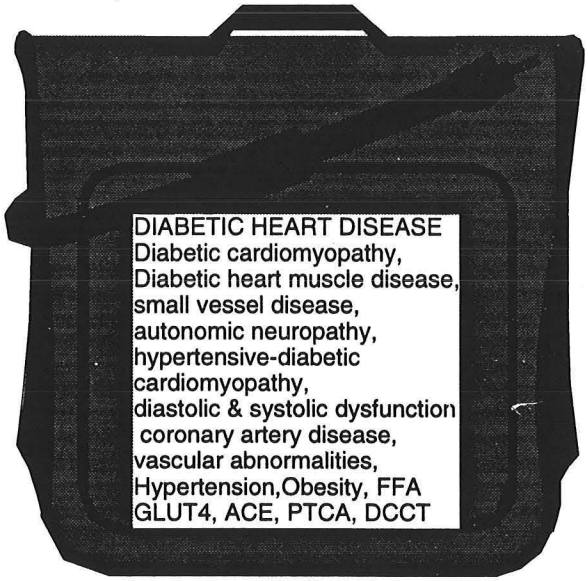
Medical Grand Rounds
The University of Texas Southwestern Medical Center
Dallas, TX

Cardiac Manifestations of Diabetes: A Mixed Bag without Sweetheart Deals



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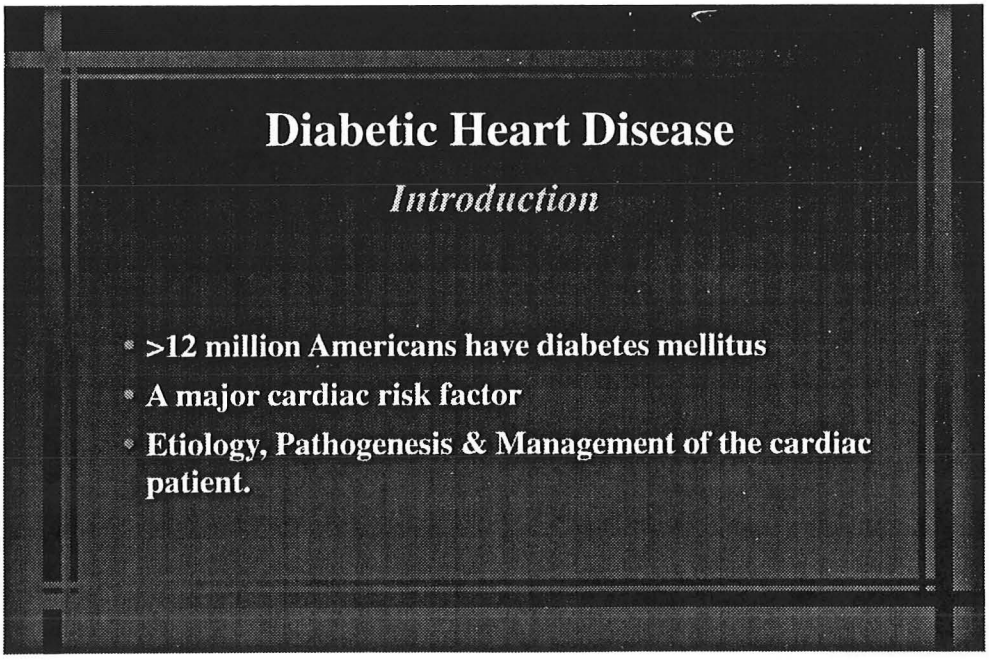
Introduction:

Diabetes mellitus is a systemic disease with disproportionate cardiovascular impact from myocardial dysfunction and overt heart failure [1]. More than 12 million Americans have diabetes making it a common public problem in both economic and human terms, (Fig. 1). Whereas autoimmune destruction of pancreatic ß-islet cells is the primary etiologic factor in insulin-dependent diabetes mellitus (IDDM), current concepts suggest that peripheral insulin-resistance and ß-islet cell failure to be the major factors in the development of noninsulin-dependent diabetes (NIDDM) [2-4]. Diabetes is a well-established risk factor for coronary artery disease although a primary defect of the heart muscle has been proposed myocardial dysfunction in diabetic patients [5]. Furthermore, just as these is not unanimity on pathogenesis of diabetes, so are efforts to characterize these cardiac manifestations of diabetes. Other major risks factors such as hypertension, cigarette smoking and obesity add substantially to cardiac disease in diabetic patients. In today's Grand Rounds, my focus on diabetic heart disease will emphasize a critical summary of earlier clinical work, evaluate important clinical challenges and diagnostic dilemmas, discuss the role of the diabetic state during myocardial ischemia as well as explore new clinical and research directions for advancing our basic knowledge to improve the management of our patients with this highly prevalent disease.

Fig.1



Insulin-dependent or Type 1 diabetes mellitus (IDDM) accounts for 10% diabetics that typically occurs in adolescents and early adulthood. Fatty acid mobilization from adipose tissue to the liver as alternative fuel source during insulin deficiency contributes to the occasionally life-threatening ketoacidosis [2]. Improved long-term survival from reduced infectious complications with insulin therapy has contributed to this population's increased risk for cardiac disease [6]. NIDDM is characterized initially by the capacity of ß cells to increase insulin secretion followed by a subsequent decline [2-4]. Overt NIDDM is due to the inability to offset the reductions in glucose clearance (predominantly by skeletal muscle) and to maintain the elevated insulin secretion in the presence of insulin resistance [7, 8]. Hyperinsulinemia with normal glucose tolerance is an independent risk factor for coronary artery disease suggesting that hormonal balance may have adverse metabolic effects in the heart [9]. Obesity exists in at least 30% of the US population and is linked to NIDDM [10]. Thus, the improved survival from more aggressive medical regimen in IDDM coupled with the prevalence of obesity-dependent NIDDM and hypertension define the denominator of diabetic patients at risk for the development of cardiovascular disease, (Fig 2).

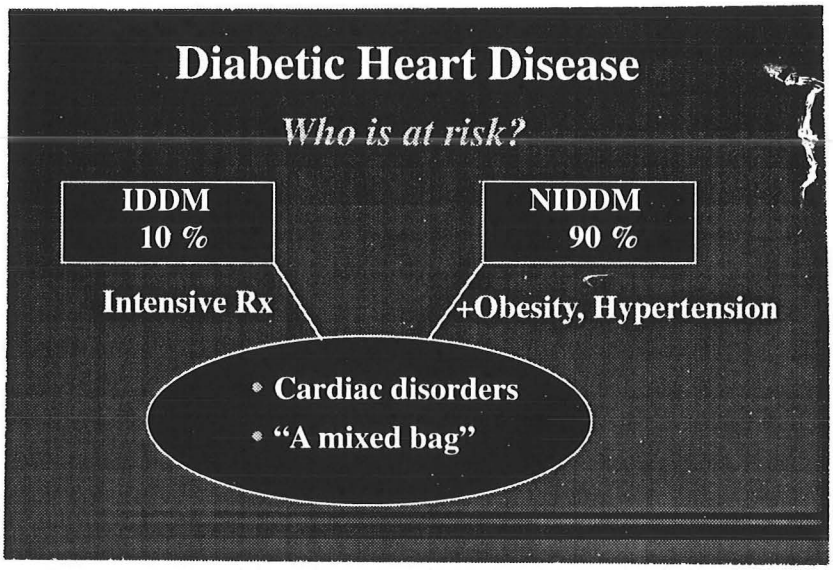


Fig. 2

History

Over a century ago, an association was made between diabetes and resting tachycardia [11]. In 1972, Rubler and colleagues originally described the cardiac abnormalities of left ventricular hypertrophy, diffuse fibrotic changes, acid mucopolysaccharide deposits and narrowing with intramural thickening of small coronary vessels in diabetic patients [12]. These investigators examined four (4)

patients of 27 patients at autopsy with diabetic glomerulosclerosis (Kimmelstiehl-Wilson disease) to characterize the microangiopathy in the heart and applied the term "cardiomyopathy" because they excluded patients with hypertension, valvular or coronary artery disease, (Fig. 3 & 4). It is questionable that hypertension, for example, could be excluded from this population with severe glomerulosclerosis. Thus the left ventricular hypertrophy and other intravascular changes could be related to hypertensive heart disease, as well. This earlier study, and several others, have contributed to the subsequent confusion since the specificity of the so-called "small vessel disease" in diabetes could not be established. These preliminary observations, however, received even greater attention in the Framingham Heart Study on congestive heart failure in diabetics [13], (Fig. 3 & 4).

