



Review

Large and micro coronary vascular involvement in diabetes

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Abstract:

Diabetes, with hyperglycemia as its hallmark, is a major risk factor for ischemic heart disease. The role of coronary disease in the adverse prognosis of diabetes is controversial although the higher prevalence and extension of coronary atherosclerosis is well recognized. The paper reviews the available evidence of coronary involvement in diabetes with particular emphases on microcirculation.

Several studies, mainly in type 2 diabetes, have documented a reduced coronary flow reserve even in absence of coronary obstructive disease and using different techniques. Microcirculatory dysfunction affects the left ventricle globally as well as regionally. However, neither the prevalence of such abnormality in the diabetic population nor its time course and its prognostic value have been investigated in specifically addressed studies. In fact, a relatively large number of studies on myocardial perfusion performed by single-photon myocardial scintigraphy in asymptomatic diabetics rather address the problem of the prevalence of silent ischemia and its prognostic value. In spite of such limitation it can be speculated from the few available studies with known coronary anatomy that the prevalence of exclusively regional disturbances of perfusion (scintigraphic defects) in absence of obstructive coronary disease is not marginal as it ranges from 11 to 63%. Extensive research is still required to define the pathogenesis and the actual clinical relevance of coronary microcirculatory dysfunction in diabetes.

Key words:

coronary artery disease in diabetics, coronary microvascular dysfunction, myocardial perfusion scintigraphy, coronary endothelial dysfunction

Abbreviations: ACE – angiotensin-converting enzyme, MI – myocardial infarction, MPS – myocardial perfusion scintigraphy, PET – positron emission tomography

Introduction

Up to 80% of diabetic patients die from cardiovascular diseases [27]. The relative risk of cardiac mortality in diabetics, as compared to non diabetics, is from 5 to 3 times higher depending on the number of other clus-

tered risk factors (Fig. 1) [39], while both the early and late case fatality rate of acute myocardial infarction (MI) are twice as higher [2, 3, 10, 20, 47]. Thus diabetes, with hyperglycemia as its hallmark, appears to be a major risk factor for ischemic heart disease and for the adverse outcome following MI. However, the multifactorial nature of the disease and its stereotyped definition, based on the arbitrary dysaggregation of factors and the conventional attribution of cut-off values to biological variables makes results of studies less clear-cut when different components of the disease are taken into consideration. As an example, the epidemiological findings reported above have

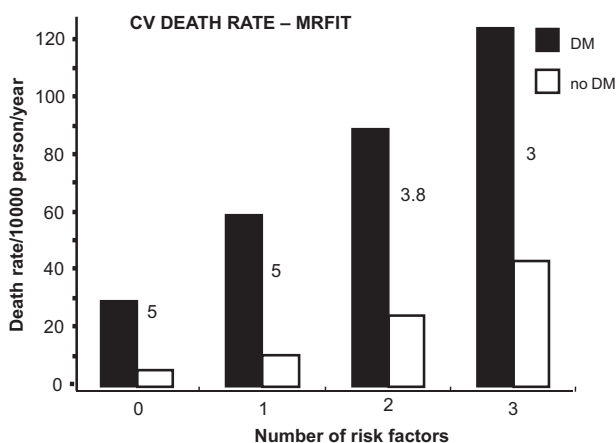


Fig. 1. Cardiac death rate in diabetic (DM) and non diabetic (no DM) patients in Risk Factor Intervention Trial Research Group (MRFITT) study. Death is from 5 to 3 times higher in diabetics according to the number of associated traditional cardiac risk factors. Modified from reference [39]

been challenged by the evolving concept of metabolic syndrome [30], a condition that from one side overlaps the old definition of pre-diabetic state and from the other aggregates, around a glycaemic disorder that does not necessarily satisfy the criteria of diabetes, multiple cardiovascular risk factors. Vascular disease actually precedes diabetes and is considered to be responsible for the 2–3 fold increase in the relative risk of death in the prediabetic state [7]. In addition, as shown in Figure 2, once diabetes was dissected from the metabolic syndrome, the prevalence of ischemic heart disease in isolated diabetes was no higher than

