Prog Cardiovasc Dis* 18: 265–76, 1976
21. Camp AD, Garvin PJ, Hoff J, Marsh J, Byers SL, Chaitman BR: Prognostic value of intravenous dipyridamole thallium imaging in patients with diabetes mellitus considered for renal transplantation. *Am J Cardiol* 65:1459–63, 1990
22. Mark DB, Hlatky MA, Califf RM, Morris JJ, Sisson SD, McCants CB, Lee KL, Harrell FE, Pryor DB: Painless exercise ST deviation on the treadmill: long-term prognosis. *J Am Coll Cardiol* 14: 885–92, 1989
23. Falcone C, deServi S, Poma E, Campana C, Scire A, Montemartini C, Specchia G: Clinical significance of exercise-induced silent myocardial ischemia in patients with coronary artery disease. *J Am Coll Cardiol* 9:295–99, 1987
24. 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* 59:61–65, 1987
25. De Belder M, Skehan D, Pumphrey C, Khan B, Evans S, Rothman M, Mills P: Identification of a high risk subgroup of patients with silent myocardial ischaemia after myocardial infarction: a group for early therapeutic revascularisation? *Br Heart J* 63:145–50, 1990
26. Ouyang P, Shapiro EP, Chandra NC, Gottlieb SH, Chew PH, Gottlieb SO: An angiographic and functional comparison of patients with silent and symptomatic treadmill ischemia early after myocardial infarction. *Am J Cardiol* 59:730–34, 1987
27. Kurata C, Sakata K, Taguchi T, Kobayashi A, Yamazaki N: Exercise-induced silent myocardial ischemia: evaluation by thallium-201 emission computed tomography. *Am Heart J* 119:557–67, 1990
28. Hecht HS, Shaw RE, Bruce T, Myler RK: Silent ischemia: evaluation by exercise and redistribution tomographic thallium-201 imaging. *J Am Coll Cardiol* 14:895–900, 1989
29. Gasperetti CM, Burwell LR, Beller GA: Prevalence of and variables associated with silent myocardial ischemia on exercise thallium-201 stress testing. *J Am Coll Cardiol* 16:115–23, 1990
30. Nesto RW, Phillips RT, Kett KG, Hill T, Perper E, Young E, Leland OS: Angina and exertional ischemia in diabetic and nondiabetic patients: assessment by exercise thallium scintigraphy. *Ann Intern Med* 108:170–75, 1988
31. Callaham PR, Froelicher VF, Klein J, Risch M, Dubach P, Friis R: Exercise-induced silent ischemia: age, diabetes mellitus, previous myocardial infarction and prognosis. *J Am Coll Cardiol* 14: 1175–80, 1989
32. Malliani A, Lombardi F: Consideration of the fundamental mechanisms eliciting cardiac pain. *Am Heart J* 103:575–78, 1982
33. Faerman I, Faccio E, Milei J, Nunez R, Jadzinsky M, Fox D, Rapaport M: Autonomic neuropathy and painless myocardial infarction in diabetic patients. *Diabetes* 26:1147–58, 1977
34. Niakan E, Harati Y, Rolak LA, Comstock JP, Rokey R: Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy. *Arch Intern Med* 146:2229–30, 1986
35. Tristani FE, Kamper DG, McDermott DJ, Peters BJ, Smith JJ: Alterations of postural and Valsalva responses in coronary heart disease. *Am J Physiol* 233: H694–99, 1977
36. Airaksinen KEJ, Ikäheimo MJ, Linnaluoto MK, Niemelä M, Takkunen JT: Impaired vagal heart rate control in coronary artery disease. *Br Heart J* 58:592–97, 1987
37. Rothschild M, Rothschild A, Pfeifer M: Temporary decrease in cardiac parasympathetic tone after acute myocardial infarction. *Am J Cardiol* 62:637–39, 1989
38. Airaksinen KEJ, Koistinen MJ, Ikäheimo MJ, Pirttiaho H, Huikuri HV, Takkunen JT: Effect of coronary artery disease on parasympathetic cardiovascular reflexes in NIDDM patients. *Diabetes Care* 13: 83–86, 1990
39. Ambepityia G, Kopelman PG, Ingram D, Swash M, Mills PG, Timmis AD: Exertional myocardial ischemia in diabetes: a quantitative analysis of anginal perceptual threshold and the influence of autonomic function. *J Am Coll Cardiol* 15:72–77, 1990
40. Hayano J, Sakakibara Y, Yamada M, Ohte N, Fujinami T, Yokoyama K, Watanabe Y, Takata K: Decreased magnitude of heart rate spectral components in coronary artery disease: its relation to angiographic severity. *Circulation* 81: 1217–24, 1990
41. Hayano J, Yamada A, Nukai S, Sakakibara Y, Yamada M, Ohte N, Hashimoto T, Fujinami T, Takata K: Severity of coronary atherosclerosis correlates with the respiratory component of heart rate variability. *Am Heart J* 121:1070–79, 1991
42. Koistinen MJ, Airaksinen KEJ, Huikuri HV, Pirttiaho H, Ikäheimo MJ, Linnaluoto MK, Takkunen JT: Diabetic autonomic neuropathy and severity of coronary artery disease in manifestation of cardiac symptoms in diabetic patients (Abstract). *Philipp J Cardiol* 19 (Suppl.): 173, 1990
43. Dae MW, Herre JM, O'Connell JW, Botvinick EH, Newman D, Munoz L: Scintigraphic assessment of sympathetic innervation after transmural versus nontransmural myocardial infarction. *J Am Coll Cardiol* 17:1416–23, 1991
44. Campbell IW, Ewing DJ, Clarke BF: Painful myocardial infarction in severe diabetic autonomic neuropathy. *Acta Diabetol Lat* 15:201–204, 1978
45. Cohn PF: Silent myocardial ischemia. *Ann Intern Med* 109:312–17, 1988