Fig. 3 Diabetic glomerulosclerosis

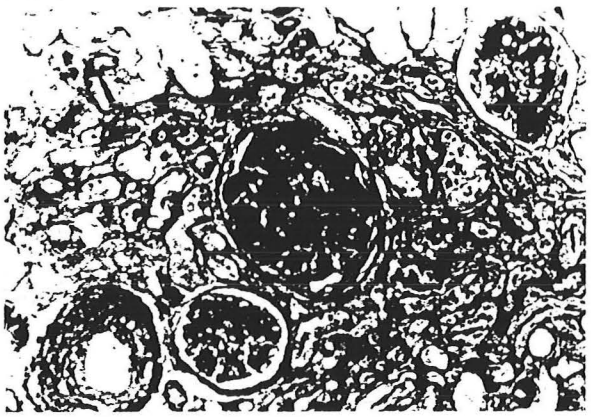


Fig. 4 Coronary Intraluminal thickening

The Framingham Heart Disease Epidemiology Study began in 1949 of 5,209 men and women aged 30 to 62 years to examine the incidence of cardiovascular disease, including congestive heart failure [13]. At biennial examinations each participant was screened with a detailed history, physical examination, chest X-ray, electrocardiogram and measurement of blood sugar and cholesterol. After 18 years' follow-up, diabetic men had a two fold and diabetic women 5 fold higher incidence of congestive heart failure compared with the nondiabetic cohorts (Table 1). When rheumatic and coronary artery disease were excluded from analysis, there was even greater incidence of heart failure in this cohort of predominantly insulin-dependent diabetics (Table 2). Thus diabetes was established as a major risk factor in the development of congestive heart failure and, perhaps, there was an independent variable not involving coronary artery disease for myocardial dysfunction.

Fig. 5

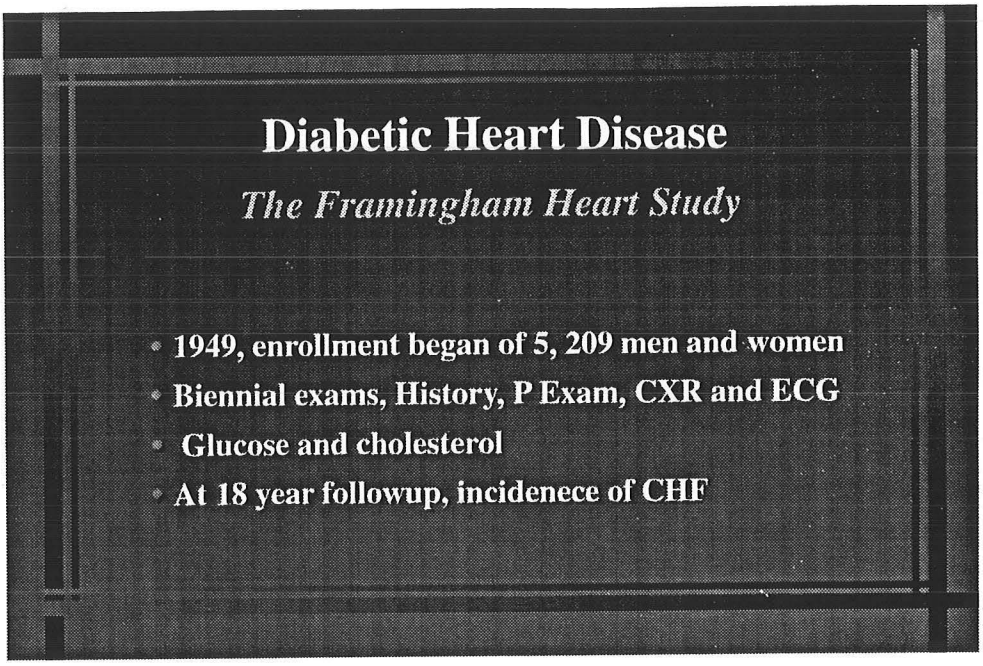


Table 1 [13]

Risk of Congestive Heart Failure According to Sex and Diabetic Status at Each Biennial Examination: 18 Year Follow-Up Study

Diabetic Status	Person Years At Risk	Incidence: Crude Annual per 10,000	Incidence: Age-Adjusted* per 10,000	Relative Risk
Men Aged 45 to 74 years				
Nondiabetic	26,988	31.87	32.14	2.36†
Diabetic	1,226	89.72	75.98	
Women Aged 45 to 74 years				
Nondiabetic	35,322	19.53	19.75	5.14‡
Diabetic	1,190	142.85	101.60	

* Indirect method.
† Significant at $P < 0.05$ (chi square = 6.50).
‡ Significant at $P < 0.01$ (chi square = 12.53).

Table 2 [13]

Annual Incidence of Congestive Heart Failure (CHF) According to Sex and Diabetic Status at Each Biennial Examination Excluding Subjects with Coronary (or Rheumatic) Heart Disease Before the Development of Failure: 18 Year Follow-Up Study

Diabetic Status	Person Years At Risk	New CHF Cases	Annual Incidence: Crude per 10,000	Annual Incidence: Age-Adjusted* per 10,000	Relative Risk
Men aged 45 to 74 Years					
Nondiabetic	23,844	32	13.42	13.53	3.79†
Diabetic	970	6	61.86	51.41	
Total	24,814	38			
Women Aged 45 to 74 Years					
Nondiabetic	32,892	30	9.12	9.23	5.48†
Diabetic	980	7	71.43	50.54	
Total	33,872	37			

* Indirect method.
† Significant at $P < 0.01$ level (chi square = 8.15 and 17.27 for men and women, respectively).

Hamby and colleagues examined 73 patients with idiopathic primary myocardial disease and proposed the term "diabetic cardiomyopathy" based on patholigic studies in three diabetics of 16 diabetic subjects who exhibited similar features as ones described as Rubler and colleagues [12, 14]. These three studies are most frequently cited in the literature as the foundations for a primary myocardial disease, perhaps