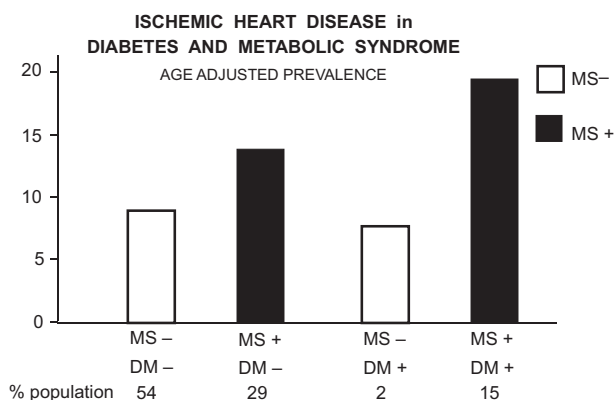


Fig. 2. Age adjusted prevalence of ischemic heart disease (IHD) in the US population over 50 years of age according to the presence (+) or absence (-) of diabetes mellitus (DM) and metabolic syndrome (MS). Modified from [1]

in subjects without diabetes (8%), in contrast with a 14% prevalence in isolated metabolic syndrome and a 19% with the combination of the two [1]. On the contrary, in patients who already suffered a MI, diabetes had a more fatal prognosis as compared to the metabolic syndrome, and the late risk of death in the latter was primarily associated with its transformation in diabetes over time [21].

From the pathogenetic point of view, beyond the difficulty of attributing a putative causality role to each component of the disease, several clinical observations remain poorly understood. While the excess of cardiac mortality in diabetes parallels the excess of coronary atherosclerosis in some reports [29], mortality after acute MI in other reports appears correlated with the severity of left ventricular dysfunction but not with the more extensive coronary disease observed in diabetes, nor with the coexisting additional cardiovascular risk factors or other end-organ diseases [45]. Moreover, treatment with angiotensin-converting enzyme (ACE)-inhibitor suppressed the excess of mortality following infarction without modifying the metabolic hallmarks of the disease [31, 47]. Thus, in alternative or in adjunction to the coronary macroangiopathy, other pathogenetic mechanisms have been proposed to explain the particularly high cardiac vulnerability in diabetes, such as coronary microcirculatory dysfunction, reduced myocardial metabolic resistance to ischemia, inflammatory and immune disorders, insulin resistance, linkage disequilibrium between diabetes and cardiovascular disease related genes, or still unknown cardiac risk factors. The existence of a hypothetical “diabetic factor” responsible for the myocardial proneness to ischemic and/or metabolic dysfunction remains the subject of continuing controversy and debate among investigators.

Aim of this paper was to review the available evidence of coronary involvement in diabetes with particular emphases on microcirculation.

Large coronary artery disease in diabetes

It is widely accepted that atherosclerotic coronary artery disease is more frequent in diabetic than in non-diabetic subjects. However, the reason for such an excess of coronary atherosclerosis is unknown. In a study on 2253 consecutive patients undergoing diagnostic coronary angiography (1984 non-diabetics and 269 diabetics), Natali et al. found that type 2 diabetes, as compared to no diabetes, was associated – especially

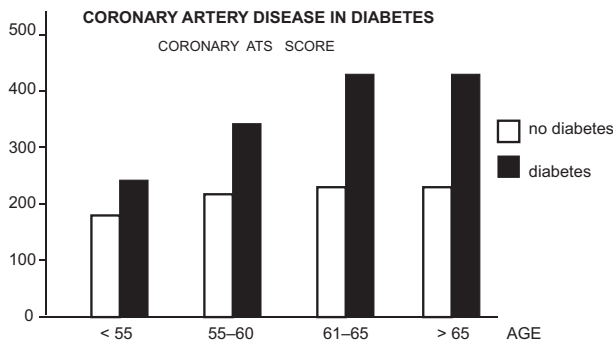


Fig. 3. Prevalence of coronary atherosclerosis (ATS) in diabetic and non-diabetic patients according to age. Modified from [29]

in women and after age adjustment – with more severe and more diffuse coronary atherosclerosis with a higher prevalence of three-vessel disease [29]. The prevalence of atherosclerotic lesions stratified by age is shown in Figure 3. The excess of coronary lesions could not be explained either by the prevalence of the other traditional risk factors or by the presence of proteinuria, an independent predictor of cardiac death during the follow-up.