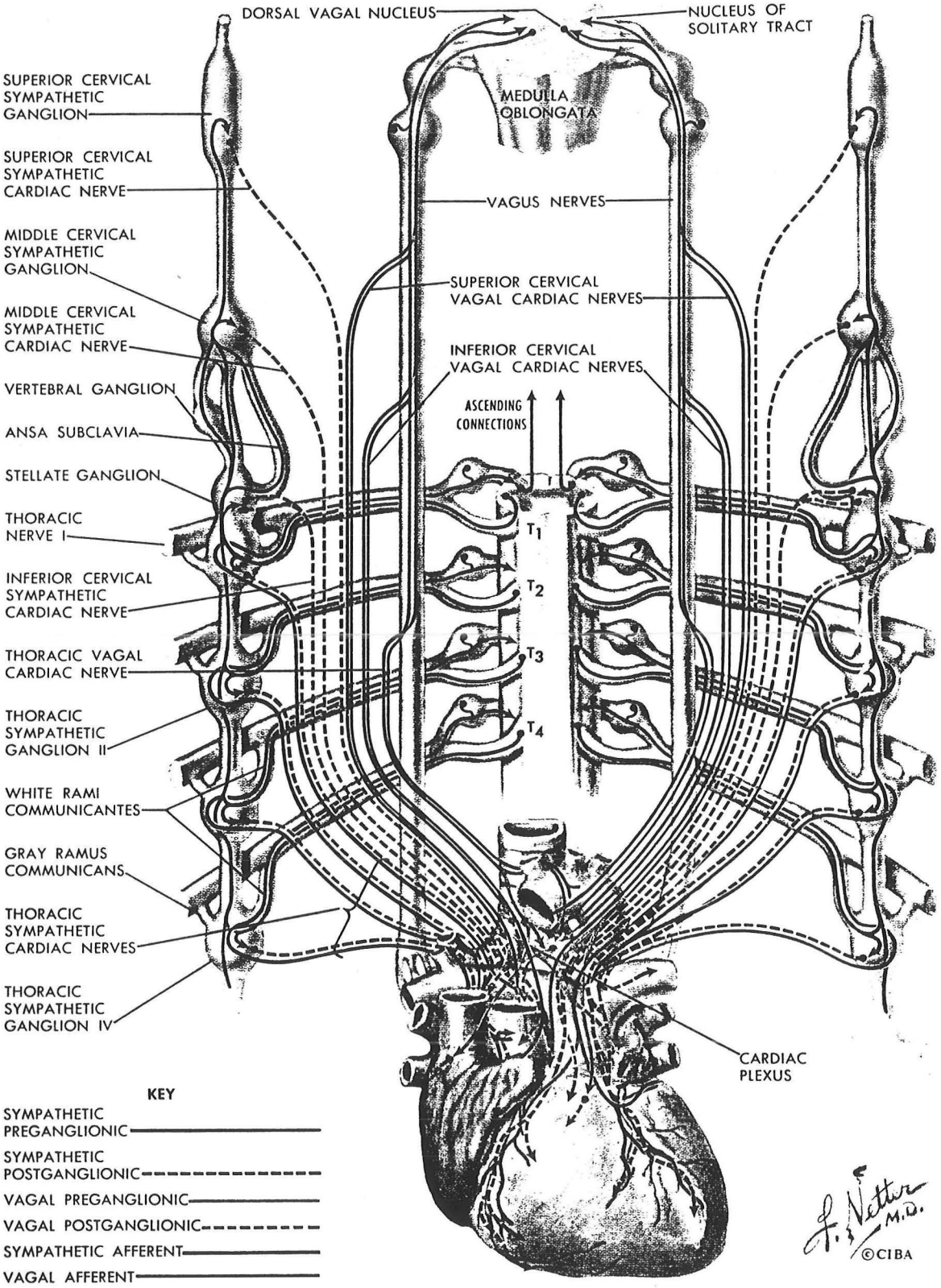
involving small vessels, and termed diabetic cardiomyopathy. Then, as now, small vessel disease remains a pathologic diagnosis and furthermore, its specificity for heart disease in diabetics have never been established.

Definitions

Cardiomyopathy refers to primary myocardial disease without systemic, valvular or epicardial coronary disease [15]. The notion that small vessel disease may contribute to myocardial dysfunction, independent of primary muscle defect, underscores the confusion and major inconsistencies that we face with the use of cardiomyopathy in diabetes mellitus. To address this issue a World Health Organization Expert Committee on Cardiomyopathies recommended the term **diabetic heart muscle disease** (DHMD) but it has not gained widespread acceptance [15, 16].

Both abnormalities in left ventricular developed pressure or systolic dysfunction and myocardial relaxation or compliance (i.e. diastolic dysfunction) are have been reported in human and experimental diabetes [5, 17]. A model of **hypertensive-diabetic cardiomyopathy** in rodents is reported to mimic the complex interactions between hypertension and diabetes in diabetic patients [18]. An important limitation of this work is that both hypertension and diabetes are independent contributors to myocardial dysfunction in addition to being major risk factors for coronary artery disease in humans. Thus, the imprecise usage of these terms can be an appropriate topic for an Expert Committee convened jointly by the American Heart Association and the American College of Cardiology to provide much needed recommendations in this area.

Fig. 6


DORSAL VAGAL NUCLEUS
NUCLEUS OF SOLITARY TRACT
MEDULLA OBLONGATA
VAGUS NERVES
SUPERIOR CERVICAL VAGAL CARDIAC NERVES
INFERIOR CERVICAL VAGAL CARDIAC NERVES
ASCENDING CONNECTIONS
SUPERIOR CERVICAL SYMPATHETIC GANGLION
SUPERIOR CERVICAL SYMPATHETIC CARDIAC NERVE
MIDDLE CERVICAL SYMPATHETIC GANGLION
MIDDLE CERVICAL SYMPATHETIC CARDIAC NERVE
VERTEBRAL GANGLION
ANSA SUBCLAVIA
STELLATE GANGLION
THORACIC NERVE I
INFERIOR CERVICAL SYMPATHETIC CARDIAC NERVE
THORACIC VAGAL CARDIAC NERVE
THORACIC SYMPATHETIC GANGLION II
WHITE RAMI COMMUNICANTES
GRAY RAMUS COMMUNICANS
THORACIC SYMPATHETIC CARDIAC NERVES
THORACIC SYMPATHETIC GANGLION IV
T1
T2
T3
T4
CARDIAC PLEXUS
KEY
SYMPATHETIC PREGANGLIONIC
SYMPATHETIC POSTGANGLIONIC
VAGAL PREGANGLIONIC
VAGAL POSTGANGLIONIC
SYMPATHETIC AFFERENT
VAGAL AFFERENT
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Clinical Features and diagnosis:

Chest pain occurs less frequently in diabetics and several distinguishing features are noteworthy [19, 20]. Both the thresholds for pain perception and the number of unrecognized infarctions are higher in diabetics (~39 %) compared to nondiabetics 22 % [21, 22]. Barret-Connor and Orchard have estimated that 30% of the deaths in diabetics are due to acute myocardial infarction alone [23]. In the Framingham cohort approximately 25% of myocardial infarctions were unrecognized by the participants and only one-half of the patients were symptomatic [24]. A further 12-15 % of the general population is considered truly asymptomatic with clinical evidence of myocardial infarction. The heart is innervated by sympathetic and parasympathetic fibers whose afferent and efferent pain fibers synapse primarily in upper thoracic and lumbosacral regions (Fig 6). This is the anatomical basis for chest pain to also be perceived in the neck, jaw and left arm but occasionally involving both arms. Radiculopathy is a sensory syndrome that may cause chest wall pain that arise from spinal nerves in the thorax. While peripheral neuropathy is most common, differences in the clinical course of diabetic heart disease are closer correlated with the development of autonomic neuropathy.

Destruction of pain fibers from myocardial injury, diffuse coronary artery disease and even central pain hyposensitivity are important considerations. Pathological studies have implicated damage both efferent and afferent nerves for abnormalities in pain perception. Even nondiabetic patients, with known coronary artery disease, but with asymtomatic ischemia by exercise electrocardiography exhibit increased ischemic pain thresholds [25].

The clinical criteria for the diagnosis of autonomic dysfunction have been received detailed attention by Ewing [26], and other workers [27], and require two or more abnormal responses during Valsalva maneuver, blood pressure response to handgrip exercise, heart rate variability, lying to standing position and postural hypotension. These tests can easily performed with a pneumatic cuff and an electrocardiogram at the bedside. Postural hypotension can occur within 5 years of the diagnosis of parasympathetic dysfunction and is specific for symptomatic autonomic neuropathy. Parasympathetic nerve function in diabetics can be assessed by measuring the expiratory/ inspiratory RR interval ratio (Fig. 7).

Diastolic blood pressure response to handgrip exercise is measured for the assessment of peripheral sympathetic function. There is approximately 50 % mortality in 5 years with almost one-third of the deaths occurring suddenly (Fig. 8). A higher prevalence from sudden death in diabetics can be correlated with insignificant coronary artery disease suggesting that other factors such as increased sympathetic tone and prolonged QT intervals may be associated with this particularly dreaded complication [28].

Fig. 7 Assessment of Parasympathetic function by heart rate variability to deep breathing [27]

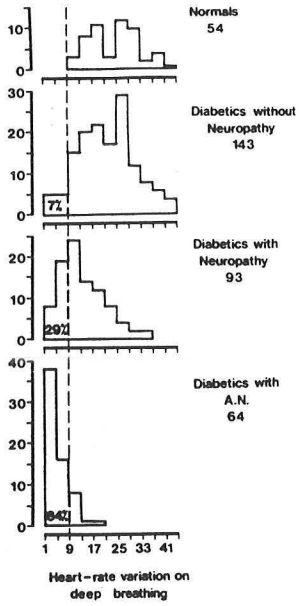
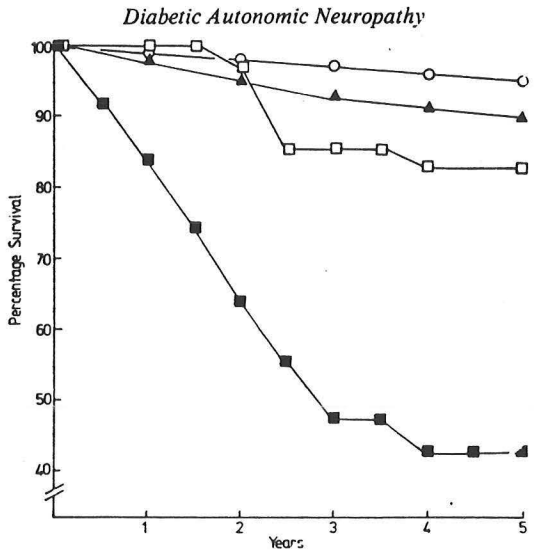


Fig. 8 Mortality in diabetics with autonomic neuropathy [26]



Five-year survival curves for age and sex matched general population (O), age and sex matched diabetic population (▲), 33 diabetics with normal (□) and 40 diabetics with abnormal (■) autonomic function tests.

Parasympathetic nerve fibers are affected before sympathetic fibers and consequently the resting heart rate is increased whereas the heart rate and blood pressure responses to exercise are blunted . Although the heart rate variability is abolished by atropine, this highly reproducible response is unaffected by ß-blockade [27]. Thus, myocardial ischemia and/or infarction can occur from imbalances in sympathetic tone, increased resting heart rate and reduced coronary perfusion pressure during hypotension [6]. Recognition and of these factors is potentially relevant in anticipating major intra-operative catastrophes because diabetics undergoing general anesthesia are 7 times more likely than nondiabetics to require vasopressors for hemodynamic support. [29].

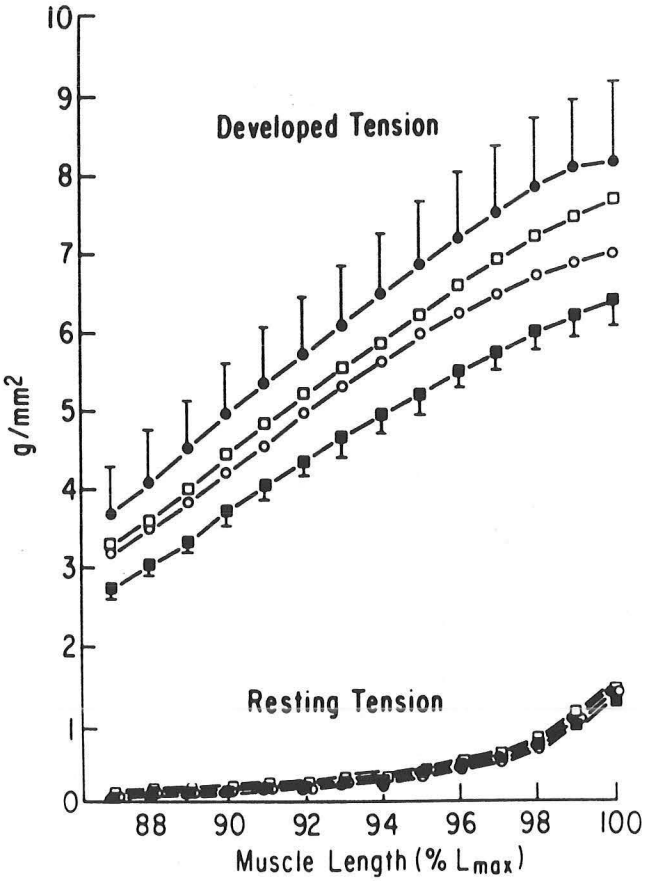
Genetics

Only a handful of genes including the converting angiotensin enzyme, apolipoprotein and fatty acid binding proteins have been linked to NIDDM and cardiovascular disease [30, 31]. A condition simulating the heritable form of hypertrophic cardiomyopathy is found in infants of diabetic mothers and is characterized by marked septal and occasional right ventricular free wall hypertrophy on echocardiography [32]. The disease is rarely fatal and the cardiac abnormalities usually resolve within six (6) months supporting the notion that it is related to the generalized organomegaly and is not result of either inherited or spontaneous mutations of the major contractile proteins [32].

Co-morbid factors and cardiac risk in diabetics.

Diabetic nephropathy, per se, in insulin-dependent diabetics is associated > 25 fold greater risk for the development of coronary artery disease. In contrast, noninsulin dependent diabetics exhibit similar, albeit increased cardiovascular risks than do nondiabetics from greater waist-to-hip ratio, hypertension, obesity and dyslipedemia [33, 34]. Fein and Sonnenblick have studied the cardiac effects of diabetes and hypertension in experimental models, Fig. [18]. Because polygenic factors have been proposed in disease pathogenesis, these studies may have important implications in populations of NIDDM patients with an increased prevalence of hypertension and obesity, such as in blacks [35].

Fig. 9. Resting and developed tension as a function of muscle length in control (closed circle); hypertensive (open circle); diabetic (open square) and hypertensive-diabetic (closed square) rats [18].



Non-insulin dependent diabetes mellitus (NIDDM) is more prevalent in blacks over other non-black populations [36, 37] that can lead to disproportionate cardiovascular consequences from myocardial dysfunction and overt heart failure [1]. Table 2 shows the admissions to Parkland Memorial Hospital with the principal diagnoses of NIDDM and IDDM for 1994 and the first half of 1995. Blacks constituted over 50% of the admissions with either classification of diabetes although this group comprised 30 % of the total admissions. Hispanics made up 20 % of the diabetic admissions (45 % of total) whereas whites who averaged one-fifth of the total admissions were roughly 25-29 % of the diabetics admitted to PMH recently.

Table 2.

PARKLAND MEMORIAL HOSPITAL

1994 ETHNICITY TOTALS

Black: 30.5% White: 20.3% Hispanic: 45.5%

NIDDM	TOTALS	BLACK		WHITE		HISPANIC		OTHER	
1994	1,281	684	53%	320	25%	228	18%	49	4%
01/95-06/95	825	447	54%	190	23%	163	20%	25	3%

IDDM	TOTALS	BLACK		WHITE		HISPANIC		OTHER	
1994	821	441	54%	238	29%	120	15%	22	2%
01/95-06/95	324	162	50%	96	29%	54	16%	12	5%

Serum levels of triglycerides, very low density lipoprotein cholesterol (VLDL) low density lipoproteins (LDL) are elevated in diabetics while the level of high density lipoprotein (HDL) is reduced compared to nondiabetics [10]. However, the significance of the lipid abnormalities remains unresolved since the total cholesterol was similar in participants with or without diabetes in the Framingham study . Increased viscosity from elevated plasma proteins and alterations in red blood cell morphology in diabetics are suggested to promote atherosclerosis through increased shear forces, plaque-fissuring and, perhaps, impeded collateral blood flow during ischemia .