Thus coronary macroangiopathy is magnified by diabetes, however its role in the excess of cardiac mortality remains controversial [29, 45].

In the last decade the presence of an endothelial dysfunction affecting large coronary arteries has been ascertained in several conditions linked to cardiovas-

cular diseases including diabetes. This acquisition has been reached through the documentation of inverted response (vasoconstriction) of coronary artery segments to intracoronary injection of acetylcholine [34] in diabetics with absence of obstructive lesions, as shown in Figure 4. Although this evidence is not specific of diabetes but is common to other cardiac risk factors frequently clustered with diabetes such as arterial hypertension, hyperlipidemia, obesity metabolic syndrome and smoking, it has been considered an early precursor of coronary atherosclerosis (pre-atherosclerotic state).

Coronary microvascular dysfunction in diabetes

It has been suggested that coronary microvascular dysfunction might contribute to the development of left ventricular dysfunction through episodes of silent myocardial ischemia. However, this topic has not been extensively investigated in diabetes likely because of the difficulties in documenting microcirculatory alterations in the clinical setting.

The study of coronary microcirculation is approached by the measurement of either coronary phasic flow (velocity) in a single coronary artery (rarely in the coronary sinus) or by the assessment of myocardial perfusion in the various regions of the left ventricle [18]. By means of such approach, microcirculation can be adequately investigated at the condition that obstructive disease of large coronary arteries is ruled out. In this instance in fact, any documented abnormality in coronary flow can be directly ascribed to microvascular abnormality. Obviously, the requirement of coronary angiography have made the study of microcirculation, so far, necessarily limited to small numbers of symptomatic or high risk diabetic patients.

Flow measurements are usually performed both in basal conditions and following a stimulation able to provoke the dilatation (hopefully maximal) of coronary microvessels. The provocative stimulus can be pharmacological (administration of coronary vasodilator drugs) or physical. The latter is usually muscular exercise, less frequently cardiac pacing; both lead to metabolically mediated dilatation through the increase in cardiac oxygen consumption. The response of coronary flow and thus the coronary flow reserve (that is simply the ratio between post-stimulus and basal flows) are considered normal when flow increases up to at least 2.5 times from baseline.

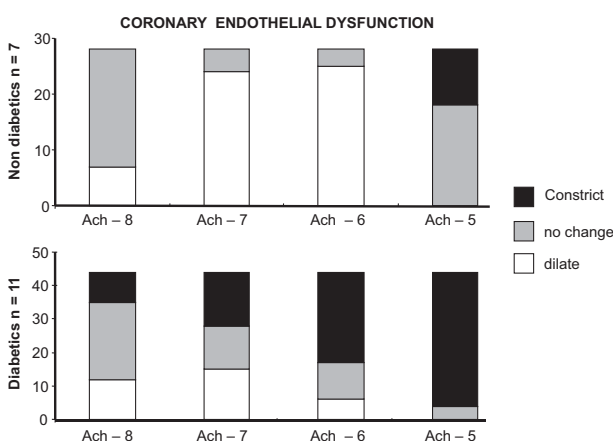


Fig. 4. Response of coronary arteries (average of 6–10 segment per patient) to progressive doses of intracoronary acetylcholine in diabetics and non-diabetics. At each dose of acetylcholine, the vasoconstrictive response is higher in diabetics. In contrast the vasodilating response to papaverine is similar (not shown). Modified from reference [34]

Several studies, mainly in type 2 diabetes, have documented a reduced coronary flow reserve. This is true for studies that measured intracoronary doppler flow both invasively [19, 28, 33] or with transesophageal echocardiography [16] as well as for studies that measured myocardial perfusion by positron emission tomography (PET) [8, 15, 22, 46]. Many of the above studies enrolled diabetic patients following the documentation of angiographically normal coronary arteries, while in the remaining coronary disease was excluded on clinical basis only. Thus it can be concluded that microcirculation becomes affected in diabetes even before the occurrence of coronary atherosclerosis. However, neither the prevalence of such abnormality in the diabetic population nor its time course and its prognostic value can be envisaged by the studies above. This information can only be obtained through studies on myocardial perfusion in large cohorts of diabetic patients. To this purpose the conventional single photon myocardial perfusion scintigraphy (MPS) appears the most adequate means [42], although the problem of excluding coexisting coronary stenoses remains.