Table 3 . Vascular abnormalities in diabetics (reviewed in \[6]).

Atherosclerotic plaque rupture
Intraluminal thrombosis formation
Endothelial dysfunction
Elevated lipids, Red HDL
Abnormal Platelets function
Plasminogen Activator Inhibitor Activity
Coagulation and fibrinolysis
Reduced prostacyclin
Increased vWF

Diagnosis

Ambulatory monitoring has been suggested as a critical adjunct in the evaluation of diabetic patients because myocardial ischemia may often be asymptomatic [19]. The widespread use of this procedure, however, is not advisable unless the status of the patient's coronary artery disease is known. Exercise stress testing, preferably with thallium scintigraphy can be an important aide in the clinical management of diabetic patients, excluding ones with peripheral vascular disease and diabetic neuropathy [38, 39]. Of note, diabetics not only have twice the amount of ST depression without pain but the delay in pain perception from the time of ST depression to angina is twice as prolonged than do nondiabetics presumably the result of autonomic dysfunction [38]. Abnormal exercise-induced left ventricular dysfunction has been reported in diabetic patients with normal resting LV systolic function and without evidence of end-organ disease although the true prevalence of this disorder has not been studied prospectively [40].

Diabetic patients are reported to exhibit abnormalities in both systolic and diastolic functions that may precede overt heart failure [5, 17, 41]. Consistent and predictable measurements of these subtle abnormalities of the cardiac cycle have proved problematic, however. Studies of systolic function in diabetic subjects have used: 1) determination of the systolic time interval that is from the beginning of the QRS complex to the second heart sound, 2) measurement of the left ventricular ejection time from the onset of the carotid upstroke to the trough of the carotid incisura, and 3) the pre-ejection period that is the simple difference between the left ventricular ejection time and the systolic interval [39, 42]. The first two parameters are obtained noninvasively by radionuclide ventriculography and are fairly reliable. Indeed, Posner and colleagues (1) found no differences in 16 insulin-dependent diabetics were compared with 30 age-matched individuals although their negative findings could be due to the small sample size under investigation [42].

Lower left ventricular preload from smaller plasma volume has been proposed to increase directly the relaxation period and reduce the early filling velocity thereby invalidating the certain critical hallmarks of "diabetic cardiomyopathy" [16]. Thus measurements of diastolic dysfunction can also be overestimated if left ventricular preload is reduced by the coincident microvascular effects of diabetes. Despite these uncertainties, there are a substantial literature of carefully executed studies in various

experimental models in support of primary muscle disease in diabetes. Unfortunately, there are few clinical studies to adequately address the natural history of this disorder in humans [35].

Fig. 10. Effect of NIDDM on myocardial contractility [43]

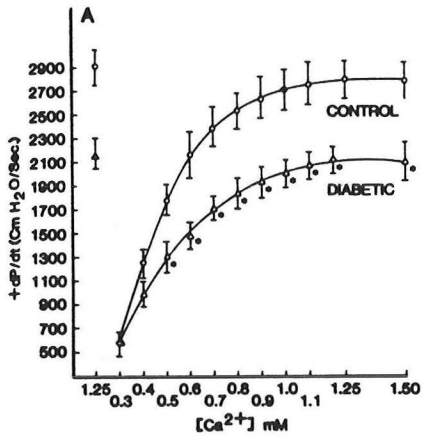
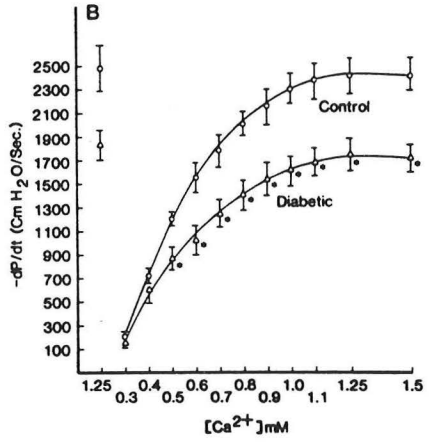


Fig. 11 Effect of NIDDM on myocardial relaxation [43]



Diastolic dysfunction in diabetics can be due to abnormal relaxation from both prolonged isovolumic relaxation and reduced rapid filling velocities, Fig 10 & 11 [5, 43]. Diabetic patients, with congestive symptoms but insignificant coronary artery disease, exhibited exaggerated increases of LV end-diastolic pressure (LVEDP) to volume challenge and elevated pressure-volume relationships [44]. Interpretations of these results must be viewed cautiously because left ventricular hypertrophy from hypertension can contribute to global LV dysfunction and raised LVEDP in diabetics with significant nephrosclerosis. A direct correlation between microvascular complications and cardiac or any other protean manifestation of disease has not been established. However, Airaksinen and colleagues found prolongation of early rapid ventricular filling in 36 diabetic women (mean age 25, range 15-35 years) with severe microvascular complications compared to a group age-matched normal women [45]. Diastolic abnormalities in diabetic patients have reported to occur earlier than systolic dysfunction although the existence of diastolic abnormalities has been questioned [46, 47].

Borow and colleagues found that a subset of young IDDM subjects, with normal systolic function but exercised-induced reductions in ejection fraction, exhibited

entirely normal indices of contractile reserve when assessment by load and heart rate-independent indexes for myocardial function. These investigators concluded that the abnormal responses with exercise were due to loading conditions, Fig 12 & 13 [46]. In practice, we consider diabetic patients with congestive symptoms or overt heart failure to have diastolic dysfunction if diagnostic studies using noninvasive imaging or angiography reveal normal systolic function.

Fig. 12 Left ventricular EF (%) obtained under rest and at peak exercise for all groups [46].

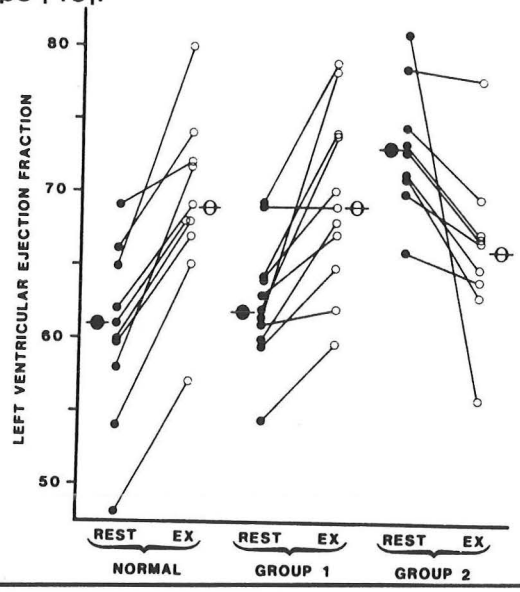
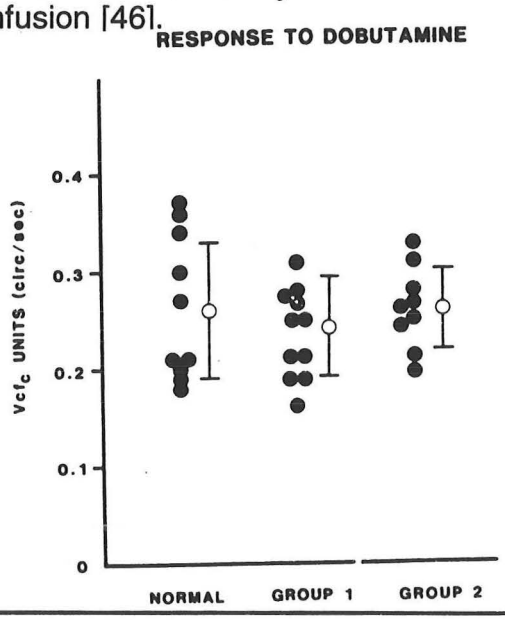


Fig. 13. Assessment of left ventricular contractile reserve by dobutamine infusion [46].



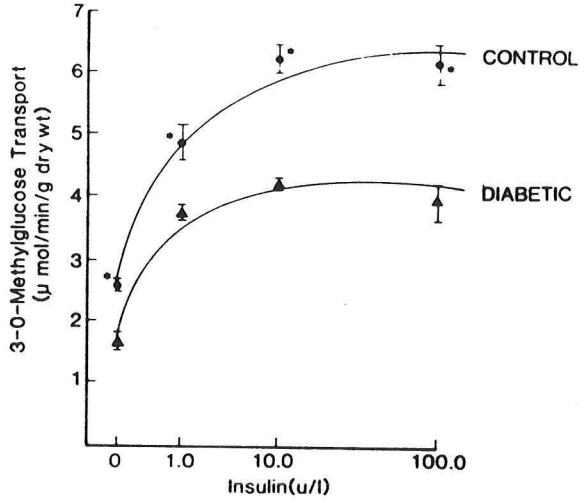
Animal models of diabetes:

Animals' models have provided important insights about the cardiovascular manifestations of diabetes. Both spontaneously and chemical-induced models in rodents and swine are used and each has important limitations with respect to the condition in humans [48, 49] . Streptozotocin or alloxan are chemical sclerosing agents that destroy pancreatic ß-cells such that the administration in rats results several weeks later in a diabetic model whose features include insulinopenia, glycosuria, polydipsia, hyperglycemia and peripheral muscle wasting [50, 51]. This is reminiscent of insulin dependent diabetes and most interestingly insulin therapy can ameliorate the development of the cardiac abnormalities, if untreated [48].

In contrast, a model of NIDDM in which glycolytic flux is found to be significantly reduced in the diabetic heart can be seen much later at times occurring 8-12 months after chemical treatment, Fig 14, [5]. Obese Zucker diabetic rats are considered an ideal model since they faithfully mimic the temporal onset of metabolic changes of

obesity-dependent NIDDM, see Fig 15 below [8, 52]. Among several available models of diabetes in mice [53], the obese, insulin-resistant, db/db murine model can faithfully recapitulate the metabolic abnormalities of NIDDM [54, 55].

Fig. 14 Effect of NIDDM on glycolytic flux in the isolated working heart [56]



Fatty acid metabolism

Fatty acid mobilization is triggered by lipogenesis and lipolytic states, from adipose tissues and is targeted to the liver where they are used as an alternative source of fuel during insulin deficiency. Conversely, NIDDM is characterized initially by insulin hypersecretion from ß cells that is followed by ß-cell failure, perhaps from lipotoxicity [2, 7]. Skeletal muscle is the major site of glucose clearance whereas the primary source of fuel in the heart is derived from fatty acids [57]. In experimental animals, maneuvers that reduce elevated plasma FFA levels are sufficient to reverse ß-cell abnormalities by increasing GLUT2 receptors and restoring glucose-stimulated insulin secretion [58]. Studies by Unger and colleagues suggest that ß-cell failure is a consequence of lipotoxicity [52]and perhaps similar or additive mechanisms contribute to cardiomyocyte failure. Furthermore, it is not known whether lipid accumulation in the heart impairs its endogenous host defenses, including the induction and expression of the heat shock genes, thereby increasing its susceptibility to ischemic injury.

Taken from Lee et al, *Proc Natl Acad Sci USA*, 91: 10882, 1994

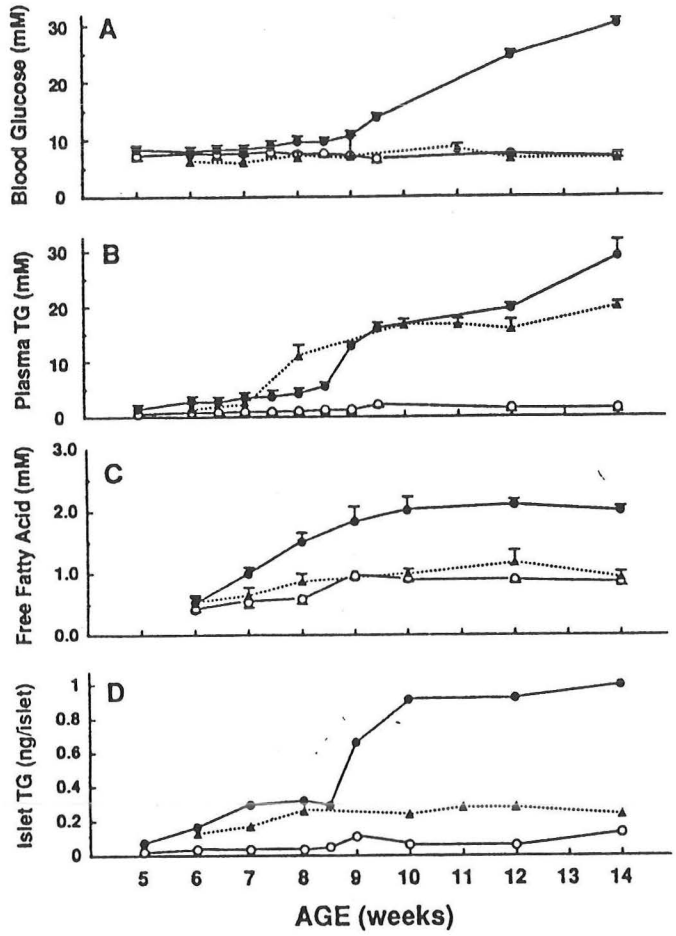


FIG. 4. Longitudinal studies of blood glucose (*A*), plasma TG (*B*), FFA (*C*), and TG content of islets (*D*) in lean male ZDF rats (*fa*/+) (○); obese female ZDF rats (*fa*/*fa*) (▲), which do not develop diabetes; and obese male ZDF rats (*fa*/*fa*) (●), which develop diabetes between the ages of 8 and 10 weeks. From Lee et al. (39).

In the Glucose Fatty Acid Cycle, the Randle hypothesis predicts that both the short and long term effects of fatty acids are to reduce the uptake, glycolysis and oxidation of glucose especially in the skeletal muscle and the heart [59, 60]. The Randle hypothesis has been validated in vivo and is mediated through mechanisms involving the pyruvate dehydrogenase complex [61, 62]. Specifically, fatty acids and diabetes stimulate the activity of pyruvate dehydrogenase kinase whose substrate is phosphofructokinase that is rendered inactive at least three serine residues by reversible phosphorylation [63]. Importantly, the effects of FFA are mediated through breakdown of the endogenous triacylglycerols as demonstrated by the specific inhibition of the mitochondrial carnitine palmityl-transferase with etomoxir, [4].

Glucose transport during ischemia

Although several studies have implicated alterations in the microvasculature, contractile proteins and calcium homeostasis in the pathogenesis of primary myocardial disease or diabetic cardiomyopathy, we do not have definitive evidence in support of these relationships and the precise mechanisms are essentially unknown in molecular terms. Ischemia is a potent stimulus to increase glucose uptake and utilization as an alternative fuel source for preservation of myocardial function, reduce myocardial enzyme release, post-ischemic ventricular recovery and prevention of ischemic contracture [57, 64]. Similar beneficial effects have been proposed for increased glucose uptake during ischemia and facilitated by the predominant insulin-responsive glucose transporters, GLUT4, in the myocardium [65, 66]. Genes encoding at least five glucose transporters have been cloned with the major GLUT2 expressed in the pancreas whereas the distribution of GLUT4 appears to be restricted to the heart, skeletal muscle and adipose tissue [67]. More recently, there is an exciting report of a mechanism for glucose uptake in skeletal muscle that is independent of insulin stimulation [68], perhaps mediated by contractile activity [69]. Conceivably, mobilization of glucose transporters sequestered in intracellular stores under basal conditions may require members of the heat shock proteins for translocation to the plasma membrane (40 % increase) during ischemia (Fig &) [66].