As compared to PET, MPS is limited by a qualitative or semi-quantitative, rather than quantitative, assessment of myocardial perfusion and its relative changes within the left ventricular walls upon stress. Advantages of MPS are the much lower cost and its broad diffusion. However, MPS studies in diabetes have been mainly performed in symptomatic patients with the purpose of detecting coronary disease non invasively. The published data concerning myocardial perfusion scintigraphy in diabetics without clinical evidence of coronary heart disease (so called asymptomatic diabetics) is scarce, and the few studies that are reported in literature do not specifically address the problem of microvascular disease in diabetes, but rather the clinical and epidemiological problem of the prevalence of silent ischemia and its prognostic value.

A partial review of such scintigraphic perfusion studies is presented in Table 1. It includes the results obtained in type 1 or 2 diabetes, mainly in type 2, in patients with neither history nor symptoms of cardiopathy, a category supposed to have a relatively low prevalence of coronary disease [4–6, 9, 12, 23, 36, 43]. Prevalence of perfusion defects in this series of studies was significant, ranging from 9 to 58% of cases, the lowest and highest figures belonging to the two largest studies. Thus the regional impairment in coronary flow reserve is present in a sizeable portion

Tab. 1. Prevalence of perfusion defect at single photon myocardial perfusion scintigraphy (MPS) in asymptomatic diabetics and percent occurrence of negative coronary angiography in positive MPS in the same patients. The latter information is available in some studies only and limited to a relatively small number of cases

Author	Positive MPS in diabetes			
	n	Type	MPS + (%)	CORO-/MPS + (%)
Milan Study [23]	925	2	12*	
Janand-Delenne et al. [12]	73	1	11*	50 (3/6)
Janand-Delenne et al. [12]	105	2	19	20 (4/20)
Castells et al. [4]	98	2	37	
Gazzaruso et al. [9]	1323	2	9*	11 (9/85)
De Lorenzo et al. [6]	180	1 + 2	26	
Cosson et al. [5]	262	1 + 2	37	63 (58/92)
Wackers et al. (DIAD study) [43]	522	2	16	
Rajagopalan [36]	1427	1 + 2	58	11 (21/187)

* Positive MPS and/or positive ECG stress test, ° mainly 2

of diabetics without clinical signs of cardiac disease. However, the attribution of such abnormality to a microvascular disease would be arbitrary because of the lack of coronary angiography in half of the studies. If one takes into consideration the studies where coronary angiography was performed in patients with positive MPS, it appears that from 11 to 63% of positive MPS contrasted with normal coronary arteries. This condition that is generally classified as a “false positive result” (relatively to the presence of coronary stenosis) might on the contrary be the expression of true perfusion abnormality. If this is the case, in diabetics with no clinical signs of cardiac disease, scintigraphic defects could be potentially ascribed to microvascular dysfunction in a significant fraction of the cases. As a matter of fact it should be considered that the scintigraphic defect becomes apparent only at the condition that a definite region of the left ventricle is underperfused relative to the other walls. A global underperfusion of the left ventricle in fact leads to an apparently normal (homogeneous) scintigram, at variance with PET that identifies the perfusion abnormality due to its ability to quantitate absolute flow. Thus it can be speculated that the detection of microvascular alterations can be underestimated by conventional myocardial scintigraphy.

As far as the pathogenetic role of scintigraphic perfusion defects is concerned, mention should be given to the observation that, in spite of the exposition of the entire coronary microcirculation to the same systemic metabolic noxa, vascular function may be compromised only regionally and that, for the same scintigraphic stress score category (severity and extension of the defect), diabetic patients tend to have slightly higher cardiac event rates as compared to non diabetics, suggesting the intervention of adjunctive factors in the determination of poorest prognosis [13].

In addition to the presence of myocardial ischemia originating from either large or small coronary vessel disease, evidence has been also collected on insufficient microvascular reperfusion in diabetic patients during acute myocardial infarction [17, 26] and reduced collateral vessels' recruitment following acute ischemia [44]. These observations could explain the higher infarct-related mortality and cardiac failure rates observed in diabetics as compared to non diabetics.