Fig. 16. GLUT4 expression in plasma membrane by immunoblot

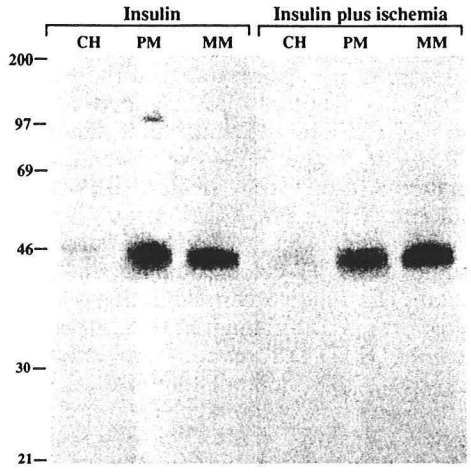
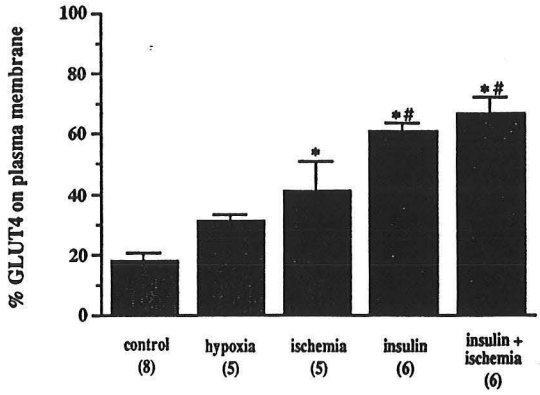


Fig. 17. Comparison of GLUL4 expression in plasma membrane under varying conditions below [66]



Cellular biology and molecular biology

Alterations in sarcolemmal and sarcoplasmic reticulum Ca^{2+} transports have been observed in diabetics and such abnormalities are thought to be less significant in NIDDM [17, 70]. However, specific defects in the activity of the Na^{+}/Ca^{2+} exchanger have suggested that contractile dysfunction is secondary to abnormal Ca $^{2+}$ handling [71]. Alternatively, some workers have proposed that abnormalities of the major structural protein myosin that exists in two major isoforms in mammalian species, termed α–MHC and ß-MHC. The α–MHC and ß-MHC isoforms form homodimers, called V1 to V3 isoforms, or pair to form a heterodimer, V2 isoform. The predominant myosin heavy chain (MHC) homodimers undergo isoform switching around birth. In the adult rodents, the VI α-MHC is the major isoform although fetal V3 isoforms can be induced during hypertrophy from aortic stenosis, chronic volume overload and diabetes [72, 73]. This up-regulation of the V3 isoforms with a lower ATPase activity has been implicated in abnormal contractile abnormality in diabetes [17, 74]. No cause and effect relationship, however, can be established and more recent evidence suggests that the influences of thyroid hormone have profound affects in isoform switching, also triggered during diabetes [75]. In some studies myosin ratios have been restored to baseline with insulin therapy [51]. The relevance of these changes in humans becomes unclear V3 is the predominant expressed normally and similar isoform switching are not observed in pathological states.

MANAGEMENT

The Diabetes Control and Complications Trial

The role of tight metabolic control on the morbidity of patients with insulin-dependent diabetes has been hotly debated and the most comprehensive study was undertaken in the Diabetes Control and Complications Trial (DCCT) [76]. This randomized multicenter study tested the hypothesis that intensive insulin therapy, to achieve glucose levels close to the normal range, will reduce the major complications of the microvascular, neurologic and cardiovascular systems. This study enrolled over 1,441 individuals aged 13 to 39 years and roughly equivalent numbers of participants were enrolled into an arm with no retinopathy (primary-prevention) or mild retinopathy (secondary-prevention) before randomization for therapy. This study cohort specifically excluded any patients with hypertensive, obese, elevated cholesterol and other evidence for coronary artery disease. The trial was stopped prematurely to report the following significant findings (Table 3):

Clinical Endpoints	Reductions in Intensive over Conventional therapy
Retinopathy	
-primary	76 %
-secondary	54 %
Microalbuminuria (> 40 mg per 24 h)	39 %
Albuminuria	54 %
Neuropathy	60%
Cardiac events	42 % (p= 0.08)

There dramatic reductions in microvascular disease, specifically retinopathy was reduced by 76% in the primary prevention group and 54 % in the secondary prevention group. Similar significant reductions were posted for the development of renal disease and neurological and autonomic disease. The results on macrovascular complications were reported only recently . The endpoints of macrovascular complications were fatal and nonfatal cardiovascular or cerebrovascular accidents, cardiac arrest or major arrhythmias, congestive heart failure and major vascular

events. Despite 42% reduction in major cardiovascular events, these results did not reach statistical significance [77]. The reasons are readily apparent but were attributable to the younger average age of 34 years in contrast to 55 years that is common for diabetics at presentation with cardiac disease. For example, in the Framingham study revealed the cumulative mortality in IDDM from coronary artery disease to be 35% by age 55, which is almost 7 times greater that the 4-8% in nondiabetics [24]. Thus in 1995, we don't have clear-cut evidence that intensive therapy reduces cardiovascular events. As mentioned earlier, diabetic nephropathy adds substantially to cardiovascular morbidity in IDDM and is substantially reduced by intensive therapy. A prediction of these findings is that the cardiovascular benefits, if present, are likely to be through multiple mechanisms.

Previous attempts to use glucose-Insulin-Potassium (GIK) therapy has not been for acute myocardial infractions are of unproved benefit [6]. The indications for standard medical regimen in the treatment of cardiac patients have been extensively reviewed at these Rounds. Briefly, beta Blockers have long been used in diabetic patients for control of angina and post-myocardial infarction prophylactic. It is uncommon for yypoglycemic episode during ß-blockade to cause fatalities [78]. Likewise, calcium channel Blockers are particularly effective in diabetic patients with hypertension and congestive heart failure. Vasodilator therapies in the management of chronic congestive heart failure include the angiotensin converting enzyme inhibitors, hydralazine and nitrate therapy. Aspirin is indicated for acute ischemic syndromes although diabetics patients synthesize greater amounts of thromboxane A_2 and are prone to increase platelet aggregation reviewed in [6].

Thrombolytic therapy:

By far, the most dramatic impact on mortality from acute myocardial infarction has been the routine use of thrombolytic therapy. In the Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI) 5 trial, the incidence of retinal hemorrhagic complications in 148 patients that received thrombolytic therapy was not higher even in patients with proliferative retinopathy, Table 4 [79]. Diabetic and nondiabetics' patients over 75 years who were excluded from this study are known to have higher complication with bleeding, however. Baseline characteristics of diabetic patients in the TAMI 5 trial (14 % of total cohort) indicated a higher prevalence of hypertension whereas a greater percentage of nondiabetics was cigarette smokers. Slightly under one-third of the diabetic patients were either insulin-dependent or controlled on diet alone whereas

the majority were on oral hypoglycemic agent. Cardiac catherization performed 90 minutes after thrombolytic therapy revealed the ejection fraction and regional function the infarct zones were similar whereas the regional function in the noninfarcted region was statistically significant lower in diabetics compared with nondiabetic patients. Diabetic women a had a 2 fold higher mortality than diabetic men. Sixty-six (66 %) of diabetic patients had multivessel coronary artery disease compared with 46 % in those without diabetics, Table 5 [79].

Table 4. Complications in diabetics and nondiabetics in TAMI trial.

Table . In-Hospital Clinical Outcome

—	Diabetes (n = 148) (%)	No Diabetes (n = 923) (%)	p Value
Death	11 (17)	6 (53)	< 0.02
Stroke (any)	1.4 (2)	1.1 (10)	
Intracranial hemorrhage	0.7 (1)	0.8 (7)	
Nonhemorrhagic	0.7 (1)	0.3 (3)	
Shock	9 (13)	10 (85)	
Reinfarction	6 (6)	3 (16)	
Reocclusion	12 (15)	11 (93)	0.826
Pulmonary edema	11 (16)	4 (38)	0.0001
Intubation	11 (16)	8 (61)	
Dialysis	0 (0)	1 (5)	
CABG	30 (43)	22 (200)	
Death, after CABG	9.3 (4)	7.5 (15)	
PTCA (acute)	32 (47)	38 (346)	
Death, after acute PTCA	12.8 (6)	9.0 (31)	
Bleeding, requiring transfusion	23 (24)	20 (143)	
Length of hospital stay (days)	10	9	
Median 25th/75th percentile	8/16	8/12	

The figures in parentheses indicate number of patients. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

Table 5. Prevalence of CAD in diabetics and nondiabetics in the TAMI trial

Table . Cardiac Catheterization Data

	Diabetes (n = 148)	No Diabetes (n = 923)	p Value
LV ejection fraction (%)	48.8 ± 12.3	51.3 ± 11.8	
Regional function (SD/chord)			
Infarct zone	−2.7 ± 1.0	−2.5 ± 1.1	0.15
Noninfarct zone	−0.13 ± 1.8	0.32 ± 1.7	0.02
Patients with 0 or 1-vessel disease	34	54	
Patients with multivessel disease	66	46	< 0.0001
2-vessel disease	40	27	
3-vessel disease	26	18	
Segments with ≥25% stenosis (no./patient)	3.4 ± 2.0	2.9 ± 1.8	< 0.002
Infarct-related artery patency (%)			
90 min after start of thrombolytic therapy	71	70	
At the end of acute catheterization (after attempted PTCA if occluded)	92	93	

Unless otherwise stated values are presented as mean value ± SD or percent of patients. LV = left ventricular; PTCA = percutaneous transluminal coronary angioplasty.

The foregoing influences of the patient's perception of their illness along with the inadequate triage at presentation may delay the administration of thrombolytic agents in this subgroup likely to derive the most benefit. Physicians have a special responsibility to advise the diabetic patients as well as their close relatives to seek medical attention promptly to ensure optimal therapy in these patients. Interestingly, when adjusted for the extent of coronary artery disease, age, left ventricular ejection fraction, location of infarction and systolic blood pressure, multivariate analysis indicated that diabetes was not to be an independent variable in mortality. These data must be confirmed but they suggest that modification of the major co-morbid factors deserves more critical attention for primary intervention.

Cardiac catherization and Percutaneous Angioplasty (PTCA): The indications for intervention for ongoing ischemic syndromes refractory to medical therapy are essentially the same for both diabetic and nondiabetic patients. Arguably, diabetics should be more 'aggressively' managed since they are at increased risk for recurrent ischemia and myocardial infractions, congestive heart failure, sudden death in the first year. Appropriate candidates for cardiac catherization are patients with complications of an acute myocardial infarction including recurrent or ongoing ischemia, pump failure and/or uncontrolled ventricular arrhythmias. The extent of coronary artery disease in epicardial vessels can be assessed and definitive therapy instituted. The risk of renal insufficiency in diabetics can be slightly greater but not prohibitive and is much better controlled with use of from contract agents with less nephrotoxicity.

Revascularization by PTCA and coronary artery bypass surgery
Revascularization by coronary artery bypass surgery are effective measures to reduce morbidity and mortality from severe ischemic heart disease. However, at presentation diabetics have more extensive coronary artery disease and between 4.5 to 5.1 % mortality rate at CABG which is twice above the rate of nondiabetics [80]. Diabetics also have a shorter long-term survival rate after CABG. Poor wound healing, infections, renal failure also contribute to prolonged length of hospitalization in patients after CABG without diabetes. Hence, percutaneous angioplasty that is shown to carry low risk and high success rate may be an effective alternative in diabetic patients suitable for revascularization of single and even multivessel coronary artery disease [81]. Diabetes mellitus is not an absolute contraindication for cardiac transplantation. However, most centers establish strict criteria and candidates considered only after exclusion of end-organ disease.

A case report

SG (1985) A 26 year old woman with a history of diabetes and hypertension was referred to my cardiology clinic for evaluation of shortness of breath. She was morbidity obese but her examination was otherwise unremarkable. Despite adequate antihypertensive regimen and diabetes control with insulin therapy, her cardiac function deteriorated. At age 27, she experienced a transient ischemic attack felt to be cardiac source and anticoagulation was instituted. Efforts at weight reduction were

unsuccessful including the patients refusal of gastric stapling procedure. Her cardiac function further worsened and she developed both exertional and rest angina on antianginal therapy but her weight she exceeded the limits of the cath lab. Her clinic visits indicated evidence of medical noncompliance with anticoagulation. She expired from a massive myocardial infarction and at autopsy her cause of death was attributed to an intracoronary embolism of her left anterior descending artery most likely dislodged from mural thrombi found in her markedly dilated left ventricle.

THE FUTURE

My purpose of citing this case is that perhaps you have likewise shared the feeling of powerlessness to alter the clinical course of a particular patient despite your very best intentions. My recollections of this patient ,who I cared for over a decade ago, was triggered upon reading the tremendous breakthrough by Dr. Friedman and colleagues at Rockefeller University with the recent cloning of the *obese* gene [82]. Maybe, this patient had a genetic disease in stead of an indiscriminate eating disorder. Such scientific strides will continue to provide even further insights into the complex relationships of diabetes, hypertension and other co-morbid factors we have discussed today. Also, advances in mammalian genetics have provided unprecedented opportunities for cardiovascular investigators to pursue fundamental questions on the events underlying acute myocardial infarction, in molecular terms. Thus, our ability to introduce (or delete) genes encoding specific proteins by genetic manipulation in animals (transgenic animals) coupled with the miniaturized techniques for physiological measurements are considered important milestone for studies in the ischemic heart [83].

High free fatty acyl CoA (FFA) levels have been implicated as critical factors in the pathogenesis of non-insulin dependent diabetes mellitus (NIDDM). Isolated islets from prediabetic Zucker rats manifest the abnormalities of blunted glucose-stimulated insulin secretion (GSIS) when perifused with elevated levels of FFA. In experimental animals, maneuvers that reduce elevated plasma FFA levels are sufficient to reverse the ß-cell abnormalities by increasing GLUT2 receptors, restore glucose-stimulated insulin secretion (GSIS) and, in principle, improve the insulin resistance of peripheral tissues. It is important to point out that these abnormalities are considered the consequence of lipotoxicity, and are not causal. We do not know whether alterations of glucose transporters in the diabetic heart increase its vulnerability to ischemic

stress. However, the inducible expression of several glucose transporters was reported in the ischemic brain regions [84] suggesting the existence of similar mechanisms in the heart. Thus, studies aimed to elucidate potential impairments of the critical endogenous system may provide important insights about the pathogenesis of diabetic cardiomyopathy and increased vulnerability from ischemic injury. Ischemia evokes complex metabolic and physiological pathways in which genes such as the HSP70 heat shock protein has been demonstrated recently to exert cytoprotective effects [85]. Our efforts at bench research will provide the necessary knowledge for unraveling the basic mechanisms of pancreatic ß-cell (and cardiomyocyte) failure that will, ultimately, provide novel strategies that enable us all to take better care of our patients at the bedside.

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