Pathogenetic considerations

The pathogenesis of coronary microcirculatory dysfunction in diabetes is still unknown. Although the review of the proposed pathogenetic mechanisms is not an object of this review, some findings are worth of reporting.

The metabolic hallmarks of diabetes, namely abnormal insulin concentration, hyperglycemia and insulin resistance all affect coronary blood flow.

Insulin stimulates myocardial blood flow in normals [11] and is able to enhance hyperemic myocardial blood flow (adenosine) in a dose-dependent manner, in normal subjects as well as in diabetics with blunted flow response to adenosine [40]. Postprandial hyperglycemia has been recently reported to produce both perfusion defects and regional abnormalities of ventricular mechanics in uncomplicated type 2 diabetics, supporting the view that postprandial hyperglycemia is a more powerful risk factor for cardiovascular disease than fasting hyperglycemia itself [38]. Finally, insulin resistance *per se* is thought to be responsible for microvascular dysfunction which are normalized by insulin-sensitizing thiazolidinedione [35] but this acquisition contrasts with the fact that coronary vascular function is impaired to a similar extent in type 1 and 2 diabetes, in spite of the inconsistency of insulin resistance in the former [8].

Oxidative stress has been postulated as the mediator of endothelial dysfunction induced by hyperlipide-

mia and hyperglycemia in diabetics through an inhibitory effect on eNOS or ATP-sensitive K-channels [14, 24, 25, 32]. Additional hypothesis is the central role of inflammation and immune disturbances [48]. In this context even slightly elevated high-sensitive CRP concentrations have been shown to be associated with reduced coronary vasoreactivity in a PET study [41].

Finally, scintigraphic studies on sympathetic myocardial innervation in conjunction with myocardial blood flow have shown that coronary endothelial-dependent vasodilation is reduced in proportion to the magnitude of cardiac sympathetic dysfunction [37]. These mechanisms are currently proposed to lead from early changes to advanced impairment of cardiac function in diabetes.

Conclusion

Diabetes greatly enhances cardiovascular disease and related mortality. It amplifies and accelerates both large and small coronary vessel diseases. The causality relationship however, between coronary involvement and clinical progression and fatality of the disease still remains elusive. Microcirculatory dysfunction is well documented even in the pre-diabetic state; it involves coronary circulation globally as well as regionally, even in absence of large coronaries obstructive lesions. However, the epidemiology, the pathogenesis and the nature itself of microcirculatory alterations remain obscure. A multidisciplinary approach and in particular the convergence of cardiologists and diabetologists in a joint research effort seems essential in order to speed-up knowledge advancement in this matter.

References:

1. Alexander CM, Landsman PB, Teutsch SM, Haffner SM: NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*, 2003, 52, 1210–1214.
2. Borghi C, Bacchelli S, Esposti DD, Ambrosioni E: SMILE Study. Effects of the early ACE inhibition in diabetic nonthrombolized patients with anterior acute myocardial infarction. *Diabetes Care*, 2003, 26, 1862–1868.

3. Casella G, Savonitto S, Chiarella F, Gonzini L, Di Chiara A, Bolognese L, De Servi S et al.: Clinical characteristics and outcome of diabetic patients with acute myocardial infarction. Data from the BLITZ-1 study. *Ital Heart J*, 2005, 6, 374–383.
4. Castells I, Salinas I, Rius F, Fraile M, Rubio L, Pereferrer D, Romero R et al.: Inducible myocardial ischemia in asymptomatic Type 2 diabetic patients. *Diabetes Res Clin Pract*, 2000, 49, 127–133.
5. Cosson E, Paycha F, Paries J, Cattan S, Ramadan A, Meddah D, Attali JR et al.: Detecting silent coronary stenoses and stratifying cardiac risk in patients with diabetes: ECG stress test or exercise myocardial scintigraphy?. *Diabet Med*, 2004, 21, 342–348.
6. De Lorenzo A, Lima RS, Siqueira-Filho AG, Pantoja MR: Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. *Am J Cardiol*, 2002, 90, 827–832.
7. DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Inter Med*, 2001, 161, 397–405.
8. Di Carli F, Janisse J, Grunberger G, Ager J: Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *JACC*, 2003, 41, 1387–1393.
9. Gazzaruso C, Garzaniti A, Giordanetti S, Falcone C, De Amici E, Geroldi D, Fratino P: Assessment of asymptomatic coronary artery disease in apparently uncomplicated type 2 diabetic patients. *Diabetes Care*, 2002, 25, 1418–1424.
10. Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*, 1998, 339, 229–234.
11. Iozzo P, Chareonthaitawee P, Di Terlizzi M, Betteridge DJ, Ferrannini E, Camici PG: Regional myocardial blood flow and glucose utilization during fasting and physiological hyperinsulinemia in humans. *Am J Physiol Endocrinol Metab*, 2002, 282, E1163–1171.
12. Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V: Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care*, 1999, 22, 1396–1400.
13. Kang X, Berman DS, Lewin HC, Cohen I, Friedman JD, Germano G, Hachamovitch R et al: Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. *Am Heart J*, 1999, 138, 1025–1032.
14. Kesavulu MM, Giri R, Kameswara Rao B, Apparao C: Lipid peroxidation and antioxidant enzyme levels in type 2 diabetics with microvascular complications. *Diabetes Metab*, 2000, 26, 387–392.
15. Kjaer A, Meyer C, Nielsen FS, Parving HH, Hesse B: Dipyridamole, cold pressor test, and demonstration of endothelial dysfunction: a PET study of myocardial perfusion in diabetes. *J Nucl Med*, 2003, 44, 19–23.
16. Kranidis A, Zamanis N, Mitrakou A, Patsilinakos S, Bouki T, Tountas N, Anthopoulos P et al.: Coronary microcirculation evaluation with transesophageal echocardiography Doppler in type II diabetics. *Int J Cardiol*, 1997, 59, 119–124.
17. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, Umemura T et al.: Diabetes mellitus is associated with insufficient microvascular reperfusion following revascularization for anterior acute myocardial infarction. *Intern Med*, 2003, 42, 554–559.
18. L'Abbate A, Sambucetti G, Haunsř S, Schneider-Eicke J: Methods for evaluating coronary microvasculature in humans. *Eur Heart J*, 1999, 20, 1300–1313.
19. Le Feuvre C, Raoux F, Beygui F, Helft G, Mogenet A, Dubois-Laforgue D, Timsit J et al.: Cumulative adverse effects of diabetes mellitus and hypertension on coronary flow velocity reserve. *Arch Mal Coeur Vaiss*, 2004, 97, 849–854.
20. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M et al.: Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation*, 1995, 91, 1659–1668.
21. Levantesi G, Macchia A, Marfisi RM, Franzosi MG, Maggioni AP, Nicolosi GL, Schweiger C et al: Metabolic syndrome and risk of cardiovascular events after myocardial infarction. *J Am Coll Cardiol*, 2005, 46, 277–283.
22. Meyer C, Schwaiger M: Myocardial blood flow and glucose metabolism in diabetes mellitus. *Am J Cardiol*, 1977, 80, 94A–101A.
23. Milan Study on Atherosclerosis and Diabetes Group: Prevalence of unrecognized silent myocardial ischemia and its association with atherosclerotic factors in non-insulin-dependent diabetes mellitus. *Am J Cardiol*, 1997, 79, 134–139.
24. Miura H, Wachtel RE, Loberiza FR Jr, Saito T, Miura M, Nicolosi AC, Guterman DD: Diabetes mellitus impairs vasodilation to hypoxia in human coronary arterioles: reduced activity of ATP-sensitive potassium channels. *Circ Res*, 2003, 92, 151–158.
25. Moreno PR, Fuster V: New aspects in the pathogenesis of diabetic atherothrombosis. *J Am Coll Cardiol*, 2004, 44, 2293–2300.
26. Moreno R, Hernandez-Antolin R, Alfonso F, Macaya C: Diabetes mellitus and acute myocardial infarction: more data supporting a poorer microvasculature reperfusion. *Am Heart J*, 2003, 146, E6.
27. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF: Lifetime risk for diabetes mellitus in the United States. *JAMA* 2003, 290, 1884–1890.
28. Nahser PJ Jr, Brown RE, Oskarsson H, Winniford MD, Rossen JD: Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. *Circulation*, 1995, 91, 635–640.
29. Natali A, Vichi S, Landi P, Severi S, L'Abbate A, Ferrannini E: Coronary atherosclerosis in Type II diabetes: angiographic findings and clinical outcome. *Diabetologia*, 2000, 43, 632–641.
30. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel

- III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*, 2002, 106, 3143–3421.
31. Nesto RW, Zarich S: Acute myocardial infarction in diabetes mellitus: lessons learned from ACE inhibition. Editorial. *Circulation*, 1998, 97, 12–15.
 32. Nitenberg A, Ledoux S, Valensi P, Sachs R, Antony I: Coronary microvascular adaptation to myocardial metabolic demand can be restored by inhibition of iron-catalyzed formation of oxygen free radicals in type 2 diabetic patients. *Diabetes*, 2002, 51, 813–818.
 33. Nitenberg A, Ledoux S, Valensi P, Sachs R, Attali JR, Antony I: Impairment of coronary microvascular dilation in response to cold pressor-induced sympathetic stimulation in type 2 diabetic patients with abnormal stress thallium imaging. *Diabetes*, 2001, 50, 1180–1185.
 34. Nitenberg A, Valensi P, Sachs R, Dali M, Aptekar E, Attali JR: Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. *Diabetes*, 1993, 42, 1017–1025.
 35. Quinones MJ, Hernandez-Pampaloni M, Schelbert H, Bulnes-Enriquez I, Jimenes X, Hernandez G, De La Rosa R et al: Coronary vasomotor abnormalities in insulin-resistant individuals. *Ann Int Med*, 2004, 140, 700–708.
 36. Rajagopalan N, Miller T, Hodge D, Frye R, Gibbons R: Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *JACC*, 2005, 45, 43–48.
 37. Schnell O: Cardiac sympathetic innervation and blood flow regulation of the diabetic heart. *Diabetes Metab Res Rev*, 2001, 17, 243–245.
 38. Scognamiglio R, Negut C, Vigili De Kreutzenberg S, Tingo A, Avogaro A: Postprandial myocardial perfusion in healthy subjects and in type 2 diabetic patients. *Circulation*, 2005, 112, 179–184.
 39. Stamler J, Vaccaro O, Neaton J, Wentworth D: Diabetes, other risk factors and 12-year cardiovascular mortality for men screened in the multiple Risk Factor Intervention Trial. *Diabetes Care*, 1993, 16, 434–444.
 40. Sundell J, Laine H, Nuutila P, Ronnema T, Luotolahti M, Raitakari O, Knuuti J: The effects of insulin and short term hyperglycemia on myocardial blood flow in young men with uncomplicated Type 1 diabetes. *Diabetologia*, 2002, 45, 775–782.
 41. Sundell J, Ronnema T, Laine H, Raitakari OT, Luotolahti M, Nuutila P, Knuuti J: High-sensitivity C-reactive protein and impaired coronary vasoreactivity in young men with uncomplicated type 1 diabetes. *Diabetologia*, 2004, 47, 1888–1894.
 42. Wackers FJ: Diabetes and coronary artery disease: the role of stress myocardial perfusion imaging. *Cleve Clin J Med*, 2005, 72, 21–25, 29–33.
 43. Wackers FJ Th, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R et al.: For the detection of Ischemia in asymptomatic diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care*, 2004, 27, 1954–1961.
 44. Werner GS, Richartz BM, Heinke S, Ferrari M, Figulla HR: Impaired acute collateral recruitment as a possible mechanism for increased cardiac adverse events in patients with diabetes mellitus. *Eur Heart J*, 2003, 24, 1134–1142.
 45. Woodfield SL, Lundergan CF, Reiner JS, Greenhouse SW, Thompson MA, Rohrbeck SC, Deychak Y et al.: Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience. *J Am Coll Cardiol*, 1996, 28, 1661–1669.
 46. Yokoyama I, Momomura S, Ohtake T, Yonekura K, Nishikawa J, Sasaki Y, Omata M: Reduced myocardial flow reserve in non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol*, 1997, 30, 1472–1477.
 47. Zuanetti G, Latini R, Maggioni AP, Franzosi M, Santoro L, Tognoni G: Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study. *Circulation*, 1997, 96, 4239–4245.
 48. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG: Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. *J Am Coll Cardiol*, 1993, 22, 1788–1794.

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